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Review

Sirt1 and Parp1 as epigenome safeguards and microRNAs as SASP-associated signals, in cellular senescence and aging

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ABSTRACT

Cellular senescence (CS) is underlying mechanism of organism aging and is closely interconnected with age-related diseases (ARDs). Thus, any attempt that influences CS, may be undertaken to reverse or inhibit senescence, whereby could prolong healthy life span. Until now, two main proposes are epigenetic and genetic modifications of cell fate. The first one concerns rejuvenation through effective reprogramming in cells undergoing senescence, or derived from very old or progeroid patients, by which is effective in vitro in induced pluripotent stem cells (iPSCs). The second approach concerns modification of senescence signaling pathways like as IGF-induced agents. However, senescence research has experienced an unprecedented advance over recent years, particularly with the discovery that the rate of senescence is controlled, at least to some extent, by epigenetic pathways and biochemical processes conserved in evolution. In this review we try to concentrate on very specific pathways (DNA damage response, DDR, and epigenetic modifiers) and very specific determinants (senescence-associated secretory phenotype, SASP-miRNAs) of human premature aging. A major challenge is to dissect the interconnectedness between the candidate elements and their relative contributions to aging, with the final goal of identifying new opportunities for design of novel anti-aging treatments or avoidance of age-associated manifestations. While knowing that aging is unavoidable and we cannot expect its elimination, but prolonging healthy life span is a goal worth serious consideration.

1. Introduction

Although cellular senescence (CS) was first accounted as an anti-cancer mechanism that occurs in a number of tissues and causes the arrest of proliferation of cells at risk of malignant transformation following exposure to potentially oncogenic stimuli, but CS plays specifically important roles in cardiovascular and cerebrovascular diseases (CVD, CBVD), both of which remain the leading cause of death and are closely linked to human premature aging, increased production of free radicals and clinical manifestation of atherosclerosis (Childs et al., 2015; Chinta et al., 2015; Tsirpanlis, 2007).

The main hallmarks of CS are listed as mitochondrial dysfunction, genomic instability, senescence-associated secretory phenotype (SASP), epigenome alterations and stem cell exhaustion (Fig. 1) (Chinta et al., 2015; Lopez-Otin et al., 2013) and the main mechanisms carrying out CS include production of reactive oxygen species (ROS), shortening of telomeres, mitochondrial damage, and cell cycle arrest by increased expression of tumor suppressors (Williams et al., 2017).

Based on kinetics of senescence induction and functionality, CS is divided into two main classes; acute and chronic senescence. Acute senescence is programmed and required for tissue homeostasis, targets a specific population of cells in the tissue and is part of tightly orchestrated biological processes such as wound healing, tissue repair and embryonic development. However, chronic senescence occurred in premature aging is not programmed and does not target specific cell types. Induction of chronic senescence occurs after periods of progressive cellular stress or macromolecular damage when tarry cycling transitions into a stable cell-cycle arrest (Chinta et al., 2015; Van Deursen, 2014). In the heart, CS and death of cardiac stem cells (CSC) lead to premature cardiac aging and heart failure. In the brain, CS would indicate neural cell death and ultimately leads to the incidence of dystrophy occurring in the cerebral cortex of aged humans in Alzheimer's disease (AD) and Parkinson's disease (PD). It is also well documented that senescent endothelial and smooth muscle cells,

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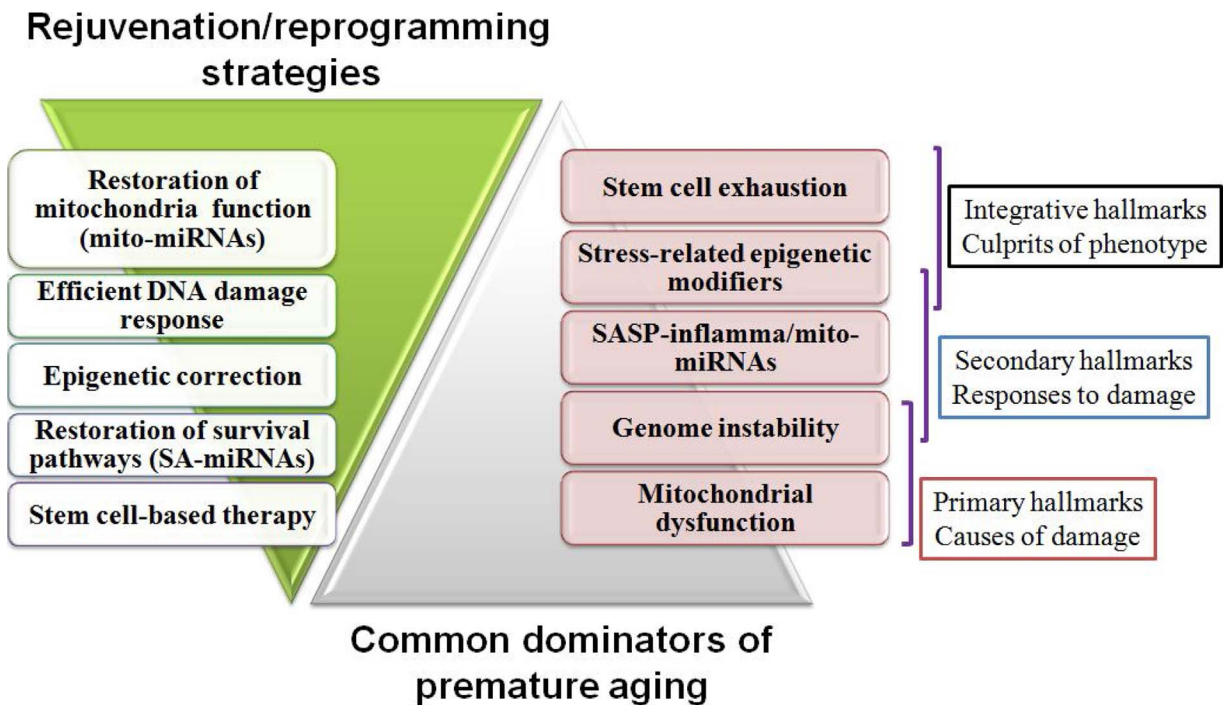

Fig. 1. (Right) Common determinants of premature aging in different mammalians, (Left) with special emphasis on new opportunities for design of novel anti-aging treatments or avoidance of age-associated manifestations in human are illustrated here. These specific pathways in aging are known as: DNA damage response (DDR), senescence-associated secretory phenotype (SASP) and related miRNAs, mitochondrial dysfunction/biogenesis with special focus on stress-related epigenetic modifiers. (Right) Senescence-associated hallmarks are grouped into three categories. Interconnectedness between the hallmarks and proposed mechanisms to prevent senescence are presented in the article.

together with low grade inflammation, participate in atherosclerosis, and senescent preadipocytes and adipocytes provide the scene to insulin resistance (Chimenti et al., 2003; Tsirpanlis, 2007). Then with age, senescent cells accumulate in a variety of human tissues where they express a complex 'senescence-associated secretory phenotype' (SASP). SASP signaling involves a variety of biologically active proinflammatory mediators, but mainly senescence-associated miRNAs (SA-miRNAs or inflamma-miRNAs). As the main contents of SASP, circulating SA-miRNAs are the indicators of senescence and are now supposed to mediating senescence signaling throughout the body by modulating the cell activity, mitochondrial function and inflammatory processes (SA/mito/inflamma-miRNAs) (Olivieri et al., 2015; Pourrajab et al., 2016; Rippo et al., 2014).

Age-related disease (ARDs) is owing to SASP and chronic senescence. Senescence in ARDs is associated with loss of proliferation-competent cells, as is observed in glaucoma, cataracts, the diabetic pancreas, and osteoarthritis, or in other cases with inflammation from the SASP, as in atherosclerosis, diabetes, AD and cancer. A major intracellular phenomenon that leads to SASP and is a major issue in aging is DNA damage response (DDR) signaling (Fig. 1) (Childs et al., 2015; Olivieri et al., 2015). DDR activation in stressed cells is triggered by genomic lesions as well as telomer erosions, which subsequently promotes acquisition of a proinflammatory SASP (mainly SA-miRNAs), and in turn elicits DDR and SASP activation in neighboring cells, thereby creating a proinflammatory environment extending at the local and eventually at the systemic level (Olivieri et al., 2015; Williams et al., 2017).

SASP-mediators can act as epigenetic modifiers locally and/or systemically that affect the efficiency of their biological effects. Epigenetic changes are one a number of emerging molecular markers of altered molecular function in aging that may be predictive of health status. Alterations in the epigenome (methylation of DNA or acetylation and methylation of histones, as well as of other chromatin-associated proteins), can induce epigenetic changes that contribute to the aging process (Lopez-Otin et al., 2013; Shah and Mahmoudi, 2015). Evidence exhibits the persistence of an "epigenetic clock" in human body. The epigenetic clock is a multivariate estimator of chronological age, in particular based on the DNA methylation levels of CpGs and tumor suppressor function (Li et al., 2015). There are multiple lines of evidence suggesting that members of the sirtuin family (SIRTs) and poly (ADP-ribose)polymerases (PARPs) are key factors associated with mitochondria function, aging epigenome and DDR in cell signaling. Some researchers have exemplified Parp1 and Sirt1 as the prototypes of two families and as epigenetically relevant enzymes whose loss of function reduces longevity in eukaryotes especially in mammals. Notably, Sirt1 and Parp1 are the most effective enzymes activated in DDR. Moreover, literature indicates a close interconnectedness between Sirt1/Parp1 and hallmarks of senescence, which play critical roles in regulation of cell proliferation, survival, and energy metabolism (Burkle et al., 2005; Canto et al., 2013; Gan and Mucke, 2008).

Conclusively, modulation of senescent hallmarks is considered as a potential pro-longevity strategy. Until now, for example, eliminating senescent cells and attenuating the SASP have emerged as attractive therapeutic strategies. However, senescent modulation or rejuvenation of senescent cells can be achieved by: epigenetic reprogramming of cells, preventing senescence-associated signaling or influencing the secretory phenotype of senescent cells. Some pharmacological interventions have already shown promising results. There should be molecular switches in CS and aging to be used as molecular targets in regenerative medicine or as a therapeutic strategy in ARDs (Olivieri et al., 2015; Pourrajab et al., 2016; Rippo et al., 2014). Then, we try to concentrate on a very specific pathway (DDR) and very specific aspect of senescence (epigenome modification and SASP-miRNAs), whose modulation may reverse/inhibit CS and prolong healthy life span.

2. Replicative senescence (RS) and stress-induced premature senescence (SIPS) in aging

According to the in vitro and in vivo evidence, the aging-related senescence is further divided into two subclasses; telomere-dependent

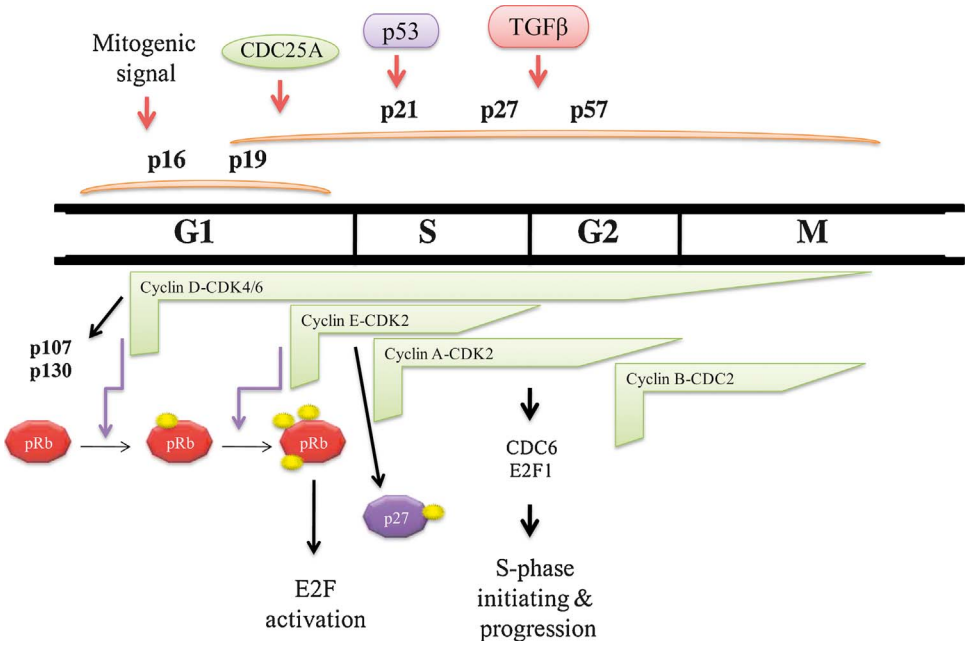

Fig. 2. The most enriched pathways across senescence and aging-associated conditions are cell cycle regulator and cyclin-dependent kinase inhibitor pathways including *p21WAF1/CIP1(CDKN1A)* and *p16INK4A* and *p14ARF(CDKN2A)*. The G1-S transition relies on the completion of phosphorylation of Rb (pRb) which without phosphate groups can sequester E2F and prevent them from activating the transcription of target genes. Cyclin D/CDK4/CDK6 combination results in pRB and leads to partial release of E2F and activation of its downstream target genes: Cyclin E and Cdc25A which removes phosphate from CDK2, facilitating it to combine with Cyclin E and further phosphorylate pRb to achieve full release of E2F and progression from G1 into S phase.

replicative senescence (RS) and stress-induced premature senescence (SIPS). The first one is resulted from telomere shortening and/or loss of telomere function and affects almost all proliferating somatic cell types in the organism. The second one is generally independent of telomere erosion and is caused by oxidative, genotoxic and oncogenic stress. However, recent papers have published that there is no distinct characteristics to distinguish them in vivo and most of the senescence hallmarks are common for both RS and SIPS, whereby the telomere erosion is not just limited to RS and is also shared by SIPS (Bielak-Zmijewska et al., 2014; Childs et al., 2015). In vivo senescence is induced by chronic DDR which can be telomere-dependent or -independent, whereby promotes acquisition of a SASP. Actually, damage to the telomeres can be irreparable, and thus results in persistent DDR and irreversible proliferation arrest of stressed cells, however, DNA damage away from telomeres does not essentially trigger senescence, but instead depending on the cell type, either is repaired to terminate the DNA-damage signal or evokes cell death. In human fibroblasts, telomeres are the source of the senescence signal, irrespective of whether senescence is triggered by short or uncapped telomeres (RS) or genotoxic stress (SIPS) (Bielak-Zmijewska et al., 2014; Lopez-Otin et al., 2013; Sikora, 2013). Indeed, telomere length is gradually decline with age in many human tissues. Reduction in telomere length was found in samples of human subjects ranging in age from newborn to over 100 years. Moreover, premature aging syndromes are characterized by short telomeres and shortening telomeres with each cell division (Lopez-Otin et al., 2013; Sikora, 2013). Organ transplants may be a striking example of unwanted therapy-induced senescence (SIPS and RS). For example, transplanted kidneys are subject to ischemia-reperfusion injury, a type of oxidative damage, as well as replicative stress as the shocked transplant has to repair inevitable tubular injury following engraftment. Both of these stresses pose a risk for renal tubular epithelial senescence. SASP-related mediators may mediate extracellular matrix remodeling, a key phenomenon to disease progression that is seen in pulmonary fibrosis (Childs et al., 2015; Chinta et al., 2015).

2.1. Mitochondria: role in cellular senescence and aging

Accordingly, mitochondria dysfunction is the main hallmark in CS and aging, which intimately involved in the pathogenesis of a variety of disorders such as metabolic syndrome and neurodegenerative and cardiovascular diseases. Accumulation of dysfunctional mitochondria during aging can therefore generate a considerable amount of ROS and oxidative stress. The oxidative stress causes DNA damage and chronic DDR which leads to low-grade inflammation and increased apoptosis rates as hallmarks of aging. Supporting this premise, atherogenesis has been linked to a combination of increased intracellular oxidative stress (ROS generation), reduced mitochondrial antioxidant pathways and oxidative DNA damage. Mutations of mitochondrial DNA (mtDNA) during aging become gradually significant and attain a state of prevalence (Lopez-Otin et al., 2013; Rippo et al., 2014; Shah and Mahmoudi, 2015). Damaged-mitochondria accumulation in the cells due to disability of genomic stability system therefore underpins the cell senescence hallmarks and has been implicated in the onset and progression of several ARDs such as PD, AD and HD. A discrete set of SA-miRNAs has been indicated to modulate mitochondrial activity (mito-RNAs) which also share “inflamm-aging” (inflamma-miRNAs). This discrete set of miRNAs can modulate mitochondria function in different cells and species and are associated with aging-related state. Examples of mito-miRNAs are including let7b, miR-146a, miR-133b, miR-106a, miR-19b, miR-20a, miR-34a, miR-181a and miR-221, which supposed to be primarily involved in maintaining mitochondrial integrity and respiratory chain (Rippo et al., 2014; Shah and Mahmoudi, 2015; Williams et al., 2017).

2.2. Characteristics of DDR in cellular senescence and aging

The most enriched pathways across CS and DDR are p16Ink4a-Rb and p14Arf-p53 (as potent anticancer mechanisms that prevent malignancies by permanently withdrawing (pre-) neoplastic cells from the cell cycle), which have been implicated as drivers of aging and ARD (Fig. 2). The pathways are functioning to prevent structural changes in the genome and preserve its integrity essential for proper function of cells and survival of all organisms (Childs et al., 2015; Chimenti et al., 2003; Lopez-Otin et al., 2013). The expression levels of cyclin-dependent kinase inhibitors (CDKIs) *p14ARF* and *p16INK4A* correlate with the chronological age of all tissues in mice and humans. De-repression of the *INK4/ARF(CDKN2A)* locus and activation of *p53/p21WAF1(CDKN1A)* pathway progressively occurs with chronological aging, and are capable to inducing senescence. Importantly, G1-S transition in human cells is regulated by checkpoints p53, p21Waf and p16Ink4a which inhibit cyclin E/CDK2 and cyclin D/CDK4/6 complexes and result in G1 and G2 arrest (Fig. 2) (Childs et al., 2015; Chinta

et al., 2015; Li et al., 2015). Importantly, studies on aged cells uncover an epigenetic state of open chromatin frame at the *p21WAF* and *p16INK4A* (as well as *p15INK4B* and *p27KIP1*) loci in senescent cells, which is different between young and aged cells and causes long-term expression of *p16INK4A* and *p21WAF*. In aged cells, FGF-2/pERK pathway silences *p21WAF* transcriptionally, which leads to reduced p21Waf protein levels and enhanced cell proliferation. In the epigenetic silencing of the *p16INK4A* and *p21WAF* loci, young cells do not depend on FGF/pERK pathway as much as those old cells do for their proliferation (Childs et al., 2015; Li et al., 2015; Magalhaes, 2004). It seems that *p21WAF* is often up-regulated first and *p16INK4A* later, possibly representing distinct phases on the path from early to full senescence.Another important fact is that activation of both CDKIs *p21WAF1* and *p16INK4A* is required to induce full senescence, however, *p21WAF1* expression levels increase in pre-senescent cells before *p16INK4A* expression. In tissue patterning, an arrest is maintained by p21 or the alternative CDK4 and CDK6 inhibitor p15Ink4b, without involvement of p16Ink4a, while expression of *p16INK4A* likely triggers fully senescent state. The molecular mechanisms by CDKIs in RS and SIPS were observed to overlap and happen in parallel (Childs et al., 2015; Li et al., 2015; Magalhaes, 2004).

Mice with chronic damage of DNA represent premature aging and progeroid phenotype which shows dramatic levels of *p19ARF* (*p14ARF* in humans) expression and senescence in tissues. This progeroid phenotype can be ameliorated by restoring DNA repair response and controlling the p16Ink4a-p53 pathway (Lopez-Otin et al., 2013; Tsirpanlis, 2007). Indeed, studies implicate expression levels and activity of p53 in early pre-implantation embryos which is expected to preserve the genome integrity and regulate the viability of stem cells and is involved in differentiation potential (Dolezalova et al., 2012). Therefore, activation of p53 in the absence of an efficient survival signals would lead to cell cycle arrest and apoptosis, while up-regulation of p53 upon effective recruitment of *AKT* pathway by appropriate DDR signals would preserve cell survival. Literature indicates a close interconnectedness between IGF-PI3K/Akt and DDR pathway which play critical roles in regulation of cell proliferation, survival, and energy metabolism. In response to a stress the p53 pathway monitors the PI3K/Akt signaling to slow down the cell growth rate and division to avoid any possible introduction of infidelity into the process of cell growth and division (Fig. 3). For example, in stressed heart, attenuation of the IGF-I/Akt pathway prevents senescence, growth arrest, and apoptosis in CPCs, whereby avoiding cardiac premature aging. Finally, the Akt cascade through phosphorylation of Gsk3/Mdm2 in nucleus, anchors p53 and leads to p53 degradation. Stabilization and full-activation of p53 would lead to senescence or death and requires the Akt-potent inhibitor PTEN and inactivation of Gsk3/Mdm2 (Feng, 2010; Lopez-Otin et al., 2013; Shah and Mahmoudi, 2015; Tsirpanlis, 2007).

2.3. Circulating miRNAs as indicators of cellular senescence and aging

Recent molecular biology discoveries have revealed that circulating levels of miRNAs are potential indicators of aging and ARDs such as heart failure and neurodegenerative diseases which include memory impairment and brain senescence. In this regard, findings indicate that circulating miRNAs are the main contents of SASP, as a burden of circulating miRNAs, which can epigenetically regulate cells locally or systematically. The SASP miRNAs are now identified as SA-miRNAs mediating mitochondria function and inflamm-aging. They play key roles in the diffusion of DDR/SASP signaling to surrounding non-damaged cells during human aging (Hooten et al., 2013; Jung and Suh, 2014; Williams et al., 2017). Investigations on circulating miRNAs have provided some interesting insights: i) they have unveiled an epigenetic remodeling program by circulating miRNAs aimed at maintaining body homeostasis during aging that can be monitored as biomarkers; ii) they suggest that secreted miRNAs may be one of the mechanisms by which loss of replicative and survival capacity is at least partly offset by cells undergoing replicative senescence; iii) they indicate that miRNA secretome is the active components of senescent cells and is a phenomenon that may modulate the rate of inflamm-aging at the cellular and systemic levels or reminisce the increased risk of ARDs (Olivieri et al., 2015; Pourrajab et al., 2016; Rippo et al., 2014). Reports also reveal miRNA profile changes during aging and document that: i) miRNAs are predominantly up-regulated during aging; ii) very long-lived individuals exhibit fewer changes in miRNA expression than merely old subjects, and iii) those miRNAs showing differential expression in old and extremely old subjects may offer insights into the role of their target genes or pathways in promoting longevity (Hooten et al., 2013; Rippo et al., 2014). There is a list of aged-related miRNAs with similar targets that is generally down-regulated in human aging or related models. This fraction of miRNAs seems required in response to stress. The list is including miR-181, miR-17-92 and miR-302 members proposed to rescue human cells from senescence (Borgdorff et al., 2010; Hackl et al., 2010; Hooten et al., 2013). Other lines of evidence strongly indicate that age-related miRNAs are Inflamma/mito-miRNAs whose expression can modulate mitochondrial activity (mito-miRNAs) and “inflamm-aging” (inflamma-miRNAs), which intimately involved in the aging process. Interestingly, this discrete set of miRNAs contains members of miR-17-92, miR-181, miR-34 family (e.g. miR-106a, miR-19b, miR-20a, miR-34a, miR-181a), and recently has been identified in mitochondria of different species and cell types (Jung and Suh, 2014; Rippo et al., 2014; Wan et al., 2011). Additionally, among the most abundantly expressed miRNAs in old long-lived models, the miR-17-92 and miR-181 members are prototype. Remarkably, these miRNAs are also interconnected with the IGF-I signaling pathway (IIS) (Guorong et al., 2009; Hackl et al., 2010; Zhang et al., 2012). A number of studies on human have shown that miR-181a expression is decreased in the brain with age, while its expression is correlated with AD pathologies. Based on these findings, researchers have also found the correlation between circulating miR-181a with the intracellular miRNA expression in the brain. Likewise, miR-181a expression decreases with age in rhesus monkeys, but its up-regulation in centenarians and in extremely old monkeys exemplifies its important role in healthy aging. Data suggest that decreased miR-181a expression may be a potential biomarker of healthy aging in humans and in non-human primates. It should be noted that bone marrow stem cell differentiation is under the control of miR-181a and, therefore miR-181a plays an important role in hematopoietic lineage development which helps to explain the high expression of miR-181 observed in both human and monkey serum (Jung and Suh, 2014; Hooten et al., 2013).

On the other side, presence of miR-17-92 and miR-302 family members is remarkable among the miRNAs down-regulated in CS and aging models. Particularly, a considerable fraction of evidence from human normal cells shows that members of miR-17-92 and miR-302-367 are required to be up-regulated in response to DNA damage (Guorong et al., 2009; Hackl et al., 2010; Wan et al., 2011). During aging, miRNA expression can be epigenetically modulated through global DNA hypomethylation and/or local DNA hypermethylation. For example, in the temporal cortex of AD patients, a profile of six miRNAs involved in the regulation of the myelination pathway were found to be down regulated by hypermethylation of their CpG sites. A common theme seen with aging is the up-regulation of miR-34a and has been shown to promote senescence in cells via inhibition of the c-myc pathway. Then as aging progresses, cells are exposed to more stresses and the promoters of miR-34 are subjected to activation by CpG demethylation (Okada et al., 2015; Williams et al., 2017). Recent findings have displayed a number of interplays between the tumor suppressor system p53, p21, and p16 with age-related miRNAs (e.g. miR302s, miR-17-92s, miR-34s, miR-181s). For instance, the most significant interplay was observed between p53 and miR-34 which turned out to be direct p53-target genes (Borgdorff et al., 2010; Dolezalova et al., 2012; Rippo et al., 2014). In aged models, miR-34 and miR-181 may create a regulatory loop with p53 pathway containing Sirt1/p53/p21 (Okada et al.,

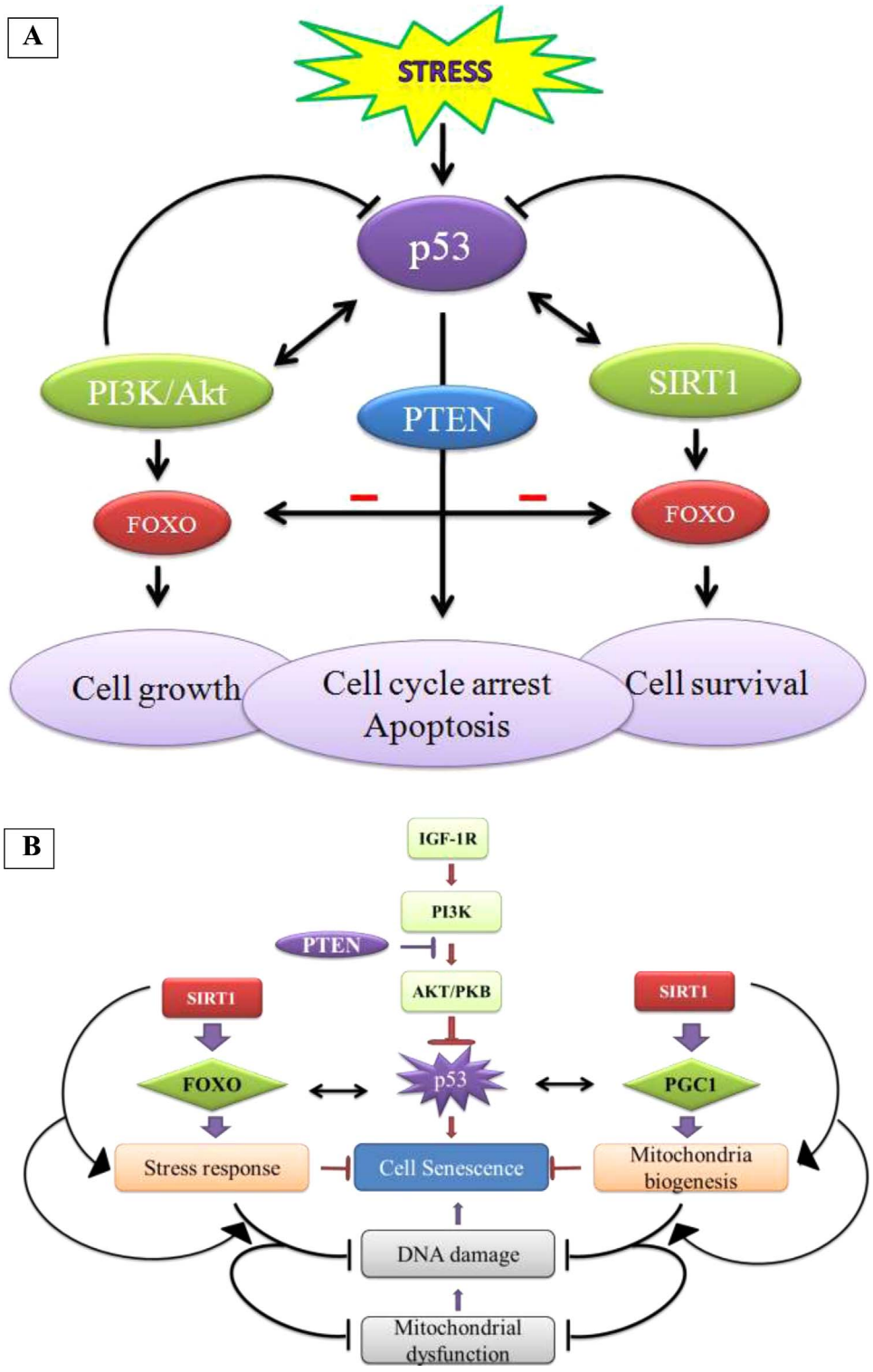

Fig. 3. Crosstalk of p53/PTEN, IGF-1/AKT and SIRT1/FOXO pathways is illustrated here. (A) Up-regulation of p53 in the absence of an efficient survival signals (Akt/Sirt1 signals), however, would lead to cell cycle arrest and apoptosis, while up-regulation of p53 upon effective recruitment of Akt/Sirt1 pathways would lead to proper activation of p53, and eventually inhibition of p53-dependent cell death. Under stress conditions, p53 is activated and positively induces PTEN which through a positive feedback loop negatively regulates PI3K/Akt pathway and leads to more activation of p53 (through a cascade involving SGK/MDM2 proteins). (B) The IGF-I signaling (IIS)/PI3K/Akt (growth promoting pathway), has interconnectedness with stress response pathway p53/Sirt1/FOXO and mitochondria dysfunction pathway Sirt1/PGC1α. Altered mitochondrial function and ROS over-generation contribute to DNA damage and CS. In contrast, efficient stress response besides mitochondria biogenesis triggers adaptive compensatory processes to confront stress and treat damage. (Molecules that may favor aging are shown in light green and violet, and molecules with anti-aging properties are shown in red. Arrows indicate activation; blunt arrows indicate suppression).

2015; Rodriguez-Ortiza et al., 2014). The miR-17-92 and miR-302 family members are the other example of miRNAs that target the 3′ UTR of the *p21WAF1* and *PTEN* transcripts, preventing their translation and function as tumor suppressors. Also, a member of the miR-17-92 family, miR-19b has been shown to target the 3′ UTR of p53, directly. DNA damage regulates miRNA expression at the transcriptional level mainly through the transcription masters p53, Myc and E2F. For example in stressed cells, the expression of miR-34 and miR-17-92 cluster is regulated via a p53-dependent mechanism, and leads to sensitization to apoptosis (Gurtan and Sharp, 2013; Guorong et al., 2009).

3. Longevity-associated enzymes sirtuins (SIRTs) and poly(ADP-ribose) polymerases (PARPs)

There is evidence that premature-aging in human cardiovascular and cerebrovascular system can be controlled via modulation of SIRT and PARP families, in particular Sirt1 and Parp1 enzymes. These evolutionarily conserved enzymes form an important component in a variety of cellular and biological processes including safeguarding genomic integrity, regulating mitochondria function, related metabolism and also inflammatory responses. They differ by cellular

Table 1
The sirtuin family members, cellular localization, function and diseases related to dysfunction of sirtuin.

Sirtuin name	Cellular localization	Function	Diseases related to dysfunction of sirtuin
Sirt1	Mainly nucleus, ubiquitous	Genome guardian, DNA damage sensor, signaling DNA repair, genome stability, CH regulation, programs stress-response master genes; NF-κB, p53, HIF-1α, FOXOs, E2F1, PGC-1α, HSF, PPARs, stimulates PI3K/Akt pathway (Borradaile and Pickering, 2009; Kida and Goligorsky, 2016), regulating ATM, Parp1 and p53, FH formation, cell cycle, autophagy, cell survival, strong deacetylase activity, acting as an NAD sensor, major stress-response enzyme control Parp1 over-activation, its expression is inhibited by Parp2 (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013; Liang et al., 2013), inducing telomerase expression, repressed by SA-miRNAs (miR-34, miR-181), acts in contrast to Sirt2 and shifts stress-induced cell death pathways toward survival (Gan and Mucke, 2008; Gurtan and Sharp, 2013; Rippo et al., 2014; Rodriguez-Ortiza et al., 2014).	Longevity (premature aging), CVD and CBVD, metabolic dysfunction, diabetes, neurodegenerative diseases (AD, PD, HD), heart failure, hearing loss, pulmonary disease or emphysema, hematopoiesis and inflammation disorders, osteosarcoma, cancer metastasis, human progeroid disorder (Borradaile and Pickering, 2009; Hall et al., 2013; Kida and Goligorsky, 2016).
Sirt2	Cytoplasm, ubiquitous	Prerequisite for mitotic entry, cell cycle control, genome stability, FOXO acetylation, repressing bacterial infection, inhibiting PI3K/Akt pathway (Kida and Goligorsky, 2016; Pillai et al., 2014), regulated by SA-miRNAs, strong deacetylase activity, acts in contrast to Sirt1 and shifting stress-induced response pathways toward cell death (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013; Gan and Mucke, 2008; Rodriguez-Ortiza et al., 2014).	Possible involvement in the aging/longevity, safeguarding against neurodegenerative disorders (AD), adiposity (Canto et al., 2013; Hall et al., 2013; Kida and Goligorsky, 2016).
Sirt3	Mitochondria	Blocks PI3K/Akt activation by ROS, repression of stress-related genes, regulation of β-oxidation, managing ATP and ROS generation, strong deacetylase activity (Canto et al., 2013; Kida and Goligorsky, 2016; Pillai et al., 2014).	CVD, insulin resistance, metabolic dysfunction, obesity (Hall et al., 2013; Kida and Goligorsky, 2016).
Sirt4	Mitochondria	Regulating lipid metabolism by attenuating PPARα and thus repress rates of β-oxidation, mitochondrial biogenesis, insulin secretion, weak deacetylase activity (Canto et al., 2013; Hall et al., 2013; Kida and Goligorsky, 2016).	Diabetes, metabolic dysfunction, obesity (Kida and Goligorsky, 2016).
Sirt5	Mitochondria	Regulating the urea cycle, repressing ketogenesis (Kida and Goligorsky, 2016).	Parkinson's Disease (Kida and Goligorsky, 2016).
Sirt6	Nucleus	Genome stability for maintenance of telomere structure through activating DNA repair and Parp1, inhibiting IGF-1/Akt signaling pathway, fatty acid metabolism (Lopez-Otin et al., 2013; Pillai et al., 2014), regulated by SA-miRNAs, weak deacetylase activity, not acting as a NAD sensor, essentially needs Parp1 to mediate its effects (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013; Rodriguez-Ortiza et al., 2014; Pillai et al., 2014).	Longevity (premature aging) extension, insulin signaling and metabolic defects, adiposity (Hall et al., 2013; Kida and Goligorsky, 2016).
Sirt7	Nucleolus	Genome stability via chromatin regulation, rDNA transcription, repressing tumor suppressor genes, crucial for development and cell differentiation, regulated by miRNAs, potential role in premature aging, regulated by SA-miRNAs, weak deacetylase activity (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013; Kida and Goligorsky, 2016).	Cardiac hypertrophy, CVD, growth defects, human carcinoma, lifespan reduction, inflammatory cardiomyopathy (Hall et al., 2013; Kida and Goligorsky, 2016).

(CVD): Cardiovascular diseases; (CBVD): Cerebrovascular diseases; (AD): Alzheimer's disease; (PD): Parkinson's disease; (HD): Huntington disease; (CH): Constitutive heterochromatin; (FH) facultative heterochromatin: (SA-miRNAs): Senescence-associated miRNAs.

localization, functions and substrates (Tables 1 and 2) (Burkle et al., 2005; Canto et al., 2013; Gan and Mucke, 2008). Both PARPs and SIRTs are NAD+ dependent enzymes that have close cross talks in stressed cells and DDR signaling. Recent discoveries about PARPs and SIRTs have established enzymes activity as a general biological mechanism in higher eukaryotic cells that not only promotes cellular recovery from genotoxic stress and eliminates severely damaged cells from the organism, but also ensures accurate transmission of genetic information during cell division (Borradaile and Pickering, 2009; Hall et al., 2013). The interest in these two families of proteins in relation to aging arises from a series of studies in yeast, flies, worms, and mammalian species that reported the emerging role of these proteins in longevity, whereby positively correlated with life span of mammalian species. *SIRT1* and *PARP1* are the single genes of these families, which have a remarkable longevity activity. Unsurprisingly, studies have unveiled close functional interplay between these two members of family (Parp1 and Sirt1). Some researchers have exemplified Parp1 and Sirt1 as the prototypes of two families and as epigenetically relevant enzymes whose loss of function reduces longevity in eukaryotes especially in mammals. Their function is critical for epigenetic regulation of chromatin dynamics. In mice, depletion of both genes results in lethality caused by increased genome instability, and exhibits an important role for these proteins in maintaining genome integrity during development (Burkle et al., 2005; Canto et al., 2013; Gan and Mucke, 2008).

Although, some of the other members of the Parp and sirtuin family have also been revealed as important regulators of cellular functions relating to ageing/longevity, nonetheless, evidence corroborates a direct functional link between Parp1 and sirt1 in cellular response to stress and in maintenance of genome integrity (Canto et al., 2013; Hall et al., 2013).

3.1. Sirtuins and their multiple roles in cell metabolism and aging

To date, seven sirtuins (SIRTs) have been described (Sirt1–7) in mammals, all of which exhibit different subcellular localizations. Among them, Sirt1 has gained much attention due to its widely acknowledged roles in promoting longevity and ameliorating age-associated pathologies. Sirt1 is mainly nuclear, although it constantly shuttles between nucleus and cytoplasm. The contributions of other sirtuins in the field of aging are also gradually emerging. Here in Table 1, we tried to summarize some of the recent discoveries in sirtuins biology which clearly implicate the functions of sirtuin proteins in the

Table 2
The poly-ADP ribosyl polymerase (PARP) names, cellular localization, function and diseases related to dysfunction of PARPs.

PARP name	Cellular localization	Function	Diseases related to dysfunction of PARPs
Parp1	Nucleus, telomeres, centrioles, centrosomes, in cell death in mitochondria	Genome guardian, DNA damage sensor, extension, regulation, protection of telomeric length, regulating ATM, p53, Sirt1, WRN, Dnmt1, H3K9 methyltransferase G9a, TRF1/2, telomerase expression, proinflammatory transcription factors (e.g. NFAT, NF-KB, AP-1, YY1, or sp1) that have key role in producing chemokines, major stress-response enzyme controlled by Sirt1, acts in contrast to Parp2 in cell reprogramming (Burkle et al., 2005; Canto et al., 2013; Nguewa et al., 2005; Quenet et al., 2009; Roper et al., 2014), antagonistic function to Parp2 at the promoters of *DNMT1* and the early response genes in the reprogramming activity (Mostocotto et al., 2014; Roper et al., 2014).	Life span (longevity of mammalian species), human progeroid disorder, lethality during embryogenesis, stroke, myocardial infarction, diabetes, shock, neurodegenerative and inflammatory disorders, allergy, type I diabetes induced by ROS, ischemia-reperfusion damage, septic shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp2	Nucleus, in cell death in mitochondria	Activated in DNA breaks, opposing Parp1 and Sirt1 in the reprogramming and stress responses, suppresses Sirt1 expression, regulating mitosis, epigenetic enzyme competing Sirt & Parp1 activity (Burkle et al., 2005; Canto et al., 2013; Liang et al., 2013; Nguewa et al., 2005; Quenet et al., 2009; Roper et al., 2014).	Lethality of embryo, resistance to antitumor drugs, ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp3	Centrioles, centrosomes, in cell death in mitochondria	Repressing G1/S transition (Burkle et al., 2005; Nguewa et al., 2005).	Resistance to antitumor drugs, ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp4 (VPARP)	Cytoplasm, in cell death in mitochondria	A component of vault particles (cytoplasmic ribonucleoprotein) (Burkle et al., 2005; Nguewa et al., 2005).	Multi-drug-resistance in cancer, ischemia-reperfusion shock, lethality of embryo (Burkle et al., 2005; Nguewa et al., 2005).
Parp-5a (Tankyrase1)	Nucleus, telomeric complex, mostly Golgi apparatus, in cell death in mitochondria	Interacting with TRF1, telomeric extension, signaling of insulin, high expression in testis, ovary, and skeletal muscle (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).	Resistance to antitumor drugs/ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp-5b (Tankyrase2)	Cytoplasm, Golgi apparatus, in cell death in mitochondria	High expression in testis, ovary, and skeletal muscle, interacting with TRF1 (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).	Rapid cell death when highly over-expressed, auto-antigen in several cancers, resistance to antitumor drugs, ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp-5c (Tankyrase3)	In cell death in mitochondria	Interacting with TRF1 (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).	Resistance to antitumor drugs, ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).
Parp-6–16	Cytoplasm, nucleus	Containing zinc fingers, RNA Recognition Motif, ubiquitination domain, cell cycle or growth-phase-related regulation (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).	Resistance to antitumor drugs, ischemia-reperfusion shock (Burkle et al., 2005; Nguewa et al., 2005; Quenet et al., 2009).

(TRF1/2): telomeric repeat binding factor 1 and 2.
The interplay between Sirt1-Parp1 is brought in the Table 3, in regard to the physiological or pathophysiological consequences of the interactions (metabolic events, oxidative stress, genomic instability and premature aging) (Canto et al., 2013; Borradaile and Pickering, 2009).

regulation of premature CS and accelerated aging. The roles of seven sirtuins in cellular processes have been extrapolated to draw interlinkage with anti-aging mechanisms (Gan and mucke, 2008; Kida and Goligorsky, 2016). Herein, sirtuins are interesting for us since regulating the stress-response expression programs of numerous master regulators of stress, such as the transcription factors nuclear factor-κB (NF-κB), p53, HIF-1α, FOXOs, E2F1, PGC-1α and HSF1. In turn, sirtuin expression is tightly regulated by different transcription factors, several of which participate with the sirtuins in regulatory feedback loops (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013). Sirt1 is a NAD +-dependent deacetylase whose expression decreases significantly with aging and has been strongly associated with premature senescence. As a potential anti-aging factor, restore its expression has been proposed to extend lifespan in animals and human (Ota et al., 2008).

Sirt1 ectopic-expression in mammalian models can ameliorate various aspects of aging, in particular, improved health of aging models. The mechanisms involved in the beneficial effects of Sirt1 are interconnected to stress response, mitochondrial biogenesis and enhanced metabolic efficiency, as a critical regulator of genomic stability (Fig. 4A) (Gan and Mucke, 2008; Lopez-Otin et al., 2013). In mammals, Sirt1 has the closest homology to Sir2 which first was shown to extend replicative lifespan in Saccharomyces cerevisiae, and subsequent reports indicated that enhanced expression of the worm (sir-2.1) and fly (dSir2) orthologs could extend lifespan in both invertebrate model systems (Lopez-Otin et al., 2013). As a prototype in sirtuin family, Sirt1 is involved in DDR signaling, and the spectrum of transcriptional targets of Sirt1 includes key controllers of mitochondrial biogenesis (peroxisome proliferator activated receptor-γ co-activator (PGC)-1α), lipid and carbohydrate metabolism (peroxisome proliferator activated receptors (PPARs), sterol regulatory element binding protein (SREBP)-1, liver X receptor (LRX), FOXOs, cAMP response element binding protein (CREB), CREB regulated transcription co-activator 2 (CRTC2), etc.) and cellular proliferation (p53). Given the dual localization of Sirt1 in both the cytoplasmic and nuclear compartment, it is not surprising that Sirt1 also deacetylates a constellation of cytosolic proteins, including acetyl-coA synthase 1, endothelial nitrogen monoxide synthase (eNOS) and components of the autophagy machinery, including the Atg family of proteins (Canto et al., 2013; Gan and Mucke, 2008; Shah and Mahmoudi, 2015).

Mammalian sirtuins (SIRTs) are best known for their participation in genome stability and chromatin maintenance directly through Sirt1, 2, 6, 7 (Table 1). However, the main sirtuins known to have the greatest involvement in DNA repair are Sirt1 and Sirt6. Among sirtuins, Sirt1 is the one known to induce telomerase (*TERT* gene) expression and probably is the most involved in maintaining constitutive heterochromatin (CH) in pericentromeric as well as telomeric regions, despite the fact that it is either absent or present at very low levels in pericentromeric heterochromatin foci. In yeast strains, Sirt1-homolog

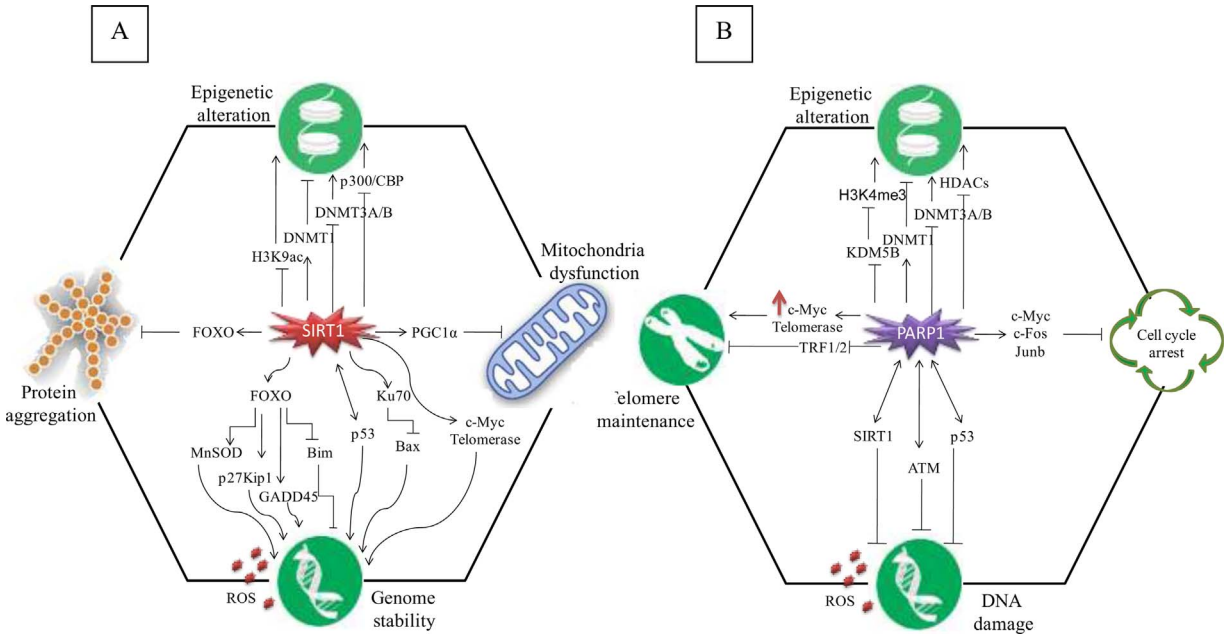

Fig. 4. Potential roles of SIRT1/PARP1 in CS are shown here. (A) The major pathways downstream of Sirt1 are including stress responses (FOXO, p53, Ku70), mitochondrial dysfunction (PGC1α), and epigenetic alteration (H3K9ac, Dnmt1 and Dnmt3a/b). Sirt1 acts to repress Foxo-induced apoptosis and potentiate Foxo-induced cell-cycle arrest and survival. Sirt1 activity maintains Dnmt1 activity and methylation of DNA by Dnmt1 at certain DNA repeats and tumor suppressor genes, while suppresses Dnmt3a and 3b which are responsible for de novo methylation and modify un-methylated DNA during aging. (B) Downstream mediators by Parp1 are including telomere maintenance (c-Myc, telomerase, TRFs), stress responses (p53, Sirt1), cell cycle activation (c-Myc, Fos, Junb). Parp1 interactions are required for chromatin de-condensation and reactivation of genes *c-MYC, c-FOS* and *JUNB* which are involved in cell cycle reactivation. The epigenetic alteration by Parp1 is including: maintenance of H3K4me3 in trimethylation form, a mark of permissive chromatin, inhibiting the histone demethylase and histone deacetylase KDM5B and Hdac, preventing aberrant hyper-methylation of CpG islands in housekeeping gene promoters by Dnmt3a/b. Interaction of Parp1 with Sirt1 and p53 is increased in response to various stresses. Arrows indicate activation; blunt arrows indicate suppression.

activity at telomeres is required for establishment and maintenance of telomeric heterochromatin. These functions of Sirt1 link it to maintenance of genomic stability by multiple mechanisms, mainly through DNA repair system (Bosch-Presegu and Vaquero, 2015; De Bonis et al., 2014; Song et al., 2011). Under stress conditions and especially when the stress crosses a certain threshold of duration or intensity (in RS and SIPS), some sirtuins, in particular Sirt1 and probably Sirt6, promote formation of facultative heterochromatin (FH) in cell cycle regulatory genes. Thus, once formed, these regions might be kept epigenetically silenced in the compacted structure until the stress wanes (Bosch-Presegu and Vaquero, 2015). Sirtuins, in particular Sirt1, help to regulate and protect genomic organization through critical roles 1) in cell cycle control, 2) chromatin structure dynamics and 3) constitutive heterochromatin (CH) maintenance. They participate in signaling and repair of DNA damage at different levels and are crucial for determining cell fate. They regulate gene transcription and chromatin structure at three levels: direct deacetylation of core histone marks in chromatin; modulation of the remaining chromatin machinery such as enzymes (e.g. HMTs and HATs) or structural factors (e.g. H1); and regulation of transcription factor function via modulation of the binding ability, stability or transcriptional activity of these factors (Canto et al., 2013; De Bonis et al., 2014; Song et al., 2011).

3.1.1. Sirt1 and its association with aging-related epigenetic marks

A variety of epigenetic alterations occurs in all cells throughout aging and affects all tissue functions during aging. Alterations in the methylation of DNA (global hypomethylation and local hypermethylation), or acetylation and methylation of histones, as well as of other chromatin-associated proteins, can induce epigenetic changes that contribute to the aging process (Bosch-Presegu and Vaquero, 2015; Lopez-Otin et al., 2013). Conceptually in chronological age setting, inhibitors of epigenetic alterations may conceivably promote longevity or improve aspects of health during aging. For example, inhibitors of histone acetyl-transferases have been shown to ameliorate the premature aging phenotypes of progeroid mice and extend their lifespan. The addition and removal of an acetyl group on lysine residues, respectively mediated by histone acetyl-transferases (HATs) and deacetylases (HDACs), is a highly dynamic and regulated process and is among the first-ever described chromatin modifications. Sirtuins constitute class III HDACs and are activated by two major types of stress: metabolic/energy stress (nutrient and calorie restriction) and genotoxic stress. Sirtuins are among the very few enzymes that participate in stress response at both the sensing and signaling levels, and they are also direct effectors of stress response (e.g. chromatin-associated functions) (Gan and Mucke, 2008; Hall et al., 2013; Lopez-Otin et al., 2013). Sirtuin chromatin function is closely related to the regulation of H4K16Ac and H3K9Ac, two histone marks that have been strongly conserved during evolution and that have well-defined roles in regulating chromatin structure. Sirt1 exhibits strong HDAC activity towards H4K16Ac and H3K9Ac, which is directly related to its capacity to coordinate the formation of CH and FH. Loss of Sirt1 correlates with a global increase in H4K16Ac and H3K9Ac, together with a loss of the heterochromatin marks H3K9me3 and H4K20me1. Sirt1 localization at specific chromatin sites results in deacetylation of H4K16Ac and H3K9Ac and direct recruitment of the linker histone H1. Subsequently, Sirt1 directly interacts with lysine methyltransferase Suv39h1 and through its functional relationship with Suv39h1 promotes establishment of heterochromatin marks H3K9me3 and H4K20me1 throughout the coding region of the gene. This is the only known mechanism behind the establishment of H3K9me3 (Bosch-Presegu and Vaquero, 2015; De Bonis et al., 2014). Deacetylation of H3K9Ac by Sirt1 profoundly and Sirt6 probably is required for H3K9m3 formation and important for maintaining telomere structure and for DNA repair. Importantly, Sirt1 first deacetylates H3K9Ac to enable methylation of this residue by Suv39h1 then through its functional relationship with Suv39h1 directly recruits it to specific regulatory regions (e.g. deacetylated H3K9Ac marks). Suv39h1 contributes to chromatin stability through its direct interaction with Sirt1 and by maintaining H3K9me3

in both pericentromeric and telomeric CH (it promotes the spreading of CH mark H3K9me3) (Canto et al., 2013; Gan and Mucke, 2008; Shah and Mahmoudi, 2015). Loss or reduced levels of H3K9me3 marks in pericentromeric and telomeric heterochromatin leads to HP1 re-localization from heterochromatic foci, which result in diminished heterochromatin levels. Sirt1 induces H4K20me1 formation which is prerequisite for H4K20me2,3 marks and is essential for chromatin condensation during mitosis and cell cycle progression. Telomere repeats are enriched in H3K9me3 and H4K20me3 which represents a docking site for the binding of heterochromatin protein-1 (HP1) and meets the criteria for a hallmark of CS in vertebrates (Bosch-Presegu and Vaquero, 2015; Lopez-Otin et al., 2013). Several reports have associated Sirt1 to H4K20me1 enrichment. H4K20me1 is a marker of facultative heterochromatin of x-chromosome and of mitotic chromosomes, but prerequisite for the establishment of H4K20me2,3 and maintaining CH at pericentromeric heterochromatin and telomeres (Fig. 4A) (Isaji et al., 2013).

At specific region sites, increased histone H4K16Ac, H4K20me3 and H3K4me3, as well as decreased H3K9me and H3K27me3 constitute age-associated epigenetic marks. Change in the permissive chromatin marks H3K9Ac, H4K16Ac, and H3K4me3, in parallel to repressive histone marks H3K9me, H4K20me1,2,3 and H3K27me3 at the particular sites constitute age-associated epigenetic alterations. Studies have shown that aging correlates with a global increase in H4K16Ac and H3K9Ac, together with a loss of the heterochromatin marks H3K9me3 and H4K20me3 at pericentromeric heterochromatin and telomeres. In particular, heterochromatin assembly at pericentromeric and telomeric repeat regions requires H3K9me3 and H4K20me3 marks, as well as HP1 binding and DNA hypermethylation, which are important for chromosomal stability (Bosch-Presegu and Vaquero, 2015; De Bonis et al., 2014; Lopez-Otin et al., 2013). Additionally, in senescent cell, there is a strong reduction in the repressive mark H3K27me3 at the *INK4A/ARF* locus and de-repression of this locus. The *INK4A/ARF* locus is normally subjected to epigenetic repression mediated by H3K27 methylation and recruitment of Polycomb-repressive complexes. Notable, normal nuclear distribution of bivalent domain H3K4me3/H3K27me3 extends longevity in nematodes and flies and is essential for efficient somatic cell reprogramming (iPSCs) in mammalians. Reprogramming process triggers senescence by up-regulating p53, *p16INK4A*, and *p21WAF1*. Induction of DDR and chromatin remodeling of the *INK4A/ARF* loci are two of the mechanisms behind senescence induction in iPSC reprogramming. Crucially, ablation of these senescence effectors improves the efficiency of reprogramming, suggesting novel strategies for maximizing the generation of iPSCs (Banito et al., 2009; Isaji et al., 2013; Li et al., 2015). Notable, Sirt1 ortholog Sir2.1 in C. elegans is essential for maintaining the mark H3K27me3 at specific region in the germ line. For example, Sir2.1 deacetylates H3K9Ac at subtelomeric regions as a prerequisite for H3K27 methylation (Bosch-Presegu and Vaquero, 2015).

However, studies have shown that up-regulation of Sirt1 beside Parp1 can contribute to overcome reprogramming-induced barriers in iPSCs. In addition, mammalian Sirt1 through modulation of DNA methyl transferase 1/3a/3b (Dnmt1/3a/3b) activity has also to maintain methylation of DNA. Sirt1 interaction with Dnmt1 in particular, preserves normal methylation of DNA at particular genomic loci such as CpG methylation of tumor suppressor loci *p16INK4A* or promoters of miR-34 genes, while Sirt1 interaction with Dnmt3a/3b leads to suppress their activity which are responsible for de novo methylation and modify unmethylated DNA (Fig. 4A) (Bosch-Presegu and Vaquero, 2015; Roper et al., 2014; Son et al., 2013).

3.2. PARPs and their multiple roles in cell metabolism and aging

On the other side, there is a family of poly(ADP-ribose) polymerases (PARPs) present in eukaryotes. PARPs now constitute a large family of 18 proteins, encoded by different genes and displaying a conserved catalytic domain, in which Parp1 (113 kDa), the founding member, and Parp2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Poly (ADP-ribosyl)ation (PAR) is an immediate stress-dependent post-translational modification of histones and other nuclear proteins that contributes to the survival of injured proliferating cells. A large repertoire of sequences presents the emerging role of this superfamily in the treatment of a number of inflammatory, cardiovascular and neurodegenerative disorders and antitumor efficacy. PARPs have been implicated in the pathogenesis of several diseases, including stroke, myocardial infarction, diabetes, shock, neurodegenerative disorder and allergy (Table 2) (Ame et al., 2004; Nguewa et al., 2005; Obrosova et al., 2005).

In particular, Parp1 and Parp2 are known to play fundamental roles in orchestrating the various chromatin-based biological tasks including transcription, DNA repair and differentiation. In this review, we propose a short overview of the more recent experimental works on the role of PARPs in longevity, with an essentially focus on the different mechanisms by Parp1 which affect cellular pathways and regulates the cell longevity (Table 2) (Burkle et al., 2005; Liang et al., 2013). Parp1 is the main catalyst of the family in living cells under stress conditions, accounting for about 90% of cellular PAR activity under DNA breakage. It functions as a negative regulator of DNA damage-induced genomic instability while is positively correlated with life span of mammalian species. Some other members of PARP family have also been engaged in cellular function relating to ageing/longevity (Canto et al., 2013; Quenet et al., 2009).

Conclusively, some SIRTs and PARPs have been identified as DNA repair proteins. It is important to acknowledge that Parp1 and Sirt1 are known as key enzymes critical in DDR signaling, while transcriptionally and functionally interconnected due to their common use of the substrate NAD+. The cross-talk between Sirt1 and Parp1 controls Parp1 activity and negatively regulates expression of *PARP1* gene promoter. Parp1 is over-expressed and mediates cell death in Sirt1-deficient mouse cardiomyocytes under genotoxic stress (Canto et al., 2013; Shah and Mahmoudi, 2015). Additionally, rapid regulation of telomere length and maintaining its structure requires the activity of both enzymes Parp1 and Sirt1 (Beneke et al., 2008; De Bonis et al., 2014).

3.2.1. Parp1 and its association with aging-related epigenetic marks

As an epigenetic factor, Parp1 function affects chromatin structure by modulating the activity and localization of DNA methyltransferases (DNMTs) and histone-modifying enzymes. Interestingly, both Sirt1 and Parp1 have been linked to maintain DNA methyltransferase1 (Dnm1) activity and methylation of DNA at numerous genomic loci. Parp1 participates in the epigenetic regulation of gene expression and marks those sequences in the genome that must remain un-methylated and then protects them from methylation (Fig. 4B). Parp1 localizes within the *DNMT1* promoter and protects it in an unmethylated state by its enzymatic activity. Dnmt1 is the most abundant and ubiquitous Dnmt whose activity is crucial for silencing tumor suppressor genes and methylation of telomeric and pericentromeric repeat sequences in normal cells, which also preserving DNA methylation needed for cell survival. Widespread genome hypomethylation are typical events occurring in the depletion of both Sirt1 and Parp1. However, both Parp1 and Sirt1 through directly interacting with Dnmt3a/3b reduce their DNA methyltransferase activity, which is needed to prevent aberrant hypermethylation of CpG islands in housekeeping genes. They mark those sequences in the genome that must remain unmethylated and protects them from methylation, thus playing a role in the epigenetic regulation of gene expression. Deregulation of Parp1 and Sirt1 activity can lead to reversal of the normal methylation pattern by (i) introducing aberrant methylation of some normally un-methylated CpG islands (*DNMT3A/3B*) and (ii) causing genome-wide hypomethylation (*DNMT1*). Thus Parp1 plays a novel role in the epigenetic regulation of aging (Fig. 4B) (Mostocotto et al., 2014; Quenet et al., 2009; Zampieri et al., 2009).

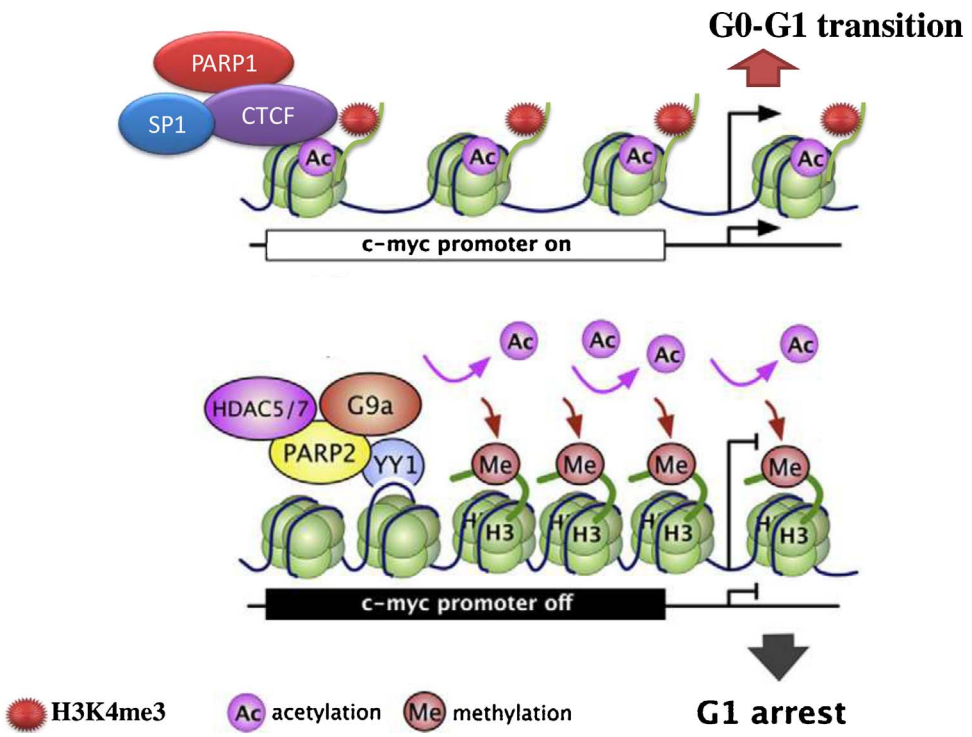

Fig. 5. An example for PARP1 and PARP2 roles in transcription regulation of cell cycle-related genes is illustrated here. Parp1 is required for chromatin decondensation modifications and exchange of negative to positive transcriptional regulators. Parp1 interacts with repressor factor SP1 and impairs its binding to target promoters. Then, interaction of Parp1 with the activator factor CTCF enhances its binding to target promoters such as *c-MYC*. In contrast, Parp2 and YY1 increase the repressive marks of cell cycle promoters. Parp2 possesses transcriptional repression activity and recruits histone deacetylases Hdac5 and Hdac7, and histone methyltransferase G9a to the promoters of cell cycle-related genes, generating repressive chromatin signatures.

Parp1 also modulates the permissive mark H3K4me3 by blocking Kdm5b binding to chromatin and inhibits demethylation of permissive mark H3K4me3. Kdm5b is a histone demethylase that acts on H3K4me3. This antagonism interaction of Parp1 with Kdm5b explains the strong correlation between Parp1 and H3K4me3 enrichment at actively transcribed promoters of *DNMT1, c-MYC, c-FOS, JUNB* and *EGR-1* loci (Fig. 5). Since then in cell reprogramming, up-regulation of both Sirt1 and Parp1 is needed to promote the de-condensation of chromatin at specific sites in response to exogenous reprogramming signals, such as OSKM. Epigenome-related function of Sirt1 and Parp1 additionally helps chromatin to preserve or reach an active configuration at specific target loci, such as *OCT4, SOX2* and *NANOG* (Fig. 5) (Bosch-Presegu and Vaquero, 2015; Mostocotto et al., 2014; Roper et al., 2014). Parp1 like as its coordinator Sirt1 is important for maintaining the integrity of CH and FH. Both proteins localize to telomeres, centromeres and rDNA, where they interact with and regulate specific partners (Quenet et al., 2009).

3.2.2. *Sirt2 and Parp2 versus Sirt1 and Parp1 in stress response outcomes*

Generally, epigenetic modifiers Sirt2 and Parp2 function to opposite the activity of their closest relatives Sirt1 and Parp1 and their-mediated epigenetic modifications of transcription factors, such as TTF1, ERα, PPARs, E2F1 and c-MYC (Gan and Mucke, 2008; Liang et al., 2013).

Sirt1 regulates gene expression at three levels: direct deacetylation of core histone marks in chromatin; modulation of the remaining chromatin machinery such as enzymes (e.g. HMTs and HATs) or structural factors (e.g. H1); and regulation of transcription factor function via modulation of the binding ability, stability or transcriptional activity of these factors. Mammalian Sirt1 has been linked to maintain methylation of DNA by Dnmt1 (Fig. 4A) (Bosch-Presegu and Vaquero, 2015; Gan and Mucke, 2008).

The Sirt1 pathway shows a high degree of interconnectivity with the IGF-I signaling (IIS). The IIS is the other most enriched pathway that shows a high degree of interconnectivity with DDR mechanisms. Numerous studies on human and adult animals have found a close association between the IIS pathway and FOXO transcription factors which function to regulate aging and correlates with highly extended longevity (Fig. 3A). Four FOXO family members are present in mammals, FOXO1, FOXO3, FOXO4 and FOXO6. All FOXOs are regulated by IIS and have physical association with Sirt1. Acetylated FOXOs are deacetylated by Sirt1. FOXOs mediate the expression of stress-response genes, and increase oxidative stress resistance, a frequent correlation of increased lifespan. Specially, the association between Sirt1 and FOXO3 and FOXO4 is increased in stress conditions.Sirt1-deacetylated FOXOs activate numerous genes that are important for controlling cellular stress (such as heat-shock proteins, superoxide dismutase (*MnSOD*), catalase and metallothionein), pathogen resistance and metabolism. The combined activity of these genes would result in increased cell stress response and longevity. However, FOXOs in crosstalk with p53 participate to induce the transcription of a variety of genes involved in apoptosis. These genes are including those involved in the stress response (*MnSOD*), DNA repair (*GADD45*), cell-cycle arrest (*p27KIP1*) and apoptosis (*BIM and Fas ligand*) pathways (Fig. 4A). Under stress, Sirt1 activation prevents the expression of cell death genes *BIM*, and *Fas* ligand, despite increasing the expression of *GADD45* and *MnSOD* by FOXOs. FOXO-induced apoptosis was reported to be repressed by Sirt1. In general, Sirt1 shifts FOXO-induced responses away from death by inhibiting apoptotic genes (*BIM*) and toward survival by promoting the expression of *GADD45*, *p27kIP1*, and *MnSOD* (Fig. 4A) (Gan and Mucke, 2008; Giannakou and Partridge, 2004; Pillai et al., 2014). Interestingly, Sirt2 functions to opposite Sirt1. Remarkable findings indicate that Sirt2 promotes fully de-acetylation of FOXO3a, whereby elevates the expression level of cell-cycle arrest factor (*p27kIP1*) and pro-apoptotic factor (*BIM*). Although Sirt2 works also in stress response, in some cases it seems to promote an opposite role compared to Sirt1. For instance in cell cycle and in neurodegenerative diseases (an important group of ARDs), Sirt1 has been found to promote survival in front of stress while Sirt2 promotes cell death (Gan and Mucke, 2008; Liang et al., 2013). In contrast to the anti-apoptotic role of Sirt1, ablation of Sirt2 was found to be beneficial in ischemia/reperfusion models and in regulating cardiac myocyte survival (Pillai et al., 2014). Notable among the IIS multiple down-stream targets, FOXO transcription factors are the most important involved in aging and conserved through evolution. There is an extensive communication between p53, PI3K/Akt and FOXOs/Sirt1 pathways to coordinate cell growth and prevents accumulation of errors in stress and restores

Table 3
Interaction of SIRT-PARP under stress conditions and related pathologies.

Affected system	Partner interaction	Mechanism	Disease
Cardiovascular system	Parp1-Sirt1	Under angiotensin II-induced stress Parp1 activation inhibits Sirt1 through NAD depletion (where Sirt1 induction protects against induced stress) (Canto et al., 2013; Borradaile and Pickering, 2009).	Cardiac hypertrophy (Canto et al., 2013; Borradaile and Pickering, 2009).
	Parp1-Sirt1	Under oxidative stress Parp1 over-activation limits NAD levels and hence Sirt1 expression (where Parp1 inhibition by Sirt1 controls Parp1 activity) (Canto et al., 2013; Borradaile and Pickering, 2009).	Heart failure (Canto et al., 2013; Borradaile and Pickering, 2009).
	Parp1-Sirt1	Under stress, NAD levels and Sirt1 activity is reduced in endothelial cells that is reverted by Parp1 inhibition (Canto et al., 2013; Borradaile and Pickering, 2009).	Atherosclerosis (shear stress on endothelium, proinflammatory conditions) (Canto et al., 2013; Borradaile and Pickering, 2009).
	Parp2-Sirt1	Parp2 activation suppresses Sirt1 promoter and mitochondrial biogenesis in vascular system. Upon Parp2 depletion, Sirt1 is released from suppression that induces mitochondrial biogenesis and vascular protection against stress and damage (Canto et al., 2013; Liang et al., 2013).	Vascular damage (Canto et al., 2013; Quenet et al., 2009).
	Sirt2-Parp1-Sirt1	Sirt1 leads to cardiac myocyte survival by the ablation of Sirt2 in ischemia/reperfusion models (Pillai et al., 2014).	Cardiac myocyte apoptosis/necrosis in ischemia/reperfusion (Pillai et al., 2014).
Central nervous system	Parp1-Sirt1	NF-κB-inflammatory signals lead to Parp1 over-activation and AIF-mediated neuronal cell death. Sirt1 activation inhibits Parp1 and has protective effects (Canto et al., 2013; Ame et al., 2004).	Trophic deprivation- and oxidative stress-mediated neuronal cell death (Canto et al., 2013; Ame et al., 2004).
	Parp1-Sirt1	Over-activation of Parp1 in oxidative stress causes depletion of NAD and ATP, which even more contribute to the pathogenesis of some forms of brain injury and neurodegenerative disorders, but activation of Sirt1 control Parp1 over-activation (Canto et al., 2013; Nguewa et al., 2005).	Stroke, neurodegenerative disorders (AD, PD) (Canto et al., 2013; Nguewa et al., 2005).
Gastrointestinal system	Parp1-Sirt1 Parp2-Sirt1	As downstream effectors, Parp1 and its relative Parp2 are over-activated by oxidative-nitrosative stress of diabetes condition, but activation of Parp1 coordinator Sirt1 and inhibition of Sirt1 competitor Parp2 may help control the condition (Canto et al., 2013; Nguewa et al., 2005; Obrosova et al., 2005).	Diabetes and its consequent complications (Canto et al., 2013; Nguewa et al., 2005; Obrosova et al., 2005).

(AD): Alzheimer's disease; (PD): Parkinson's disease.

cellular homeostasis after stress is resolved (Giannakou and Partridge, 2004; Lopez-Otin et al., 2013). However, in aged cells, under stress conditions and in the reduced levels of Sirt1, p53 is full-activated, whereby negatively regulates PI3K/Akt pathway and positively induces PTEN which in turn in a feedback loop through a dephosphorylation cascade of SGK/Mdm2 proteins (kinase/the E3 ubiquitin ligase) leads to stabilization and more activation of p53 and indirectly induces FOXO-targeted apoptotic genes (Fig. 3A) (Pillai et al., 2014). In contrast, Sirt1 acts to preserve cell survival via de-acetylation of FOXOs and co-activator PGC1α, the master switchers which participate directly to regulate the stress response programs. Also through PGC1α and FOXO-related pathways, Sirt1 protects mitochondria function (Fig. 3B). In mammalians, de-acetylation of FOXOs and PGC1α by Sirt1 controls the transcription of genes participating in mitochondrial biogenesis, lipid and carbohydrate metabolism, however, telomere attrition is a cause of p53-mediated repression of PGC1α, which consequently reduces mitochondria biogenesis (Fig. 4A) (Gan and Mucke, 2008; Shah and Mahmoudi, 2015; Giannakou and Partridge, 2004). Telomere attrition and mitochondrial deficiency in aged cells can be then attributed to decrease levels of Parp1 and Sirt1 both of which participating to preserve telomere length and modulate mitochondrial biogenesis via transcriptional co-activator PGC1α (Fig. 4) (Beneke et al., 2008; De Bonis et al., 2014).

In human G0-rested cells, up-regulation of Parp1 causes cell cycle reactivation via up-regulation of genes needed for G0-G1 transition, and leads to release from quiescence. In S-phase entry, Parp1 up-regulates *E2F1* expression by promoter activity. In addition, Parp1 acts as a co-activator of E2F in activation of S-phase genes during re-entry of quiescent cells into cell cycle (Simbulan-Rosenthal et al., 2003), whereas its relative Parp2 functions in two ways to decrease the activity or amount of Parp1-targeted transcription factors. Parp2 first functions as a transcriptional co-repressor of Parp1-targeted genes through recruiting histone deacetylation and histone methylation which generating repressive chromatin signatures. Parp2 represses the transcription of cell cycle promoters *E2F1* and *c-MYC*, therefor opposites Parp1 function and results in a prolonged G0/G1 accumulation. Findings indicate that Parp2 interacts with DNA-binding factor YY1 and recruits histone modifiers (histone deacetylases Hdac5 and Hdac7 and histone methyltransferase G9a) to the promoters of cell cycle-related genes through which alters chromatin signatures and resulting in transcriptional repression of cell cycle regulators (Fig. 5). Second, Parp2 may repress Parp1-related signaling through post-transcriptional activity such as those observed in transcriptional repression of transcription factors TTF1, ERα, PPARα, PPARβ, and PPARγ. In addition, findings indicate that Parp2 acts as transcriptional co-repressor of Sirt1, which occupy the *SIRT1* promoter and decrease the expression of *SIRT1* (Liang et al., 2013; Roper et al., 2014; Simbulan-Rosenthal et al., 2003). Likewise, Sirt2 functions to opposite de-acetylation process by Sirt1. Sirt2 not only in its own competes with Sirt1 for NAD+ substrate and decreases cellular levels of NAD+ and ATP under stress condition, but also functions somehow to opposite Sirt1-mediated transcriptional regulation of transcription factors, such as FOXOs and PGC1α (Gan and Mucke, 2008; Pillai et al., 2014). Given the emerging roles of miRNAs interestingly, some miRNAs may control Parp2 and Sirt2 expression levels. For instance; miR-149 may increases NAD+ levels and Sirt1 expression in stressed cells through inhibiting Parp2 expression which ultimately leads to increased mitochondrial function and biogenesis by a Sirt1/PGC-1α–depended mechanism (Mohamed et al., 2014).

Inhibition of Parp2 and Sirt2 as closest relative to Parp1 and Sirt1, respectively may be protective for stressed cells not only by controlling their oppose modifications, but also by preserving cellular NAD+ reservation for Sirt1.

3.3. The emerging role of Sirt1/Parp1 as genome guardians

Sirt1 and Parp1 might be accounted as the key components in DDR system, whose expression defined in high levels in germ cells and ESCs of mammals. They act as SOS elements to genome integrity (Haince et al., 2007; Shah and Mahmoudi, 2015). However, Sirt1/Parp1 expression is dramatically lower in aged individuals than those in younger

subjects, which can be associated with lose of genome integrity and cellular homeostasis in response to stress. Even more, decline of Sirt1/Parp1 enzymes is associated with induced CS and cell cycle withdrawal in proliferating cells (Carbone et al., 2008; Sasaki et al., 2006). The mechanism by which Sirt1/Parp1 conserve cell longevity is defined to be through the regulation of: (a) cell-cycle, (b) chromatin structure and gene expression, (c), p53 pathway and DNA repair and (d) regulation of mitochondrial function. Sirt1 is the close coordinator of Parp1 activity as elucidated in Tables 1–3 (Haince et al., 2007; Song et al., 2011). Not surprisingly, Sirt1 and Parp1 activity of cells are positively correlated with life span of mammalian species. For example, difference between the longest-lived and the shortest lived species (human and mice) tested is about five-fold and may be due to different Parp1 expression levels or its accessory interacting factors. Parp1 deficiency in mice facilitates sensitivity to cell death and early embryonic lethality under stress conditions and DNA damage. One instance in human is Werner syndrome (a human premature aging disorder) where the WRN factor is deficient. The WRN factor physically interacts with Parp1 and functionally cooperates in preserving genome stability in vivo. Or, decline of Parp1 expression in aged individuals is associated with lose of genome integrity and cellular homeostasis in response to oxidative stress (Burkle et al., 2005; Canto et al., 2013).

Sirt6 is the other sirtuin linked to Parp1 activity and chromatin structure, however, Sirt6 is the sirtuin that is most involved in single-strand break and DSB DNA repair mechanisms. Under DNA damage, Sirt6 is activated and involved in base excision repair and DSB signaling. Interestingly, Sirt6 is recruited to DNA damage sites, where it stimulates PAR activity of Parp1 by directly interacting with ADP-ribosylating Parp1 (at Lys521), so inducing the repair which consequently might result in Parp1 over-activation (Canto et al., 2013; Shah and Mahmoudi, 2015), whereas, Sirt1-dependent deacetylation of Parp1 blocks Parp1-PAR activity and somehow protects cells from Parp1-mediated death. Sirt6 over-expression did not stimulate DNA repair in Parp1 knock-out cells, indicating that Parp1 is essentially required to mediate the effects of Sirt6 in DNA damage. Of note, Sirt6 did not seem to affect the acetylation status of Parp1. Experiment cases have shown that Sirt1 in contrast to Sirt6 exert opposite effects on Parp1 activity (inhibits PAR activity, Tables 1 and 3), hence the ability of Sirt1 to retain Parp1 in a deacetylated state which blocking its PAR activity (low activity state) (Hall et al., 2013; Quenet et al., 2009). As a deacetylase, the Sirt1 deacetylation of various target proteins which are mostly involved in stress responses (e.g. p53, FOXOs and Ku-70), modulating or promoting their activity. For example, deacetylation of p53 by Sirt1 de-stabilizes the tumor suppressor protein p53 and attenuates the transcriptional activity of p53 toward its downstream targets, which are mostly involved in stress response. In a similar fashion, members of the FOXO family, important transcription factors that transactivate a number of stress genes such as *p27KIP1*, *GADD45*, and *BIM*, are deacetylated by an interaction with Sirt1, leading to the modulation of transcriptional activity. Under DNA damage, Sirt1 deacetylates Ku-70 protein, which promotes survival (Giannakou and Partridge, 2004; Roper et al., 2014). Notable, Sirt1-mediated deacetylation negatively regulates the activity of pro-apoptotic molecules including Bax and p53. Both Sirt1 and Sirt3 can deacetylate Ku-70 to sequester Bax away from mitochondria thus inhibiting apoptosis. In another step, Sirt1 and Akt signaling can cooperate to regulate cellular survival through the modification of p53. P53 is an acetylated protein and this post-translational modification is indispensable for its function. Deacetylation of p53 by Sirt1 renders it inactive or to degradation. Deacetylated p53 binds to Mdm2, an E3 ubiquitin ligase which promotes the proteasome-mediated degradation of p53. Akt acts synergistically in this process by phosphorylating Mdm2 at S166 and S186 and promoting its association with p53. Sirt2 is another sirtuin which has been studied for its role in regulating cardiac myocyte survival. In contrast to the anti-apoptotic role of Sirt1, ablation of Sirt2 was found to be beneficial in ischemia/reperfusion oxidative stress. The hearts of mice treated with a specific pharmacologic inhibitor of Sirt2 were found to be protected from ischemic injury. These studies suggest the contrasting roles of sirtuins in the regulation of cardiomyocyte apoptosis (Pillai et al., 2014).

Sirt1/parp1 enzymes are indicated to promote DNA repair signaling through ATM-depended and -independed mechanism. A number of factors are involved in these pathways which have been conserved across species and have been shown to function in regulating lifespan. Through ATM-dependent pathway for example, Sirt1 would fasten DNA repair system by prompting activation of ATM-effector checkpoint kinase Chk2 and γ-H2AX foci formation in the genome (Haince et al., 2007; Song et al., 2011).

Fallowing DNA damage, p53 as an inducible protein accumulates in the nucleus, beside Parp1. Interestingly, the increased expression of p53 has been shown to parallel the expression of Parp1 in DNA damage, and these expression apparently precede the other events. Not surprisingly, both p53 and Parp1 have accordingly been “classified” as guardians of the eukaryotic genome. In particular, p53 over-loads and full activation are modulated through de-acetylation and poly(ADP-ribosyl)ation by Sirt1 and Parp1, respectively (Pillai et al., 2014; Mendoza-Alvarez and Alvarez-Gonzalez, 2001; Wiman, 2013). Efficient binding of p53 to its specific DNA-binding consensus sequences is depended on the level of its poly(ADP-ribosyl)ation by Parp1. Importantly, the covalent modification of p53 by Parp1 influences the differential affinities of p53 for DNA-binding sites in the vicinity of target genes which encode effector proteins that induce cellular processes: examples are *p21/CDKN1A* (G1-arrest), *14-3-3s* (G2-arrest), *NOXA*(pro-apoptotic) and *PUMA* (apoptosis). The decision between these outcomes is determined by differential affinities of p53 for these sites. Meanwhile, p53 transactivation of mitochondrial dysfunctional genes, including *BAX*, *PUMA*, and *NOXA* is responsible for apoptosis (Mendoza-Alvarez and Alvarez-Gonzalez, 2001; Wiman, 2013).

In particular, Parp1 and Sirt1 the two epigenetic enzymes have coordinate function to positively influence telomere structure, throughout two mechanisms; up-regulation of telomerase through c-MYC-depended transcriptional activation and through blocking DNA-binding activity of telomeric repeat binding factor 1 and 2 (TRF1 and TRF2) (Fig. 4). Importantly, Parp1 and Sirt1 declining in somatic cells would weaken compensatory process against telomere shortening which consequently impairs tissue regeneration from primitive progenitor cells by reducing their proliferation capacity. Telomere shortening subsequently would weaken compensatory process for tissue-renewal and would deplete tissues from replicating stem cells whose low-level telomerase-expressing progeny goes to apoptosis (Beneke et al., 2008; De Bonis et al., 2014).

Until now, tankyrase-1, tankyrase-2, Parp2 as well as Parp1 have been found in association with telomeric DNA and interact with TRF1 and TRF2, thus block their DNA-binding activity and controlling telomere extension by telomerase (Ame et al., 2004; Nguewa et al., 2005).

In human normal cells, in response to oxidative stress and in an active DDR, TRF1 and TRF2 expression is up-regulated by a p53-depended mechanism, without involvement of p16Ink4a pathway. In this respect, stress-induced cellular responses would promote G2 cell cycle arrest Up-regulation of TRF1 and TRF2 by p53-p21 pathway reflects a telomere-focused protective response by DNA repair system. Both TRF1 and TRF2 are engaged in multiple roles at telomeres, including telomere protection, replication, sister resolution and maintenance of length. Up-regulation of TRF proteins by a p53/p21-depended manner subsequently increases the pool of telomere-unbound TRFs which consequently promote the inhibition of ATM and attenuation of DDR (Mytych et al., 2015). Human telomere function requires both specific DNA-binding proteins, TRF1 and TRF2. TRF2 protects chromosome ends, and TRF1 regulates telomere length. Over-expression of TRF1 in a telomerase-expressing cell line leads to progressive telomere shortening, whereas inhibition of TRF1 increases telomere length. TRF1 does not control the expression of telomerase itself but is thought to act in cis

by inhibiting telomerase at telomere termini. PAR activity by PARPs inhibits the ability of TRFs to bind to telomeric DNA. Among PARP family, ADP-(ribosyl)ation of TRF1 by Parp1 and Parp5a releases TRF1 from telomeres, opening up the telomeric complex and allowing access by telomerase. However, the loss of TRF1 is not sufficient for telomere elongation, which shows that telomere elongation by Parp1 is telomerase-dependent and needs Sirt1. Parp5a (Tank1) targets only TRF1 and just functions as a positive regulator of telomere length while, Parp1 modify both TRF1/2 and therefore simultaneously causes elongation, regulation and protection of the telomere length. Parp1 and Sirt1 activity also is directed at other telomere-associated factor, telomerase (m*TET* gene), and might enhance rather than inhibit the activity of this target protein (Beneke et al., 2008; De Bonis et al., 2014; Mytych et al., 2015; Nguewa et al., 2005). In reprogramming iPSCs, Sirt1 is required for efficient telomere elongation, and this effect is mediated by a c-MYC-dependent regulation of the *mTET* (telomerase gene). As mentioned above, Parp1 activity has been implicated at telomeres and protection of telomeres from inappropriate DNA damage processing activities (Table 2) (Beneke et al., 2008; De Bonis et al., 2014).

Parp1 beside its relative coordinator Sirt1 is important for maintaining the integrity of CH and FH. Both proteins localize to telomeres, centromeres and rDNA, where they interact with and regulate specific partners. As an example, Sirt1 directly recruits Suv39h1 at specific regulatory regions both pericentromeric and telomeric CH. Suv39h1 is an important methyltransferase contributing to chromatin organization by maintaining H3K9me3 and H4K20me1 marks in both pericentromeric and telomeric CH. Suv39h1 is recruited at specific regulatory regions and regulated by Sirt1. Loss of both Suv39h1 and its close variant Suv39h2 in mice results in complete loss of H3K9me3 marks in pericentromeric heterochromatin as well as reduced H3K9me3 levels in telomeres (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013). Although, other SIRTs or PARPs in addition to Sirt1 and Parp1, are also involved in a way or another in DDR and genome stability and the loss of some of them in mice (e.g. Sirt6 or Sirt7) may have an aging phenotype, but with respect to the much stronger premature aging phenotype by Parp1 and Sirt1, we preferred to focus on these two enzymes and introduce other PARPs or SIRTs minimally in a table (Tables 1 and 2) (including their name, cellular localization, function, diseases related to dysfunction of the enzyme) (Burkle et al., 2005; Hall et al., 2013).

However, DNA damage in weak compensatory action of Sirt1 would trigger over-activation of Parp1 which consequently causes cells overloading of p53 signaling and directing cell cycle toward apoptosis (Bosch-Presegu and Vaquero, 2015; Canto et al., 2013).

4. The role of SA-miRNAs in cellular senescence and aging

Human aging is presented by a low-grade systemic inflammation characterized by elevation of circulating SA-miRNAs and proinflammatory cytokines (inflamm-aging). Such a state is associated with frailty and the development and progression of severe, age-related conditions that include CVD, CBVD, type 2 diabetes mellitus, and neurodegenerative diseases (Olivieri et al., 2015; Pourrajab et al., 2016; Rippo et al., 2014). The age-related increase in the burden of cells with DDR leads to SASP acquisition. SA-miRNAs are the main content of SASP and are defined as an identifiable secretome from senescent cells. SA-miRNAs are expressed to modulate cell function, especially to regulate mitochondria activity (mito-miRNAs). They are known as direct indicator of cell senescence and inflamm-aging (inflamma-miRNAs). In particular, SASP miRNAs are defined to play the key role in diffusion of DDR/SASP signaling to surrounding non-damaged cells during human aging, thereby creating a proinflammatory environment extending at the local and eventually the systemic level (Hooten et al., 2013; Olivieri et al., 2015; Rippo et al., 2014).

The SASP miRNAs (SA/inflamma/mito-miRNAs), are actually circulating miRNAs now increasingly recognized as indicators of cell senescence, as well as, potential biomarkers of ARDs. Lines of evidence additionally link SASP-related miRNAs and “inflamm-aging” to the mitochondria dysfunction (Hooten et al., 2013; Rippo et al., 2014).

Especially, the major constitutes of the SA-miRNAs are inflamma/mito-miRNAs (miR-181a, miR-34a, miR-146a, miR-106a, miR-19b, miR-20a, miR-221), which actively modulate mitochondria function (Olivieri et al., 2015; Rippo et al., 2014). Findings also indicate that SA-miRNAs modulate the rate of inflamm-aging at the cellular and systemic level. Indeed, the mito-miRNAs (miR-181a, miR-34a and miR-146a) are not confined only to the mitochondrial function/dysfunction, but are certainly involved in inflammation during cell aging via modulation of Bcl-2 family members (Rippo et al., 2014). The expression of SASP-miRNAs is regulated by p53-depended or -independed mechanism and/or by related tumor suppressors. In turn, SA-miRNAs can modulate common tumor suppressor system p53, p21 and p16 and would promote or inhibit full senescence (Rippo et al., 2014; Williams et al., 2017). For instance the genomic region around the miR-34 gene contains a putative p53-responding element that causes the transcription of this SA-miRNAs being activated by a p53-dependent mechanism. The promoters of the miR-34 family genes are subject to inactivation by CpG methylation. In contrast, p53 over-expression represses miR-17-92 expression via a p53-depended manner. The repression of miR-17-92 mediated by p53 is modulated through preventing the TATA-binding protein (TBP) transcriptional factor from binding to a TATA box that overlaps with the p53-binding site.ARDs (Gurtan and Sharp, 2013; Okada et al., 2015).

4.1. Senescence-inhibiting miR-17-92 across the PI3K/Akt and p53-p21 pathways

The miR-17-92 analogous family consists of miR-17/18a/19a/20a/19b-1/92a-1 (miR-17-92 polycistron) which are clustered on chromosome 13, miR-106a/18b/20b/19b-2/92-2/363 (miR-106a-92 polycistron) which are clustered on chromosome X, and miR-106b/93/25, which are clustered on chromosome 7 (Fig. 6). The miR-17–92 cluster is found to be commonly down-regulated in several human replicative and organismal aging models. Humans with hemizygous germ-line deletion of miR–17 ~ 92 develop Feingold syndrome, characterized by microcephaly, short stature, and digital abnormalities (Gurtan and Sharp, 2013; Hackl et al., 2010). The miR-17-92 family clusters have been found to be ubiquitous in all human tissues and directly involved in cell signaling pathways; IIS-PI3K/Akt and p53-p21, by direct targeting of the key components of these pathways such as *PTEN* and *p21(CDKN1A)*. On one side, miR-17-92 promotes PI3K/Akt pathway by down-regulating *PTEN* (the potent inhibitor of IIS-PI3K/Akt pathway), on the other side acts to repress the p53-p21 signaling by directly targeting *p21WAF* (a strong inhibitor of cell cycle). Remarkably, the IIS-PI3K/Akt pathway is the most conserved age-controlling pathway in evolution, and the FOXOs are amongst the PI3K/Akt multiple targets (Fig. 3) (Guorong et al., 2009; Gurtan and Sharp, 2013; Lopez-Otin et al., 2013; Wan et al., 2011). On the cellular level, PI3K/Akt inhibits FOXO translocation to the nucleus and sequesters it in cytoplasm, through a phosphorylation cascade which is inhibited by PTEN and SGK. Under stress and PTEN up-regulation by p53, the activity of PI3K/Akt pathway is reduced which allows FOXOs to translocate to the nucleus where its transcriptional activity can be regulated either by Sirt1 or p53 levels (Fig. 3). In this regard, down-regulation of miR-17-92 occurred during aging causes increased levels of *PTEN*, *p21WAF* and *p14/ARF* which functions to suppress the IIS/Akt pathway and diminishes cell survival capacity. The expression of miR-17-92 is usually associated with cell survival and proliferation, while reduced expression of miR-17-92 is generally associated with apoptosis or CS. In aged heart, decreased level of miR-17-92 has been observed in failure-prone subjects and human failing heart, but not in healthy aged heart. In studies on old subjects, miR-17-92 levels were significantly higher in the old healthy subjects who were free of disease. This up-regulation of miR-17-92 is supposed to correlate with the age-related adaptation of

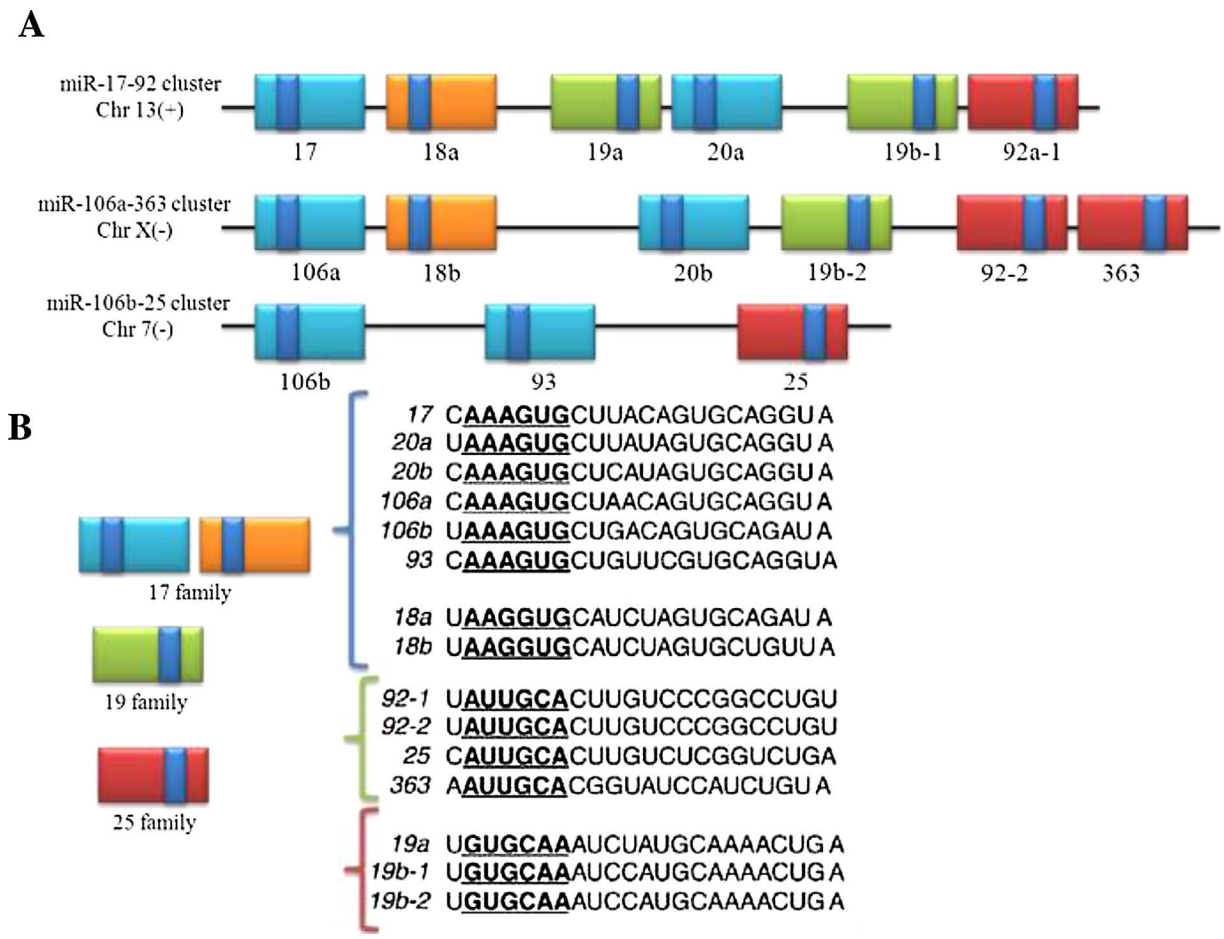

Fig. 6. The chromosomal positions and the sequences of mature transcripts of the miR-17-92 family members are illustrated here. (A) Gene structure of prologues miR-17-92, miR-106a-363, and miR-106b-25 are shown here. The pre-miRNA sequences are indicated as boxes, with mature miRNA sequences denoted in darker shades. Three miRNA gene clusters can be found based on three gene families on human chromosomes 13, X and 7. Related family members are indicated by color. (B) Sequences of miRNAs. Each miRNA is grouped based on seed relationship. Seeds are boldfaced and underlined.

cells in old healthy organs such as heart and brain (Giannakou and Partridge, 2004; Gurtan and Sharp, 2013; Hackl et al., 2010). It should be noted that, the degree and duration of stimuli would determine degree of stress response and therefore alterations of miRNA profile in human cells. For example, 20 Gy ionization irradiation causes up-regulation of miR-17-92, while 40 Gy irradiation leads to full expression of miR-34 and miR-16. Targets of the first group are PTEN/p53/p21 pathway, while late-responding miRNAs act in opposite direction and target cell surveillance pathway Sirt1/p53/p21. In stressed cells, up-regulated miR-17-92 would certainly control p53 overload and its-related pathways, however, enforced expression of miR-17-92 in p53-p21 loss-of-function displays genome instability and accelerates various oncogenic phenotypes observed in human tumor cells (Guorong et al., 2009; Hackl et al., 2010; Shin et al., 2009). Importantly, ectopic expression of miR-17-92 and miR-302-367 in human quiescent cells helps cells to re-entry the cell cycle and results in the promotion of G1–S transition as a consequence of *p21WAF* and *p14/ARF* silencing (Figs. 2 and 7) (Borgdorff et al., 2010; Gurtan and Sharp, 2013). For re-entry into the cell cycle and inducing the G1/S transition, up-regulation of miR-17-92 family members is required, as the key components down-regulating the p53-p21-Rb pathway. Accordingly, at the early stage of up-regulation, miR-17-92 directly targets Rb2/p130, accounting for subsequently reduced level of Rb2/p130 mRNA and cell clonal expansion. Data provide an emerging role for miR-17-92 to coordinate the timing of cell cycle progression through interacting with both the pRb-E2F and p53-p21 pathways. Notable, major transcription factors c-Myc and E2F induces the transcription of miR-17-92 cluster which in turn creates a negative auto-regulatory feedback loop with E2F (Dolezalova et al., 2012; Pickering et al., 2009). Some of miR-17-92 main targets have been defined as critical players in regulating the chromatin structure. The miR-17-92 family directly regulates the expression of chromatin regulatory genes *SIN3B*, *HBP1*, *SUV420H1*, and *BTG1* and pro-apoptotic gene *BIM*. *SUV420H1* is a histone methyl transferase that dimethylates and trimethylates H4K20 (H3K20me2,3). *SIN3B* is needed to recruit HDACs to the genes involved in proliferation and cell cycle regulation (Bosch-Presegu and Vaquero, 2015; Gurtan and Sharp, 2013).

4.2. Rejuvenation role of miR-302-367 through reprogramming mechanism

Data imply that the aging is unavoidable and we cannot expect its elimination, but prolonging healthy life span is a goal worth serious consideration. Reversal or inhibition of CS could prolong healthy life span, thus many attempts have been undertaken to influence cellular senescence. One of the main approaches until now is concerning cell reprogramming by induced pluripotent stem cells (iPSCs), which in vitro is accordingly effective even in cells undergoing senescence, or derived from very old or progeroid patients. The iPSCs generated from senescent and centenarian fibroblasts had reset telomere size, gene expression profiles, oxidative stress and mitochondrial metabolism. There is a common view on using miRNAs as an example to antagonizing CS, and posits miRNAs as beneficial agent in manipulating life span. Amongst, miR-302-367 which is highly conserved and vertebrate-specific has been identified as miRNAs whose ectopic expression can

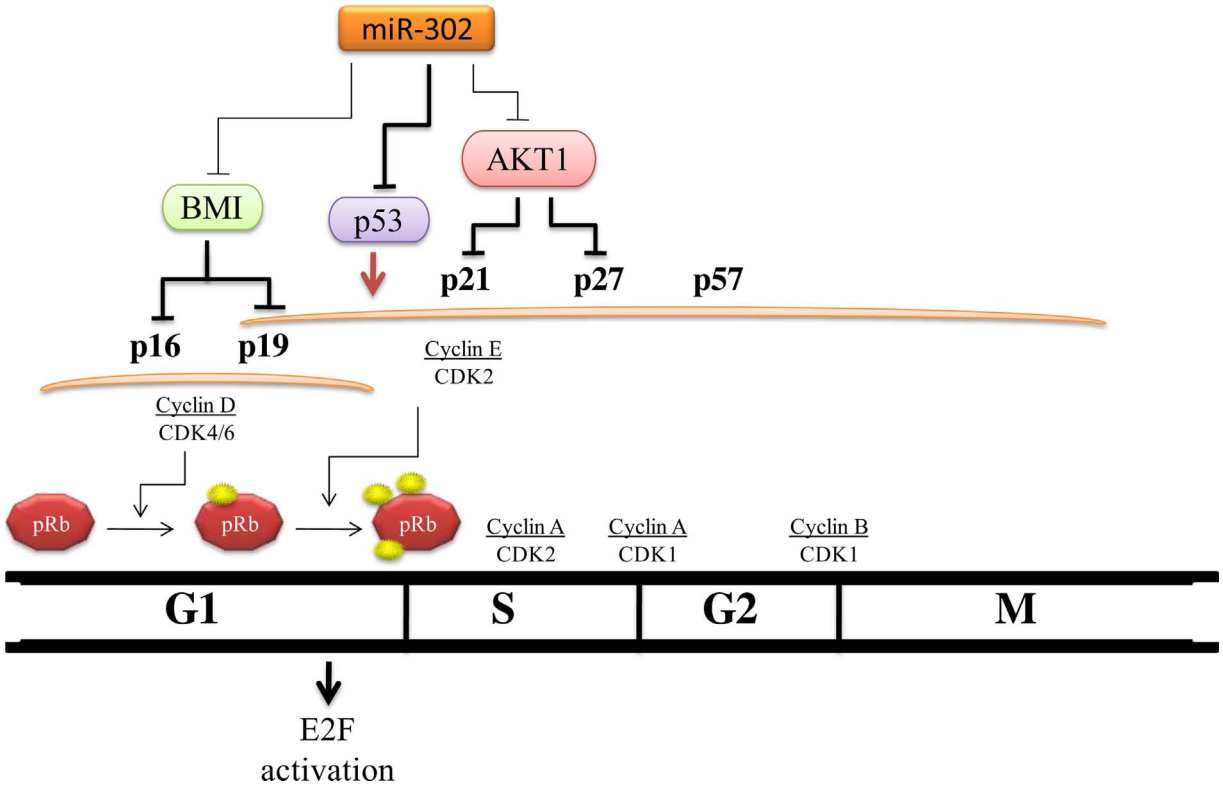

Fig. 7. Proposed mechanism for miR-302-367-mediated cell cycle regulation in human cells is illustrated here. The miR-302-367 not only suppress the p53-p21 axis, but also may concurrently target BMI and AKT in somatic cell reprogramming (SCR) and in cancerous cells, whereby suppresses cell robust proliferation. Relative quiescence at the G1 state prevents possible random growth and/or tumor-like transformation of reprogrammed cells, which leading to a more accurate and safer process by which premature cell differentiation and tumorigenicity are both inhibited. Both pathways; the G1 transition stimulator cyclin D and the cell growth signaling pathway Akt1-p27Kip1/p21Waf1 are targets of ectopic miR-302-367 in cancerous cells.

induce cell reprogramming (Fig. 8) (Gao et al., 2015; Lipchina et al., 2012; Sikora, 2013). Generally, miR-302/367-mediated reprogramming is supposed to be through at least three mechanisms; i) targeting some epigenetic factors to erase methylation induced during cell aging. The reprogramming of somatic cells requires unique DNA methylation pattern characteristic of pluripotency and undifferentiated status of ESCs by using the same mechanism. Indeed, miR-302 silences lysine-specific histone demethylases 1 and 2 (AOF1 and AOF2) and methyl-CpG binding proteins 1 and 2 (MECP1-p66 and MECP2); down-regulation of these important epigenetic genes seems to facilitate reprogramming of epigenome to pluripotency state, ii) miR-302 and Oct3/4, Sox2, Nanog, and others form a reciprocal positive feedback loop in the miR-302-367 transfected cells. Indeed, miR-302 over-expression would induce the expression of Oct4, Nanog, and Sox2 in iPSCs, at the levels that are observed in normal hESCs. The pluripotent status of iPSCs is maintained by a reciprocal positive loop between miR-302-367 and Oct4, Sox2, Nanog and other factors, iii) targeting senescence-associated pathways such as the p53-p21, PI3K/Akt and TGF-β-Nodal-Smad-2/3 pathways, mediates the conventional reprogramming of somatic cells (Gao et al., 2015; Kuo et al., 2012). Results from studies represent data that over-expressed miR-302 fine-tunes cell reprogramming and is implicated in complete iPSC reprogramming. The over-expressed miR-302 cluster caused conversion of partial to fully reprogrammed iPSC by suppressing MBD2 expression, whereby increasing *NANOG* expression. The methyl-DNA binding domain protein 2 (MBD2) as an epigenetic suppressor, blocks full reprogramming of somatic cells to iPSC through direct binding to the *NANOG* promoter whereby preventing *NANOG* transcriptional activation. Expression of exogenous miR-302 cluster was efficient in attaining a fully reprogrammed iPS state in partially reprogrammed cells by relieving MBD2-mediated inhibition of *NANOG* expression. In the other word, miR-302 positively controls the level of pluripotency-related biomarkers, including Oct3/4, Ssea-3/4, Sox2, Nanog, and Lin-28, while negatively modulates the Nodal inhibitor Lefty (Kuo et al., 2012; Lee et al., 2013; Lipchina et al., 2012). Particularly, the miR-302-367-mediated iPSCs are tumor-free, due to that miR-302 contains self-regulating anti-tumor effects. Notable, miR-302 inhibits the tumorigenicity of human pluripotent stem cells, because the miR-302 family hinders the progression of G1 phase and blocks G1 to S cell cycle transition by targeting and co-suppression of CDK4/6 and CDK2 in human iPSCs (Fig. 7) (Lin et al., 2010). Furthermore, ectopic expression of the miR-302-367 cluster in human cervical cancer cells inhibited cell proliferation and tumor formation by blocking the G1/S cell cycle transition. The miR-302-367 cluster acts through a new cell cycle regulatory pathway in which directly down-regulates both *cyclin D1* and *AKT1* and indirectly up-regulates *p27KIP1* and *p21WAF1*, leading to the suppression of cervical cancer cell proliferation (Cai et al., 2013; Lin et al., 2010). Moreover, over-expressed miR-302a inhibits the G1/S cell cycle transition in prostate cancer, by directly binding to *AKT* 3′-UTR, which results in subsequent alterations of the Akt-GSK3β-cyclin D1 and Akt-p27Kip1 pathway. These results reveal miRNA-302 as a tumor suppressor in cancer cells. By targeting *AKT* in cancer cells, miR-302 would elevate the expression of Akt-downstream effector *p27KIP1* and *p21WAF1*, which inhibits cell proliferation through the Akt1-p27Kip1/p21Waf1 pathway (Fig. 7) (Cai et al., 2013; Zhang et al., 2015).

Nowadays, miR-302-367 has been identified to be involved in major cell signaling pathways such as cell growth pathway PI3K/Akt and the DDR pathway, by targeting the expression of key components of these two pathways such as *AKT*, *PTEN* and *p21(CDKN1A)* (Figs. 3 and 7) (Dolezalova et al., 2012; Zhang et al., 2015). Recently a comprehensive list of miR-302-367 targets has been identified which shows miR-302-367 involvement in a number of cellular process whose regulation by miR-302–367 may promote pluripotency and reprogramming, such as cell cycle, epigenetic changes, metabolism and vesicular transfer. The

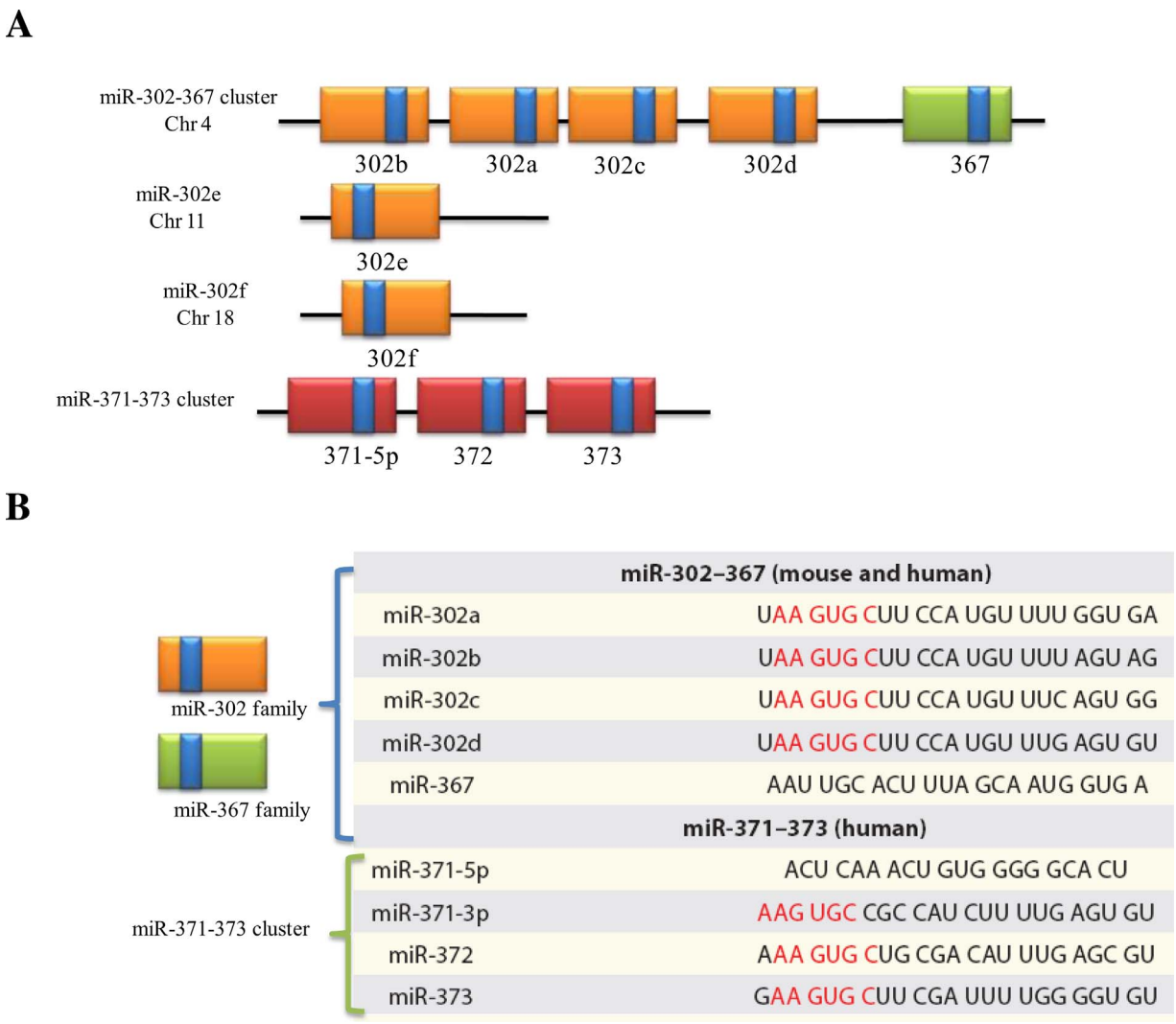

Fig. 8. The chromosomal positions and the sequences of mature transcripts of the miR-302-367 family members are illustrated here. (A) The miR-302–367 and miR-371–373 clusters are expressed in human cells. The pre-miRNA sequences are indicated as boxes, with mature miRNA sequences denoted in darker shades. (B) The clusters share a common-seed sequence, shown in-red, which is the key determinant of target gene recognition, suggesting that they share functions in pluripotency and early embryonic development.

3′-UTRs of all targeted transcripts have been found enriched for the 'AGCACUU' motif, complementary to the 'AAGUGCU' motif, the miR-302-367 family seed sequence (Fig. 8). Evidence from hESCs indicate that *p21(CDKN1A)* is a potent target of miR-302-367. Simultaneously, miR-302-367 silences *PTEN* (a potent inhibitor of Akt pathway), to promote cell cycle progression, and further silences *CDK2*, *CDK4/6* and *BMI-1* (a strong suppressor of *CDKN2A*), to promote *p16INK4A* and *p14/p19ARF* expression which delay G1 phase and give time to cell to check for DNA damage (Figs. 3 and 7) (Cai et al., 2013; Lin et al., 2010). In different conditions, the miR-302–367 members play two opposing roles in regulating the PI3K/Akt pathway. In human normal proliferating cells, miR-302–367 promotes PI3K/Akt signaling by targeting its inhibitors *PTEN* and *p21(CDKN1A)*, while in carcinoma cells acts to inhibit cell cycle progression through activating the *AKT*-downstream effector *p27KIP1* and *p21WAF1* (Figs. 3 and 7) (Cai et al., 2013; Zhang et al., 2015).

The above considerations bring this suggestion that in aging cells modulation of senescence-associated pathway p53-p21 by these miRNAs may rescue human cells from senescence or apoptosis through direct targeting of *p21(CDKN1A)* expression and modulation of up-regulated p53-p21 pathway.

4.3. Senescence-promoting miR-181 as a mito/inflamma-miRNA

Known members of miR-181 are including miR-181a/b/c/d. The firs members miR-181a and miR-181b are transcribed from two separated gene loci (miR-181a-1/miR-181b-1 and miR-181a-2/miR-181b-2), and miR-181c and miR-181d are transcribed from another locus (Fig. 9) (Xu et al., 2013). Several studies have documented miR-181a as an inflamma-miRNA involved in mitochondria function (mito-miRNA). Importantly, evidence has regarded miR-181a as inflammatory-related secretory miRNAs which share some common features such as: i) differential expression in senescent and young cells, making them senescence-associated (SA)-miRNAs; ii) the ability to modulate inflammatory pathways, making them inflamma-miRNAs; iii) differential expression in total plasma/serum or in microparticles/exosomes of patients with the major ARDs. In this regard, at least three miRNAs (miR-181a, miR-146a, miR-34a) are considered to be consistent with this scenario and may constitute an inflamma/mito-miRNA system that can affect the systemic proinflammatory status and exert adverse effects on the pathways and mechanisms involved in organismal homeostasis (Hooten et al., 2013; Jung and Suh, 2014; Rippo et al., 2014).

Amongst miRNAs targeting genes involved in the production of ROS and inflammatory cytokines, miR-181a/b/c is an important example of age-related miRNAs that up-regulates ROS production and

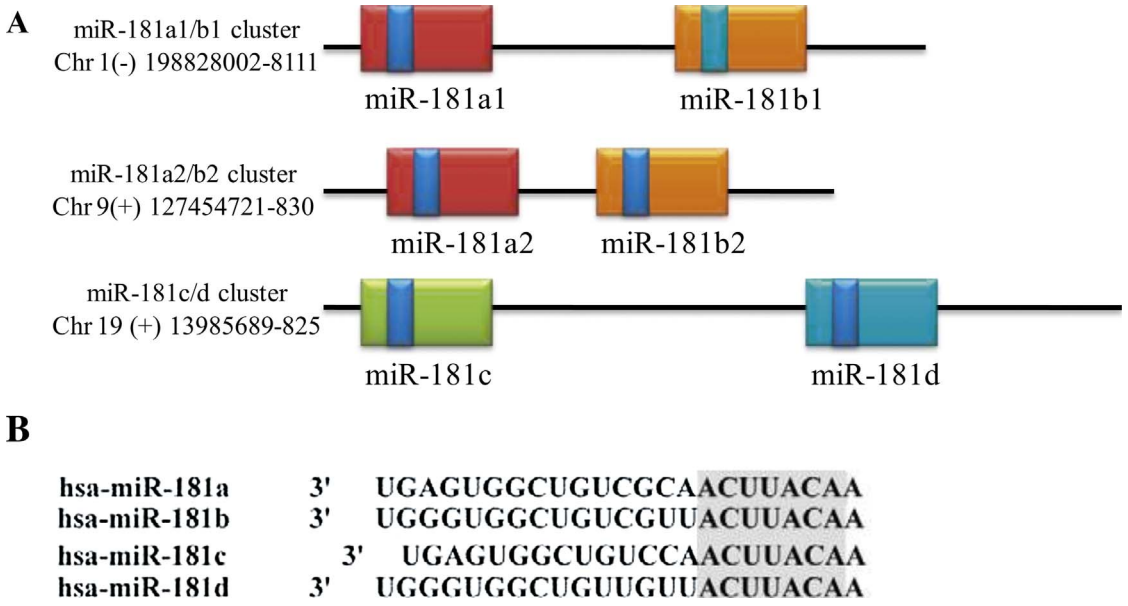

Fig. 9. The chromosomal positions and the gene structure of the miR-181 family members. (A) The pre-miRNA sequences are indicated as boxes, with mature miRNA sequences denoted in darker shades. Three miRNA gene clusters can be found on human chromosomes 1, 9 and 19. Related family members are indicated by color. (B) Each miRNA is aligned based on seed relationship. Seeds are denoted in darker shades.

inflammatory responses with age (Jung and Suh, 2014; Williams et al., 2017). In a study on miRNA expression levels in sera from young (mean age 30 years) and old (mean age 64 years) healthy individuals, there was a significantly lower levels of miR-181a in older individuals which showed an age-related alterations in miRNA levels in human serum (Hooten et al., 2013). Among miRNAs down-regulated in aged individuals, miR-181a was found to correlate negatively with the anti-inflammatory cytokines TGFβ and IL-10. Additionally, miR-181a targets several inflammatory-cytokine mRNAs including those encode IL-1β, IL-1α, IL-6, IL-8, IL-10, TNFα, TGFβ, FGF2, HMGB1 and LIF (Jung and Suh, 2014). Also, miR-181c has been found down-regulated in the brain and serum of AD patients and in the serum of AD risk models. Herein, miR-181 is represented as a prototype of SASP-inflamma/mito-miRNAs, previously found to be associated with mitochondrial (directly and indirectly) function and senescence pathways (Das et al., 2014; Rippo et al., 2014; Saunders et al., 2010). Current findings put miR-181a/b/c in the discrete set of mito/inflamma-miRNAs that can modulate mitochondrial activity, and primarily are involved in inflamm-aging. Their modulation of mitochondria function, as the main target of mito-miRNAs, is intimately involved in the aging process and could mediate the loss of mitochondrial integrity and function in aging cells, inducing or contributing to the inflammatory response and to age-related diseases. Findings reveal that over-expressed miR-181c in the aged heart leads to the reduced expression of mitochondrial complex IV subunits, which consequently results in increased levels of matrix calcium and activation of citric acid cycle dehydrogenases that increase the flow of protons and electrons into the electron transport chain which shunts electrons into alternate pathways, culminating in increased ROS production. Mechanistically, miR-181c binds to the 3′-end of the mRNA of a mitochondrial gene, mt-COX1, a subunit of complex IV of the respiratory chain, and initially results in a decrease in mt-COX1 protein, complex IV remodeling, and increased production of reactive oxygen species (Das et al., 2014; Rodriguez-Ortiza et al., 2014; Saunders et al., 2010). However, in the aged brain, over-expressed miR-181a/b was shown to directly target *SIRT1* and *c-FOS*. Up-regulation of miR-181a/b in the brain of AD patients leads to impairments in synaptic plasticity and neuronal loss, two important features displayed in AD disease. In AD, up-regulation of miR-181a/b in the hippocampus of aged individuals targets *c-FOS* and *SIRT1*, proteins may critically be involved in memory formation and synaptic plasticity. Importantly in the hippocampus of AD models, miR-181a/b expression, in opposite to miR-181c, is significantly up-regulated, in compare to age-matched healthy wild-type mice. Increased expression of miR-181 was not detected in old healthy mice and humans (Jung and Suh, 2014; Rodriguez-Ortiza et al., 2014). The reports emphasize on the importance role of miR-181a/b/c/Sirt1-mediated deacetylation in the heart and neurodegenerative disease and, as mentioned previously, on the maintenance of mitochondrial functions during aging (Fig. 1). The mitochondrial function is particularly depended on PGC-1α, the master regulator of mitochondria number and function, which is directly deacetylated and activated by Sirt1 (Fig. 3B). Also, miR-181 up-regulation causes FOXO and p53 remain in fully acetylated forms by which facilitating cell cycle arrest, wherein the apoptotic activity of FOXO and p53 is no longer suppressed by Sirt1 (Fig. 4A). Thereby, down-regulation of miR-181a/b/c in the hippocampus and heart of aged individuals respectively appears beneficial in preserving mitochondria function and exerts robust protection against neuronal injury induced by ROS or other stressors (Saunders et al., 2010). Moreover, to elucidate miR-181 function in DDR, we should consider the Sirt1-ATM-p53 pathway. *SIRT1,* the potential targets of miR-34a and miR-181, plays a critical role in regulating cellular level of activated p53 and ATM. Both miRNAs through targeting *SIRT1* mRNA lead to p53 and ATM up-regulation in the cell which may display apoptosis via p53-p21 axis. Then, up-regulated miR-181 may create a reciprocal feedback loop with p53-p21 axis which enforcing the p53 pathway, like as those observed in miR34/Sirt1/p53 auto-regulatory feedback loop (Wang et al., 2011; Zhao et al., 2010). Indeed, miR-181 and miR-34 both are SASP-miRNAs which can participate in premature aging through modulating senescence-associated pathways including the mitochondrial respiration (miR-181) (mito-miRNA), DDR (miR-181 and miR-34), and cell death (miR-34) (Fig. 1(Right)). In a study on aging of human skin, it was found that the expression of miR-181a is increased during senescence of dermal fibroblasts and its over-expression is sufficient to change cell adhesion and remodel the extracellular matrix. These findings indicate that up-regulated miR-181 is able to modulate the levels of adhesion proteins and extra-cellular matrix components, such as integrin-αV and collagen XVI, the compositional remodeling of dermis and epidermis occurring during skin aging (Mancini et al., 2012). In human leukemia cells, miR-181a/b over-expression acts as a ‘molecular switch’ in the Lin28–let-7 reciprocal loop by up-regulating let-7 function. In mammalian, Lin-28

genes have role in proliferation and growth, and is commonly activated in tumors by suppressing let-7 and enhancing the expression of Myc. In many adult tissues, let-7 is expressed abundantly and functions as a tumor suppressor. The mammalian Lin-28 genes are also targets of let-7, and constitute a conserved negative feedback loop. Many mammalian let-7 targets have been identified and are strongly characterized by their roles in growth, metabolism, and development pathways. In total, miR-181 targets Lin-28 which may regulate proliferative and metabolic pathways, at least in part through modulation of let-7 (Li et al., 2012).

4.4. Apoptotic miR-34 across three p53/miR-34 feedback-regulatory loops

One particular aging-associated miRNA of note is miR-34 which is clearly up-regulated during aging in all animals. Ectopic expression of miR-34a has been found to contribute to apoptosis, cell cycle arrest, or senescence. One of the potential direct targets of miR-34a is *SIRT1* mRNA which as a novel modulator of vascular endothelial cell homeostasis, playing a key role in angiogenesis through the deacetylation of FOXO1. In the endothelium, up-regulated miR-34 leads to reduced expression of *SIRT1* and causes endothelial cell senescence which is accompanied by impaired angiogenic function. Also, expression of miR-34 in endothelial progenitor cells would lead to endothelial progenitor cell senescence (Gurtan and Sharp, 2013; Zhao et al., 2010). There is a positive-feedback loop between miR-34 and p53-p21 axis: p53 directly activates the expression of miR-34, and miR-34 targets directly *SIRT1* mRNA (a potent de-stabilizer of p53), thus prevents *SIRT1*-mediated deacetylation of p53, which consequently results in the accumulation of p53 and up-regulation of related genes. Notable, p53 acetylation on lysine 382 increases after miR-34 expression and increases the transcriptional activity of p53, which can lead to the expression of pro-apoptotic genes (Okada et al., 2015). Additionally, miR-34 constitutes two another positive-feedback loop with p53, through targeting the potent inhibitors of p53; E3 ubiquitin ligase YY1 (p53/miR-34/YY1), and MDM4/HDM4 (p53/miR-34/HDM4). These known positive-feedback loop between p53 and miR-34 strengthen further the p53 pathway upon which exerts a robust tumor suppression response. Interrupting these feedback loops between miR34/p53 provides a selective advantage for cancer cells (Gurtan and Sharp, 2013; Okada et al., 2015). Additionally, studies in human carcinoma cells (hCCs) have indicated that miR-34 is able to restore the tumor suppressing function in human cells deficient for p53. Notable, loss of miR-34 in hCCs makes them resistant to p53-induced apoptosis used in chemotherapy. Accordingly, miR-34 induces tumor suppressor function through a Sirt1/p53-independent mechanism, by directly targeting HDAC1 a direct regulator of *p21WAF1* (Zhao et al., 2013). However, as a DDR/SASP-miRNA, DDR promotes miR-34 up-regulation throughout the p53-dependent or independent mechanism which allows DDR to regulate the expression of a large number of proteins involved in senescence. In DNA damage and repair-related responses, expression of miR-34 causes down-regulation of a group of genes promoting cell cycle such as *Cyclin-D1* (*CCND1*) and *CDK6*, and leads to a permanent G1 phase (Rippo et al., 2014; Wan et al., 2011).

Recently, miR-34a has been identified in mitochondria of different species and cell types (mito-miRNA), and has been indicated in a discrete set of inflamma-miRNAs (including miR-181a, miR-146a), participating to modulate mitochondrial activity, by targeting *SIRT1* and *BCL-2* family members which may, interfere with mitochondrial function and integrity (Rippo et al., 2014; Zhao et al., 2010).

5. “Stem cell aging” hypothesis and tissue regeneration theory

The “stem cell aging” hypothesis clearly defines stem cell exhaustion as an underlying mechanism of body aging and reduced potential of tissues regeneration. The hypothesis declares both types of CS (RS and SIPS) as underlying mechanisms of declining in regenerative potential of the body (Bielak-Zmijewska et al., 2014; Childs et al., 2015). In aging heart, for instance, the cardiac progenitor cell (CPC) pool reflects the ineluctable genetic/epigenetic clock which is determined by telomere shortening and DNA erosions (RS, SIPS), wherein by necessity up-regulates cell-cycle inhibitor pathways p14Arf/p53/p21 and p16Ink4a/Rb and collectively generate a differentiated progeny that rapidly acquires cell cycle arrest and the senescent phenotype to conditioning organ aging. Thereby, senescence and death of CPCs both lead to premature cardiac aging and heart failure. In aged diseased hearts, cell regeneration is disproportionate to the accumulation of old dying cells, leading to cardiac de-compensation. But yet, the senescent heart contains some functionally competent CPCs that have the properties of stem cells. This subset of telomerase competent CPCs have long telomeres and, following activation, are able to migrate to the regions of damage, where they generate a population of young myocardium to reversing the aging process (Chimenti et al., 2003; Gonzalez et al., 2008).

On the other side, we have usually to culture and expand adult stem cells prior to their application, by the way telomere erosion is happened and eventually triggering a permanent DDR. Adult stem cells as a promising tool for cellular therapy and regeneration strategies become senescent in vitro in culture condition. In this setting, the tumor suppressor pathway p53-p21 is up-regulated which subsequently causes permanent cell cycle arrest at G1 (Magalhaes, 2004). Additionally, reprogramming-induced senescence (RIS) is a barrier of reprogramming, triggered by up-regulation of p53, *p21WAF1/CIP1* and *p16INK4A*. CS impairs successful reprogramming of somatic cells into iPSCs, which renders reprogramming slow and stochastic. De-condensation of *INK4A/ARF* locus due to chromatin remodeling can be one of the mechanisms behind RIS. Enforced expression of four reprogramming factors OSKM (Oct4, Sox2, Klf4, and c-Myc), is closely associated with the activation of *INK4A/ARF* pathway, which causes CS or apoptosis, a result lowering the reprogramming efficiency (Banito et al., 2009).

5.1. Early role of Sirt1/Parp1 in stem cell pluripotency-rejuvenation strategy

Sirt1/Parp1 expression is much higher in mouse and human ESCs than in differentiated tissues. In the absence of either Parp1 or Sirt1 or upon inhibition of their activity, stem cells exhibit a decrease in key pluripotency genes as they cannot maintain the ground state of pluripotency. There is evidence that epigenetic modification by Sirt1/Parp1 in pluripotency loci favors iPCs reprogramming. The axis has been mentioned as important epigenetic switches essential specifically for the early stages of iPSC reprogramming. The couple is concomitantly required at the early and essential stage of somatic cell reprogramming, preceding the induction of transcription at endogenous pluripotency loci for reprogramming of somatic cells into iPSCs (Chiou et al., 2013; Saunders et al., 2010; Son et al., 2013). In mouse and human ESCs, Sirt1/Parp1 are involved in the expression of core-pluripotency loci OCT4, SOX2, c-MYC and NANOG whereby regulate self-renewal and pluripotency properties. Accordingly, up-regulated couple occupies the key loci OCT4, NANOG, SOX2, *STELLA, TET1* and *ZFP42*, which protecting pluripotent loci from progressive epigenetic repression. The safeguarding roles of Parp1/Sirt1 in preserving pluripotency state is found in both human pluripotent stem cells (hPSCs); hESCs and hiPSCs, and/or overcoming the pluripotency deficits and reprogramming barriers in iPSCs (Doege et al., 2012; Roper et al., 2014; Yoon et al., 2014).

Sirt1 and Parp1 are needed in erasing the somatic epigenetic signatures as typified by DNA methylation or histone modification at silent pluripotency loci and inducing the pluripotency state. Sirt1/Parp1 function helps to restore chromatin in the active configuration at special target loci and establishing the alternative epigenetic marks especial for ESCs (Fig. 10). From data it is assumed that Sirt1/Parp1 activity is required for epigenetic modification of *OCT4*, *SOX2*, *c-MYC* and *NANOG* loci in iPSCs, to induce full activation of pluripotency loci and favor reprogramming efficacy (Doege et al., 2012; Mostocottoet al.,

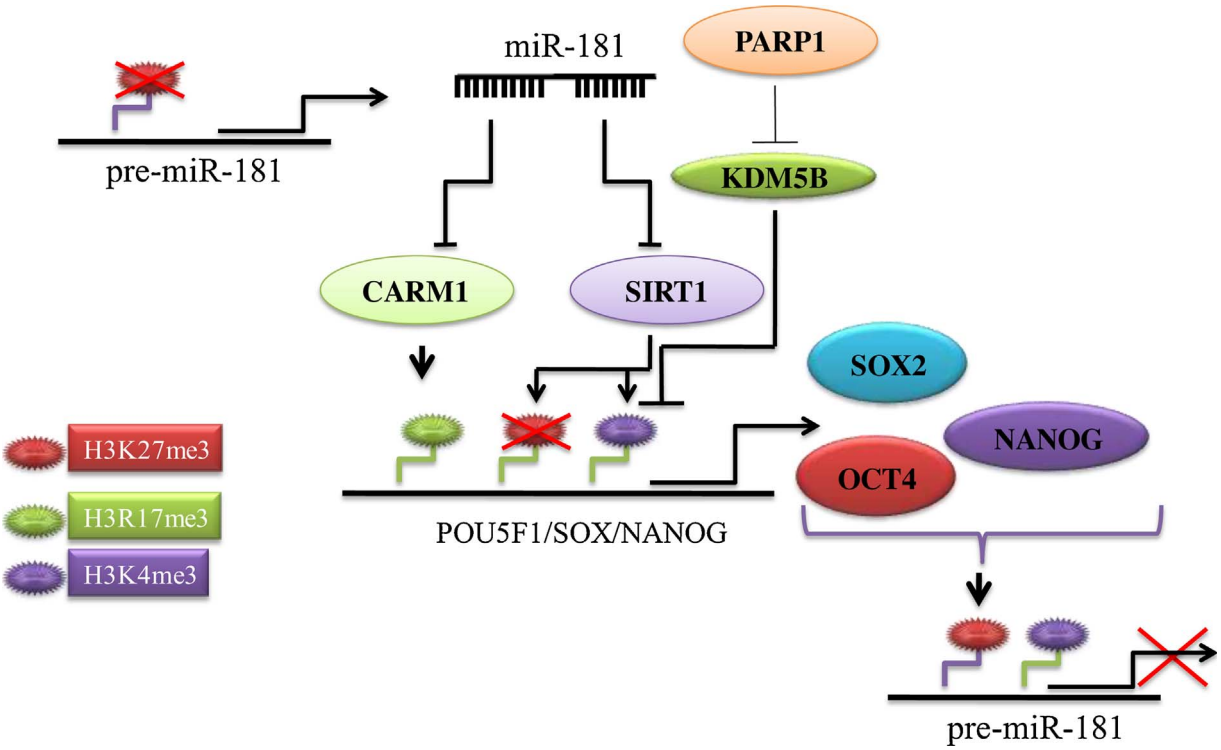

Fig. 10. A regulatory loop between miR-181, SIRT1/PARP1 and core-pluripotency factors is illustrated here. (A) Ectopic miR-181 down-regulates the expression of *SIRT1* and *CARM1,* through which negatively regulates the expression *of NANOG, SOX2,* and *OCT4*. Carm1 creates the active signature H3K17me3 at the *OCT4, NANOG* and *SOX2* loci. Sirt1 (by erasing H3K27me3 and creating H3K4me3) and Parp1 (by creating H3K4me3) lead to activation of core-pluripotency promoters. The core-pluripotency factors in turn in a negative circuitry manner recruit H3K27 methylases to the miR-181 promoter to inhibit its expression. In differentiated hESCs, H3K27me3 is erased from miR-181 promoters due to diminished activity of core pluripotency factors. Sirt1 and Parp1 by a similar mechanism may get chromatin to an active configuration at the target loci; DNA methyltransferase1 (*DNMT1)*, *OCT4, SOX2* and *NANOG*.

2014; Roper et al., 2014). Parp1 as an instance affects chromatin signatures by modulating the activity and localization of Dnmt1/3a/3b and histone-modifying enzymes. For example, it has been shown that poly(ADP-ribosyl)ation by Parp1 blocks the chromatin binding of Kdm5b, a histone lysine demethylase acting on H3K4me3, and inhibits its activity (Fig. 10) (Chiou et al., 2013; Mostocotto et al., 2014). Moreover, through its ability to interact with and to modify co-repressor and co-activator complexes, Parp1 plays an important role in the cell cycle reactivation of resting cells by regulating the expression of immediate early response genes (e.g. *DNMT1, c-MYC, c-FOS, JUNB and EGR-1*) (Mostocotto et al., 2014). Interestingly, Parp1/Sirt1 maintains the DNA methylation patterns in normal cells through its localization on the specific sites and marks those sequences in the genome that must remain unmethylated and protects them from methylation, thus playing a role in the epigenetic regulation of gene expression. Additionally, Parp1 localizes within the *DNMT1* promoter and protects it in an un-methylated state by its enzymatic activity. Parp1 protection of *DNMT1* locus from epigenetic repression by DNA methylation is specifically important to maintain the pluripotent nature of ESCs by ensuring the transcriptional activity of key pluripotency genes such as *NANOG*, *OCT4, SOX2, TET1* and *TET2.* Notable, mammalian Dnmt3a and 3b are responsible for de novo methylation and modify un-methylated DNA; whereas Dnmt1 is responsible for maintaining methylation patterns of ESCs (Doege et al., 2012; Zampieri et al., 2009). In addition, date has found a similar role but not identical for another Parp family member, Parp7, however, Parp1 and Parp2 imply antagonistic roles in both chromatin decondensation and chromatin compaction and function in an opposing manner (Liang et al., 2013; Roper et al., 2014). Accordingly, during iPSC generation, Parp1 and Sirt1 are recruited to telomeres and are required for efficient post-reprogramming telomere elongation. Telomeres are also “reprogrammed” to adopt features similar to those of ESCs; iPSC telomere length increases in a telomerase-dependent manner, and this elongation continues with cell passages after reprogramming, until they reach a length comparable to that of ESCs. Then, elevated level of Parp1/Sirt1 is necessary for proficient telomere elongation and genomic stability of iPSCs of mammalian origin. This effect might be mediated by a c-Myc-dependent up-regulation of the *TERT* gene (telomerase). Deficiency in these enzymes leads to accumulation of chromosomal aberrations and de-repressions of telomeric heterochromatin (Beneke et al., 2008; De Bonis et al., 2014). There is in vivo direct evidence that Parp1 through auto-regulatory feedback loop with *c-MYC* reactivates human quiescent cells. Upon stimulation of human quiescent cells, Parp1 and c-Myc induces the promoter regions of each other. Notably c-Myc directly interacts with *PARP1* promoter and leads to *PARP1* up-regulation in iPSCs. In turn, association of Parp1 to the c-MYC promoter region is needed for cell cycle reactivation of human quiescent fibroblasts. The molecular mechanisms by which the enzyme induces c-MYC transcription, was shown to be through its association to c-MYC promoter and by modulating the activity of chromatin modifiers histone lysine demethylase and deacetylases acting on lysine 4 of histone H3. Parp1 also interacts with SP1 factor and impairs its binding to the target promoter *c-MYC*. In contrast, Parp1 interacts with CTCF and enhances its binding to the target promoter *c-MYC*. According to the data presented here, the similar mechanism and prompt accumulation of Parp1 on the promoters of early response genes; *c-FOS, JUNB, EGR-1* and *DNMT1* is expected to cause chromatin de-condensation and stimulate cell cycle reactivation in human resting cells (Fig. 5) (Chiou et al., 2013; Mostocottoet al., 2014). Moreover, enforced expression of Sirt1 and Parp1 is assumed to improve nuclear re-distribution of histone marks such as H3K27me3 in primary cells, during reprogramming. Sirt1 in coordination activity with Parp1 would enrich the occupancy modification of the active histone mark (H3K4me2) and, in parallel, decrease the occupancy of the repressive histone mark (H3K27me3) at the core-pluripotentency

loci (Fig. 10) (Roper et al., 2014; Son et al., 2013). In this setting, up-regulated Sirt2/Parp2, as the closest relative to Sirt1/Parp1, is postulated not only through epigenetic modification and repression of transcription factors opposites Sirt1 function, but also through competing for substrate and decreasing cellular levels of NAD+ weaken the Sirt1/parp1 axis (Bosch-Presegu and Vaquero, 2015; Liang et al., 2013; Quenet et al., 2009). Given the emerging roles of miRNAs in the regulation of cell fate, it is assumed that some miRNAs may control the expression of Sirt1/Parp1, at least indirectly through the Sirt2/Parp2 axis (e.g. miR-149) (Mohamed et al., 2014).

Interestingly, inhibition of other HDACs; class I and II (by Valproic Acid (VPA)) would lead to improving cloning efficiency in mouse cloned blastocysts by enhancing activation of Sirt1 which particularly is related to proper nuclear distribution of H3K27me3 (Isaji et al., 2013).

5.2. MiR-302-367 and miR-17-92 as somatic counterparts in stem cells

A subset of age-related miRNAs is also known as hESC-specific miRNAs including miR-302-367 and miR-17-92. They are the most abundant-miRNAs in hESCs which in the later stage toward differentiation change to other sets of miRNAs including in particular miR-181, miR-17-92 and miR-15 sets. In the first stage of stem cell biology; the miR-17-92 and miR-302-367 family was found to preserve pluripotency in stem cells, while the second set can be tissue-specific miRNAs. Interestingly, the miR-17-92 family is present in both set of miRNAs and all cell types. Importantly, the undetectable levels of CDK inhibitors (*p16(CDKN2A)* and *p21(CDKN1A)*) in hESCs is due to high levels of miR-302-367 (Gao et al., 2015; Gu et al., 2008). Data from resting cells indicate that ectopic-expression of miR-302-367 would induce cell cycle re-entry, through up-regulating cyclin E-CDK2 and cyclin D-CDK4/6 and inducing G1 transition (Figs. 2 and 7). Some novel approaches proposed to generate iPSCs by using miR-302-367 (Gao et al., 2015; Kuo et al., 2012). Remarkably, the miR-302-367 ectopic expression exhibits combinatory effect in inducing p16/p14(p19) expression throughout which delaying the G1–S transition and would result in a relatively attenuated cell cycle rate similar to that of 2–8-cell-stage embryonic cells in early mammalian zygotes (20–24 h/cycle). These findings provide a means by which ectopic miR-302-367 produces iPSC, besides controlling tumorigenicity throughout which improves the safety of iPSCs in compared to the fast proliferation rate of iPSCs induced by four defined factors Oct4-Sox2-Klf4-c-Myc (12–16 h/cycle). Previously, in generating iPSCs, oncogenic factors such as c-MYC and KIF4 were frequently used which boost proliferative rates of iPSCs, whereby induce tumorigenicity or senescence. Studies on the role of miR-302–367 in promoting iPSC generation exhibited that ectopic-expression of miR-302–367 would improve reprogramming efficiency by overcoming any of these barriers (Anokye-Danso et al., 2011; Gao et al., 2015). Ectopic miR-302-367 up-regulates reprogramming Oct3/4-Sox2-Nanog factors and importantly in a circuitry manner, Oct3/4-Sox2-Nanog and Rex1 factors act as transcriptional activators of miR-302-367. A direct target of miR-302-367 is MBD2, an epigenetic suppressor of core pluripotency factors through direct binding to promoter elements and blocking full iPSCs reprogramming. Accordingly, miR-302-367 silences *MBD2* epigenetic suppressor of the *OCT3/4-SOX2-NANOG* loci and induces co-expression of these factors in somatic cell reprogramming. The *OCT3/4-SOX2-NANOG* co-expression is needed for conversion of partially to fully reprogrammed cells (Lee et al., 2013).

Similarly, up-regulated miR-17-92 family members; miR-17-5p, miR-20b, miR-93, miR-106a, and miR-106b in human mammary epithelial cells (HMECs) helped to re-entry the cell cycle and resulted in the promotion of G1–S transition, while rescued cells from Ras-induced senescence by inhibiting p21Waf1/Cip1-depended pathway (Borgdorff et al., 2010). In regarding cell reprogramming, hESC-specific miR-17-92 is known to induce the G1/S fast transition and promote rapid proliferation by suppressing several key regulators of the G1/S transition including five members of the CyclinE/CDK2 regulatory pathway (*p21(CDKN1A)*, *p27(CDKN1B)*, *p57(CDKN1C)*, *p16(CDKN2A)* and *Rb)* (Hackl et al., 2010). For re-entry the cell cycle and inducing the G1/S transition, essentially up-regulation of miR-17-92 is required as the key components down-regulating the pRb-E2F pathway.In normal diploid human cells, up-regulated miR-17 and miR-20a govern the G1/S transition and rescue cells from senescence by tempering E2F1 concentration. In human stem cells, E2F activity is controlled by miR-17-92 which may additionally target E2F expression. Inhibition of miR-17-92 in stem cells would result in premature accumulation of E2F1 which leads to an accumulation of DNA double-strand breaks and G1/S arrest. Accordingly, at the early stage of up-regulation, miR-17-92 directly targets Rb2/p130, accounting for subsequently reduced Rb2/p130 mRNA and clonal expansionthereafter the miR-17-92 cluster is defined to negatively control the E2F expression which regulating Rb2/p130-E2F pathway (Borgdorff et al., 2010; Pickering et al., 2009). Importantly, the transcription factor Myc as a key switcher in the cell cycle regulation up-regulates miR-17-92 to suppress specific target genes to maintain cell survival and autonomous proliferation. Myc is a transcriptional regulator of a multitude of genes for example; chromatin regulatory genes *SIN3B, HBP1, SUV420H1,* and *BTG1*, as well as the apoptotic gene *BIM*. Via up-regulation of miR-17-92, Myc suppresses the expression of these genes. Furthermore, miR–17∼92 has been recently defined to enhance the induction of pluripotency by miR-302. These reports suggest that miR–17∼92 as a somatic counterpart to the miR-302 family, wherein it can also contribute to the de-differentiation and plasticity of tumors. Interestingly, the seed sequence of miR-17 family (AAAGUGC) overlaps with those of miR-302 family (AAGUGCU) (Figs. 6 and 8). Both families repress common targets that regulate proliferation genes, such as *LATS2* and *p21(CDKN1A)*, and differentiation genes, such as *LEFTY1*, *LEFTY2*, and *TGFβ-R2* (Gurtan and Sharp, 2013; Kuo et al., 2012).

5.3. The reciprocal inhibitory loops by miR-181 in stem cell pluripotency

The reports proposed that miR-181 can function as an ‘epigenetic switch’ in lineage specification. From the literature also, an inhibitory indirect link between miR-181 and the core pluripotency factors Oct4, Sox2, and Nanog is assumed. There is accordingly a reciprocal regulatory feedback loop between miR-181/GCNF/core pluripotency factors, as a novel pathway involved in the modulation of hESC pluripotency. GCNF is an orphan nuclear receptor expressed in germ cells, and is the best characterized transcriptional repressor of *OCT4* and *NANOG* expression in primary cells. Upon up-regulation of GCNF, the expression of miR-181a is induced. GCNF-mediated repression of *OCT4/NANOG* mitigates *OCT4/NANOG* repression of miR-181 and causes the up-regulation of miR-181a in ESCs. Up-regulated miR-181 then through a negative-regulatory feedback loop represses *OCT4/*SOX*/NANOG* expression.

Down-regulation of *SIRT1* by miR-181 may lead to down-regulation of pluripotency markers (Gu et al., 2008; Saunders et al., 2010; Xu et al., 2013). In this regard over-expressed miR-181 can regulate Sirt1/Parp1 and core-pluripotency factors expression (Fig. 10). Ectopic miR-181 down-regulates the expression of *SIRT1* and *CARM1,* through which negatively regulates the expression of *NANOG, SOX2,* and *OCT4.* CARM1 (histone H3 arginine methylase 1), creates the active signature H3K17me3 at the *OCT4, NANOG* and *SOX2* loci (Saunders et al., 2010; Xu et al., 2013). Sirt1 (by erasing H3K27me3 and creating H3K4me3) and Parp1 (by creating H3K4me3) lead to the activation of core-pluripotency promoters. The core-pluripotency factors in turn in a negative circuitry manner recruit H3K27 methylases to the miR-181 promoter to inhibit its expression. In differentiated hESCs, H3K27me3 is erased from miR-181 promoters due to diminished activity of core pluripotency factors. Sirt1 and Parp1 by a similar mechanism may get chromatin to an active configuration at the target loci; *DNMT1*, *OCT4, SOX2* and *NANOG* (Bosch-Presegu and Vaquero, 2015; Mostocotto et al., 2014; Roper et al., 2014).

6. Conclusion

Rejuvenation of senescent cells is a road to postponing human aging and age-related disease. The two main approaches are epigenetic and pharmacological modifications of cell fate. However, knowing that aging is unavoidable we cannot expect its elimination, but prolonging healthy life span is a goal worth serious consideration. In this review, we try to concentrate on very specific pathways and very specific aspects of CS, the most popular molecular events interconnected with aging, which at least theoretically may be used in regenerative medicine or as a therapeutic strategy in ARDs. For instance although, other members of Sirtuin and PARP family are also involved in aging DDR and genome stability and the loss of some of them in mice (like Sirt6 or Sirt7), showed some stronger aging phenotype, the authors preferred to focus mostly on Parp1 and Sirt1 as paradigm of the family and for their much prototype roles in DDR and aging phenotype. Furthermore, SASP is one of the most important hallmarks of senescence. SASP is characterized by pro-inflammatory mediators and SA-miRNAs which are emerged as attractive targets in therapeutic strategies. In this regard, SASP-related miRNAs, at least theoretically, were offered as opportunities for design of anti-aging treatments or avoidance of age-associated manifestations. Theoretically, a combinatorial strategy by a required combination of ectopic miRNAs or treatment with epi-drugs may be used, as a new opportunity and an efficient strategy in regenerative medicine to engineering cells.

Conflicts of interest

The authors confirm that there are no conflicts of interest to disclose.

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