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EXPERT REVIEW

Cancer and Alzheimer's disease inverse relationship: an age-associated diverging derailment of shared pathways

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Abstract

Several epidemiological studies show an inverse association between cancer and Alzheimer's disease (AD). It is debated whether this association is the consequence of biological mechanisms shared by both these conditions or may be related to the pharmacological treatments carried out on the patients. The latter hypothesis, however, is not sustained by the available evidence. Hence, the focus of this review is to analyze common biological mechanisms for both cancer and AD and to build up a biological theory useful to explain the inverse correlation between AD and cancer. The review proposes a hypothesis, according to which several molecular players, prominently PIN1 and p53, have been investigated and considered involved in complex molecular interactions putatively associated with the inverse correlation. On the other hand, p53 involvement in both diseases seems to be a consequence of the aberrant activation of other proteins. Instead, PIN1 may be identified as a novel key regulator at the crossroad between cancer and AD. PIN1 is a peptidyl-prolyl *cis-trans* isomerase that catalyzes the *cis-trans* isomerization, thus regulating the conformation of different protein substrates after phosphorylation and modulating protein function. In particular, *trans*-conformations of Amyloid Precursor Protein (APP) and tau are functional and "healthy", while *cis*-conformations, triggered after phosphorylation, are pathogenic. As an example, PIN1 accelerates APP *cis*-to-*trans* isomerization thus favoring the non-amyloidogenic pathway, while, in the absence of PIN1, APP is processed through the amyloidogenic pathway, thus predisposing to neurodegeneration. Furthermore, a link between PIN1 and tau regulation has been found, since when PIN1 function is inhibited, tau is hyperphosphorylated. Data from brain specimens of subjects affected by mild cognitive impairment and AD have revealed a very low PIN1 expression. Moreover, polymorphisms in PIN1 promoter correlated with an increased PIN1 expression are associated with a delay of sporadic AD age of onset, while a polymorphism related to a reduced PIN1 expression is associated with a decreased risk of multiple cancers. In the case of dementias, in particular of Alzheimer's disease, new biological markers and targets based on the discussed players can be developed based on a theoretical approach relying on different grounds compared to the past. An unbiased expansion of the rationale and of the targets may help to achieve in the field of neurodegenerative dementias similar advances to those attained in the case of cancer treatment.

Cancer and Alzheimer's disease epidemiology

In this very last decade, there has been an increasing interest among researchers in studying a possible relationship between cancer and Alzheimer's disease (AD). Since the first studies, which reported a reduced risk of developing cancer for patients with Alzheimer-type dementia (DAT) and, vice versa, a reduced risk of developing DAT for cancer patients [1–3], several and more recent epidemiological studies confirmed an inverse association between cancer and AD. Cancer history decreases the risk of AD [4–6] and, in the same studies, epidemiologic data from independent cohorts also reported that patients with AD show a reduced risk of developing cancer. Notably, in their 2013 population-based study, Musicco et al. [6] found that risk of cancer in patients with AD was halved and the risk of AD in patients with cancer was reduced by 35%. A similar inverse association with cancer has been reported for

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Parkinson's disease (PD) [7–9] and other neurodegenerative diseases [10], but not for vascular dementia (VaD) amongst white older adults [3]. In this regard, Roe et al. [3] investigated, through a population-based study, a possible association between time of first cancer hospitalization and prevalent dementia (AD, VaD or mixed AD/VaD) and a correlation between cancer history and time of diagnosis of dementia. They found that patients with AD had slower rate of cancer hospitalization compared to individuals without dementia, while the same significant correlation was not found for patients with VaD and mixed AD/VaD [3]. Moreover, they found that white patients with cancer history had slower rate of diagnosis of dementia compared to participants with no cancer history, while such association was not significant for VaD patients [2].

While recent studies revealed that the mutual and inverse association between cancer and AD is reported in several ethnic groups [2–6; 11–15], Nudelman et al. [11] pointed out how this significant and inverse association was primarily identified in white non-Hispanic cohorts. Accordingly, the studies considered for this association provided significant evidence that the risk of AD is reduced in white non-Hispanic patients with cancer history [2–6; 10, 16]. Notably, in their 2010 work, Roe et al. [3] noticed that ethnicity was the prevalent cancer variable to be used to model a possible correlation between cancer history and the time of first dementia diagnosis. After the models being repeated separately by ethnicity, they found that while white participants with cancer history had slower rate of AD diagnosis (compared to participants with no cancer history), the opposite effect was observed in other ethnic minorities. The reasons behind these ethnicity-based differences may be due to cancer type, but also cancer incidence, differences in detection, treatment, risk factors, cultural aspects, lifestyle and genetic factors [17, 18].

Interestingly, the parameters that may be included while studying the relationship between cancer history and AD could not be limited to ethnicity-based disparities or cancer types. As a matter of fact, a survival analysis of age of AD onset not only indicated a later median age of AD onset for patients with cancer history - compared to those who previously did not have tumors - showing that cancer history is protective against AD, but also that this protection conferred against AD appears to have a "dose-effect" trend. Results indicated that individuals who previously had two cancers of different origin showed a later mean age of AD onset compared to individuals who previously had one or no prior cancer [11].

Although most studies which investigated a possible association between cancer and AD pointed out the existence of inverse co-morbidities, also the hypothesis of a direct correlation was considered. In their 2017 work, Sánchez-Valle et al. [19] explored the molecular hypothesis which could explain inverse and direct co-morbidities between AD and cancer, focusing in particular on glioblastoma and lung cancer. Their data build upon previous epidemiological studies which found that patients with AD have lower risk of developing lung cancer [6, 13] and higher risk of developing glioblastoma [4, 6, 20]. Through transcriptomic meta-analyses, they identified a number of genes deregulated in opposite direction in AD and lung cancer and other genes deregulated in the same direction in AD and glioblastoma, providing further data that may strengthen the hypothesis for inverse co-morbidity AD-lung cancer and for direct co-morbidity AD-glioblastoma [19]. Noteworthy, in all epidemiological studies and meta-analyses considered to explain the existence of a correlation between AD and cancer, glioblastoma is the only type of brain tumor taken into account for the analyses. It should indeed not be surprising that intervening directly on the brain tissue – as in the case of a pharmacological treatment for glioblastoma as well as surgically on the tumor itself – may lead to changes in the regulation of central cellular biological mechanisms. Hence, the disruption of homeostasis and the deregulation of specific molecular pathways could lay the basis for the observed direct co-morbidity between a neurodegenerative disease such as AD and glioblastoma. It should also be noted that the paper by Jon Sánchez-Valle et al. is the only one tracing the direct relationship between AD and glioblastoma and that the latter was the only brain tumor considered as well as AD the only neurodegenerative disease.

The availability of national registries of patients and cancer medications in various countries will help to clarify several of the unanswered questions, helping to move forward the field.

Biology versus treatment as influencers

Although a variety of studies – both epidemiological researches and meta-analyses – provided significant data supporting the existence of a correlation between cancer and AD, there is still an ambiguity whether this association is due to biological mechanisms shared, to some extent, by both these conditions or is something related to the pharmacological treatment carried out on the analyzed patients. In particular, the latter may interfere in the regulation of molecular processes shared by cancer and neurodegeneration, thus influencing both diseases' onset.

Based on the findings that patients with dementia have a decreased risk of cancer [3–6; 13, 21] and individuals with cancer history have a decreased risk of subsequent dementia [3–6, 11], in 2018 van der Willik et al. investigated the possible association between Mild Cognitive Impairment (MCI) and cancer [22]. In their paper, it is documented that

subjects with MCI have an increased risk of AD. However, noteworthy, this clinical state encompasses several subtypes of cognitive dysfunction of varied etiologies, none of which necessarily progresses to AD. In particular, MCI subclassifications include an amnestic form (aMCI), characterized by isolated memory impairments, and one non-amnestic (naMCI) in which other cognitive functions rather than memory are mostly impaired. Within these groups, aMCI subjects showed about 10-fold higher odds of developing AD [23]. van der Willik et al. [22] hypothesized that if there is a biological mechanism underlying the correlation between dementia and cancer, this should also be reflected in the correlation between MCI and cancer. Through a large population-based study, they found that while dementia was associated with a decreased risk of cancer, in line with previous studies, MCI was correlated with a borderline significant increased risk of cancer. Furthermore, this increased risk was especially prominent for amnestic MCI patients.

It is important to note that MCI is an early clinical and transitional stage from normal cognition to dementia, thus there is not a specific pharmacological treatment for this condition. In particular, clinical trials including aMCI patients treated with cholinesterase inhibitors were unable to show an improvement in cognitive functions of these patients or a slower conversion rate to AD, further suggesting a different biological pattern in comparison with AD patients [24–27]. Accordingly, the authors analyzed patients in a non-treatment condition and observed a correlation that is also found between aging and cancer, that is an age-associated increased risk of cancer [28, 29]. This may be explained by the fact that aging is a common risk factor for both dementia [30] and cancer. On the other hand, the population-based studies that found an inverse association between AD and cancer analyzed patients with diagnosed AD and individuals with history of cancer. Since these are both pathological conditions for which there is a specific pharmacological treatment, it is possible to hypothesize that the treatment itself – with a variety of drugs, each with a specific target – has a spectrum of effects on the physiology of the cells, affecting biological mechanisms and molecular pathways and changing the progression rate of the pathology. This can disrupt the normal pathophysiological evolution and bring imbalance in the regulation of a variety of processes linked to the usual clinical development of the disease. Clinically, this can be reflected in a time-shift of AD onset in individuals with history of cancer and, vice versa, in a lower risk of uncontrolled cell proliferation in AD patients [11].

Although a significant number of studies supports the hypothesis that pharmacological treatments can affect progression and onset of AD and/or cancer, other considerations must be taken into account. Concerning AD, it is important to note that the number of drugs commonly used to clinically treat this disease is low. The treatment is based on the use of acetylcholinesterase inhibitors (AChEIs) and memantine, an NMDA antagonist, but not all AD patients respond to this therapeutic approach [31, 32]. Notably, these same drugs are active only in a specific time window, therefore very long-term treatments, which can potentially explain the inverse co-morbidity and the decreased risk of cancer in AD patients, are not carried out [33]. From a biological point of view, the modulation of acetylcholinesterase (AChE) expression and activity has been related to cell proliferation and tumorigenesis. Accordingly, high levels of cholinesterase activity are found in ovarian tumors [34], brain tumors [35] and in different types of carcinoma [36], while amplification of AChE gene was found in various types of leukemias [37], nervous system tumors [38] and ovarian carcinoma [39]. In this regard, Ben Aziz-Aloya et al., in 1993, found binding sites for transcription factors associated with the regulation of cell growth and proliferation in the promoter region of the human AChE gene, suggesting that its amplification may influence the increased proliferation of cancer cells, thus supporting its involvement in tumorigenesis [40]. Moreover, it is reported that AChE expressed in tumors may feature abnormal structure, aberrant catalytic activity [41] and, at least among cholinesterases produced by brain tumors, differences in substrate specificity and susceptibility to inhibitors [35]. On the other hand, it is reported that the irreversible inhibition of cholinesterase by organophosphorous molecules increases tumorigenesis [41]. Accordingly, epidemiological studies found an increased risk and a higher developing rate of leukemias and brain tumors in the farmers, the group with the highest risk of occupational exposure to organophosphorous poisons [42]. However, it is important to note that common drugs used in the pharmacological treatment of AD are reversible inhibitors and no association with tumors has been reported as adverse effect.

Altogether, these observations about efficacy, duration and possible consequences of cholinesterase inhibition could exclude the involvement of the treatment itself in the decreased risk of cancer for AD patients. Consequently, there is the possibility that during the transition phase from MCI to AD some biological events take place, leading to the conversion towards AD and, at the same time, reducing the risk for cancer development, possibly acting on common regulatory genes or molecular pathways. Regarding cancer, on the contrary, there are several drug options commonly used to clinically treat this disease, each one with a different and specific molecular target according to the cancer type. Moreover, dealing with cancer survivors, the pharmacological treatment carried out was resolutive for the pathology. Therefore, the same remarks on drug treatment for the decreased risk of cancer for AD patients cannot be made for

the decreased risk of AD for patients with a history of cancer, as every case of tumor is pharmacologically treated in a tailored manner. Even if it cannot be excluded that the treatment itself has an effect on the different incidence of AD in patients survived to a cancer, the variety of treatments and molecular targets argues against this hypothesis. However, recent evidence highlights how anti-cancer drugs targeting mTOR have been found to play a role in mitigating the progression of AD and PD by reducing iron accumulation. This suggests the possibility that selective anti-cancer drugs may indeed have modulatory effects on the pathophysiology of AD and PD, and thus they may be used also as adjuvants in treating these neurodegenerative diseases [43]. Also, Frain et al. have shown in a subgroup of patients that selective cancer therapies may have a favorable outcome on AD incidence [44]. In addition, it has been recently observed that inhibition of the Src family kinase Fyn with saracatinib rescued impairments in synaptic density, learning and memory, and tau accumulation and led to a significant increase of hippocampal synaptic density in a mouse AD model and reversed memory deficits and synaptic loss in AD model mice [45]. Interestingly, Fyn kinase is involved in oligomeric Aβ-NMDA excitotoxicity [46]. However, a recent clinical trial on the effect of saracatinib on the metabolic decline in AD largely failed the primary outcome, indicating the need for further research [47]. A note should be added on the response to cancer therapy as a function of age. Indeed, it should be stressed that concerning cancer therapy, the average 5 years survival rates for common cancer subtypes in North America are 65-95% in pediatric patients and 14-56% in adults [48]. This difference between pediatric and adult cancer survival and the variability of the latter may reflect the fact that the age-associated changes in selected genes may intervene altering the survival when facing cancer cell invasion. Young organisms may have better resilience resources, but it is also tempting to speculate that genes at the crossroads between cancer and neurodegeneration may be involved. Indeed, one would expect that the derailment of the latter ones will be less involved at young ages.

Since the hypothesis that drug treatment may explain the existence of an inverse correlation between cancer and AD is not fully supported by the literature, it is plausible to hypothesize that the latter association relies on the interplay of common biological mechanisms, including common regulatory genes and pathways. This is exactly the target of the present review.

Molecular pathways

A growing body of epidemiological and scientific evidence points to the existence of shared pathways between neurodegeneration and oncogenesis. This led to the proposal of biological theories and mechanisms that may explain the inverse correlation between AD and cancer. There are four key and relevant theories (detailed below) which may be considered for enucleating this hypothesized association and each one takes into account processes evolving synchronously, even if in divergent directions, driving cancer or neurodegeneration, respectively [49].

Warburg effect theory

The Warburg Effect, commonly defined as the metabolic shifting from oxidative phosphorylation towards aerobic glycolysis that occurs in different types of tumors [50], is at the basis of a biological theory hypothesized to underlie the inverse epidemiological correlation between AD and cancer. Since the core of this theory focuses on an abnormal response of either proliferative or regenerative processes in cancer and brain cellular system respectively, the aberrant regenerative events in AD pathogenesis may be correlated with a Warburg-type bioenergetic metabolism. In this regard, since in AD the pathological accumulation of the abnormal cellular products beta-Amyloid (Aβ), hyperphosphorylated tau (p-tau) and proinflammatory cytokines causes degeneration at neuronal and synaptic level [51], AD itself can be considered a metabolic disease triggered by bioenergetic malfunction caused by the increasing effect of age-related impairments, like somatic mutations and oxidative damage. As a consequence, affected neurons may offset this imbalance by upregulating the oxidative metabolism, a process collectively called Inverse Warburg Effect [52]. Moreover, dysfunctional responses like glial proliferation, aberrant neuroplasticity and cell re-entry in mitosis – triggered by a biosynthetic brain cycle that supports an abnormal regenerative response and maintains itself exploiting tumorigenesis-associated biosynthetic resources– may increase neuronal and synaptic loss rate and neurotoxicity [53]. According to this theory, the biosynthetic resources are primarily shifted to support AD pathogenesis or cancer. In case of cancer disease, the unrestrained anabolic activity typical of tumorigenesis could divert the normal brain-prioritized dispensation of biosynthetic resources. This deprivation dampens the brain anabolism, including all the biosynthetic activities that sustain active excitotoxic neurodegeneration, thus possibly causing the time-shifting of AD development [54].

Although the increased cell anabolism, which drives and sustains unrestrained cell proliferation, is thought to hamper or at least cause a time-shift of AD onset [11, 52, 54, 55], further considerations on the Warburg Effect do not support this biological theory as the pivotal mechanism at the basis of the inverse correlation AD-cancer. As a matter of fact, not only not all tumors characterized by high proliferation

rates and upregulating aerobic glycolysis feature an undamaged oxidative phosphorylation [56], but also this same bioenergetic mechanism is essential for tumor progression in different cancer types [57]. Therefore, since not all tumors regulate their metabolic activities in the same way due to different bioenergetic demands, this theory may not encompass all the different cases considered and does not appear likely to explain the biological mechanism that possibly underlie this inverse association.

Two-Hit Hypothesis theory

According to the "Two-Hit Hypothesis", bioenergetic metabolic impairments due to oxidative stress and aberrant mitotic signaling are essential and promoting factors for cell cycle re-entry in neuronal cells and unrestrained cellular proliferation in cancer cell systems [52, 58–60]. In this regard, while the molecular pathways proposed to underlie this hypothesis are the effectively microtubule (MT) stabilization and mitosis for tumor cells, for neuronal cells an attempted completion of the cell cycle and a dysregulated MT stabilization, which possibly induce the generation of abortive neurons, have been suggested [59, 61, 62]. An attempted re-entry in the mitotic cell cycle has been reported in several occasions of neuronal death. There is evidence of cell cycle involvement in neuronal degeneration in adult organisms and, in AD brain cells, cell cycle-related proteins were found in neurons at risk of death [63–70]. Accordingly, unscheduled re-entry and block of the resolution of the cell cycle process lead to neuronal loss in AD [63, 64, 66, 68, 69], thus leading to nerve cell death due to genetic imbalance caused by genome aneuploidy [61]. It has been reported that in AD Aβ, the main constituent of amyloid plaques [71], may produce a proliferative signal – marked by the expression of protein involved in G1/S transition and DNA duplication – tolerated by astrocytes but not by neurons, that eventually results in neuronal cell death [72]. This was in line with previous data suggesting that cell cycle activation might precede neuronal cell death in AD [69] and that the activation of unscheduled cell cycle could be a common factor in different forms of neuronal apoptosis [72].

Metabolic Deregulation Hypothesis

The "Metabolic Deregulation Hypothesis" [53] suggests that the association between AD and cancer may find its genetic and molecular explanation in mutual and exclusive molecular pathways that drive a proliferative or a pro-apoptotic response [49]. According to this hypothesis, the main factors that play a role in the differential molecular regulation are aging, oxidative stress, DNA damage, mitochondrial dysfunction, sirtuin 1 (SIRT1) suppression and aberrant mitotic signaling [49, 73]. In this regard, the specific and inverse fine-tuning of the expression of a series of genes and the activation of the correlated molecular pathways, in particular p53, Peptidyl-prolyl *cis-trans* isomerase NIMA-interacting 1 (PIN1), Wnt (Wingless Int-1) and the ubiquitin-proteasome system (UPS), may be the pivotal determinants that lead to either the proliferation or the apoptosis pathways [74–76]. Accordingly, the same pathway that promotes an unrestrained cellular proliferation and possible metastasization also could exert a brain neuroprotection effect. Vice versa, the activation of anti-proliferative pathways could hinder neuronal cell cycle re-entry and mitosis and confer a neuroprotection effect.

Unfolded Protein Response theory

The fourth relevant theory relies on the deregulation of the Unfolded Protein Response (UPR) system [77], which could serve as a main biological target for both AD and cancer. This conserved cellular pathway is a protective biological mechanism induced while the cell faces cellular and endoplasmic reticulum (ER) stress. It ensures the maintenance of homeostasis by exerting an adaptative role in protein quality control and assures proper protein synthesis, folding and secretion [78]. Consequently, an undamaged UPR system is necessary for the proteolytic elimination of unfolded and damaged proteins as well as for the synthesis of new proteins. The UPR system is activated in different human disorders, including cancer and neurodegenerative disease [79, 80], and can exert opposite effects, mediating both cell survival by promoting anti-apoptotic pathways and cell death processes, depending on the nature, strength and duration of the source of cellular stress [81, 82]. According to this theory, in the brain cellular system, UPR pathway is relevant for the maintenance of the cellular homeostasis in case of an increased oxidative stress. A dysfunctional UPR system in brain cells causes impairment in the protein translation process, increase in Aβ oligomerization and neurotoxicity that ultimately can lead to neuronal death [77]. Concerning cancer, rapidly growing tumor cells face a variety of restraints for growth, ranging from external stressors like hypoxia, insufficient vascularization and glucose deprivation to internal stressors like oncogenes activation, genome instability and somatic mutation, that lead to an increased demand for ER pathways involved in protein homeostasis. As a matter of fact, cancer cells increase UPR system activity to subsist cellular stress and prevent cell death [83, 84] and several studies reported a prolonged and increased activation of ER stress genes in different types of solid tumors [85, 86].

Molecular players, the merging theory

Although the biological mechanisms proposed so far seem to encompass the different hallmarks and pathophysiology of both AD and cancer, these same hypotheses, if taken individually, appear unlikely satisfactory to explain the inverse correlation between these two diseases. On the contrary, a "merging hypothesis", according to which a subset of molecular players – notably, p53, Wnt, UPS and PIN1 – common to three of the biological theories here considered is involved in complex molecular interactions, is rather plausible.

p53, Wnt and UPS

p53 is a well-studied protein characterized by a short half-life and activated in response to a variety of stress sources like DNA damage, oncogenes activation and hypoxia. p53 protects the cell genome integrity [87, 88] by promoting the repair of potentially tumorigenic DNA damage [89] and the transcription of cell growth arrest factors [90], thus preventing the proliferation of damaged cells through apoptosis or cell senescence [91]. A mutated or inactivated p53, characterized by a loss of its function, is common in many human cancers [92], while its upregulation and enhanced activity in the brain have been associated with neurodegeneration in people with dementia [93–95]. Moreover, it has been suggested that a dysfunctional p53 in non-replicating cells could be involved in aberrant cell cycle progression [61]. Interestingly, while a loss-of-function of p53 is correlated with an increased carcinogenesis, specific gain-of-function alleles are associated with decreased cancer incidence concomitant with an accelerated aging [96], suggesting an involvement of p53 in pathways with opposite purposes. It has been reported that a conformationally altered p53 obtains novel transcriptional features [97, 98] and that conformational alterations of p53 are involved in cancer development [99], modulating a set of genes encoding for transcriptional modulators for its oncogenic activity [100–102]. Noteworthy, p53 has been suggested to have a crucial role in both aging and neurodegenerative disorders, including AD [103–108], as an increased rate in its activity is correlated with organism aging and senescence establishment [109, 110]. Moreover, in mice models, it has been demonstrated that p53 is required for both axonal outgrowth and regeneration [111, 112] and that the loss of wild-type p53 conformation could jeopardize the ability of the brain to restore new axonal connections after a toxic damage [113]. Accordingly, this "gain and loss of function" of p53 conformers scenario may correlate this pivotal molecular player with the "Two-Hit Hypothesis", as p53 functions appear to be involved in supervising the balance between cancer suppression and age-promoting processes [114]. Indeed, further evidence regarding p53 may also correlate this protein to the other two theories considered in this review.

Concerning the "Metabolic Deregulation Hypothesis", among the different factors that play a role in differentially regulating the same molecular mechanisms that may underlie the shared pathophysiology of both AD and cancer, aging, oxidative stress and SIRT1 suppression [49, 73] could be of central interest for this theory. In fact, it has been reported that high Reactive Oxygen Species (ROS) levels increases DNA damage, triggering a mutagenic process that can affect the structure and, hence, the function of proteins [115]. Thus, an impaired p53 activity due to ROS effects, which induce the oxidation of thiol into disulfides promoting p53 cross-linking and the formation of aggregates, can be attributed to alterations in its tertiary structure and may potentially be involved in cancer development [95, 116]. Moreover, a complex loop interaction between ROS, p53 and SIRT1 may also be considered, since it has been observed that while low ROS levels are associated with cell survival through antioxidant pathways induction, high levels of ROS act as apoptotic inducers [117], suggesting that both p53 and SIRT1 levels and their discontinuous activity may lead to different cellular arrangements by promoting different molecular pathways and cellular processes [118]. The role of SIRT1 appears even more prominent in the light of the complex network and downstream effects of the SIRT1-p53 regulatory axis. SIRT1 is a key epigenetic transcriptional regulator that in addition deacetylates p53 at the C-terminus on Lys382 in a NAD(+)-dependent manner [119], decreasing its transcriptional activity and the expression of its downstream targets. In this regard, SIRT1-p53 axis regulation has important effects on the somatic cells' arrangement relating to tissue regeneration and repair, since SIRT1 inhibits cell cycle arrest and p53-mediated apoptosis and concurrently enhances DNA repair, cell survival and proliferation [118]. This key role of SIRT1 in protecting and regulating the cell from stress-induced p53-dependent aging and senescence [120–122] is supported by the evidence that a genotoxic stress-promoted p53 stabilization through acetylation leads to its accumulation inside cells, promoting the transcription of $p21^{Cip1}$ (Cyclin-dependent kinase inhibitor 1), p53 regulated modulator of apoptosis (PUMA) and Bcl-2-associated X (Bax), which are molecular mediators involved in cell cycle arrest, senescence and apoptosis [123]. A persistently activated and sustained p53, possibly due to lack of SIRT1 activity and consequent increase of p53 acetylation, has been suggested to trigger senescence or apoptosis, promoting cell death and suppressing cancer risk [119]. Moreover, it has been observed that acetylation of p53 on Lys320 promotes neurite outgrowth through the regulation of expression of coronin 1b – an actin-binding

protein – and the Rab13 GTPase, that associates with the cytoskeleton [111]. Altogether, these observations may lead to the hypothesis that while in cancer an enhanced SIRT1 activity – due to lack of its inhibitors, such as the two proteins Hypermethylated In Cancer 1 (HIC1) and Deleted in Breast Cancer 1 (DBC1) – could promote cell survival and proliferation through p53 deacetylation, in neurodegeneration a lack of its activity and a consequent increase in acetylated p53 content may enhance aging and senescence.

Regarding the "Deregulated UPR System Theory", since p53 activity is pivotal in regulating pro- or anti-apoptotic pathways and UPR can mediate both cell survival and cell death processes [81, 82], UPR dysfunctional activity on p53 regulation through UPS may have different outcomes, possibly leading to either cancer or neurodegeneration development. Concerning AD, in brain cells protein translation impairments and increased Aβ oligomerization due to a dysfunctional UPR system – which is then not able to remove this protein excess – have been observed [77]. In addition, higher p53 expression in the brain tissue of AD patients [124, 125] and, more precisely, around Aβ senile plaques [126] have also been reported. In this regard, the modulation of amyloidogenic vs non-amyloidogenic pathway and the parallel UPR System activity may have a prominent role in AD development. Concerning the non-amyloidogenic pathway, an increase in APP intracellular C-terminal domain (AICD), derived from Amyloid Precursor Protein (APP) processing has been found to stimulate the expression of functional p53 [127, 128], which is then able to exert its activity. On the contrary, Aβ, one of the products of the amyloidogenic pathway, has been related to the activation of a molecular pathway that involves homeodomain-interacting protein kinase 2 (HIPK2), Zyxin (an adapter protein involved in HIPK2 regulation) and p53 in an altered conformation [129]. In particular, Aβ 1-40 and 1-42 can induce Zyxin deregulation, affecting HIPK2 transcriptional repressor activity on metallothionein 2 A (MT2A) promoter, in turn able to alter MT2A production, that induce an altered conformational state of p53, which is no longer able to activate its canonic genes. Consequently, no responses to cellular damage take place, suggesting the accumulation of dysfunctional neurons [129]. Accordingly, in this scenario a dysfunctional UPR System may have a key role in the deregulated clearance of both Aβ and altered p53. Interestingly, in another neurodegenerative disorder, i.e., Huntington disease, the expression of the mutant huntingtin causes DNA damage, leading to p53 phosphorylation on Ser46 by HIPK2, and promotes PIN1 interaction with p53 (see below) [130].

Regarding cancer, ER pathways involved in protein regulation are required in order to sustain the uncontrolled proliferation and, at the same time, to face growth restraints such as hypoxia and genome instability. However, the correlation between UPR System and p53 in cancer does not appear as strict as in AD. In fact, while in AD a dysfunctional UPR, concomitant to Zyxin-HIPK2-p53 pathway deregulation, may be hypothesized to participate to the molecular basis of the pathology, in cancer cells p53 conformers are intrinsically different and insensitive to UPR System activity, which eventually is increased [83, 84]. As a matter of fact, the impaired ubiquitination of conformationally altered p53 – due to either sequence mutation or other tertiary structure changes – stabilizes p53 and prolongs its half-life due to inefficient degradation through E3 ubiquitin-protein ligase Mouse Double Minute 2 homolog (MDM2), which is a direct transcriptional target of p53 [99]. According to this, in cancer disease rather than a dysregulated UPR System – which is, in fact, upregulated – a loss of p53 wildtype structure impairs its UPS-mediated regulation, which may explain UPR System involvement in this pathology.

Although different aspects of p53 activity may correlate with all three biological theories here discussed and considered, it is possible that it can serve as a disease marker rather than the pivotal molecular player that underlies the inverse relationship between cancer and AD. This observation is further supported by recent data showing the development of different approaches useful to detect the different p53 conformations aimed to implement devices for clinical practice [131, 132]. p53 involvement in both diseases rather appears to localize downstream to or as a consequence of the aberrant activation of other proteins, which in turn may be the molecular players that are actually able to explain this inverse co-morbid condition. As an example, p53 is functionally regulated by PIN1 [133, 134]. Upon DNA damage and expression of p53-activating oncogenes, p53 is specifically phosphorylated on Ser33, Thr81 and Ser315 allowing PIN1 to interact with p53 and to catalyze conformational changes in its structure in order to enhance its DNA-binding activity and transactivation function [133, 134]. In addition, these structural changes allow additional modifications, influencing p53 ability to interact with other proteins, which in turn promote p53 full stabilization and activation. Notably, upon DNA damage, PIN1-deficient cells not only lack p53 activation and timely accumulation, but also show a misfunctioning checkpoint control after DNA damage [134]. Moreover, PIN1 has also been shown to regulate p53 pro-apoptotic and mitochondrial functions [135]. Indeed, upon facing intense cellular stress, HIPK2 phosphorylates p53 on Ser46, allowing its interaction with PIN1, which in turn stimulates p53 mitochondrial localization by promoting its monoubiquitination [135]. In addition, PIN1 binding to p53 facilitates its dissociation from MDM2 and apoptosis inhibitor iASPP (inhibitory member of the ASPP family), thus enabling p53 transcription-independent apoptotic activity [130, 136].

Cytoplasmic p53 then translocates on the outer mitochondrial membrane to interact with Bcl-2 (B-cell lymphoma 2), Bcl-XL (B-cell lymphoma-extra large) and Bak (Bcl-2 homologous antagonist/killer) – members of the Bcl family of mitochondrial permeability regulators – and either inhibit or activate them, thus triggering waves of mitochondrial outer membrane permeabilization (MOMP) and apoptosis before p53 transcription-dependent activity [137].

On the basis of these observations, we focused our attention on PIN1, since UPS and Wnt seem to be involved in a more downstream position in the central cellular pathways converging on cancer and neurodegeneration.

PIN1

PIN1 is a peptidyl-prolyl *cis-trans* isomerase (PPIase) that catalyzes the *cis-trans* isomerization of specific pSer/Thr-Pro motifs undergoing a Pro-directed phosphorylation and regulates the conformation of different protein substrates after phosphorylation, adding another layer of protein function control [138–140]. Due to its catalytic features and its involvement in different central molecular mechanisms, such as cell cycle, transcription, splicing regulation and maintenance of protein folding [141], PIN1 is now considered a new molecular timer capable of modulating a variety of targets in different cellular processes, being able to control duration and amplitude of cellular responses [141]. PIN1 expression appears to be correlated with cell proliferative capacity, as it displays very low expression in non-proliferating cells while it is over-expressed in most human cancers, including lung, prostate, breast, colon [142] and brain [143]. In cancer, different post-translational modifications (PTMs), including dephosphorylation [144], phosphorylation [145] and desumoylation [146], activate PIN1. Furthermore, a variety of oncogenes promotes oncogenesis by increasing PIN1 production, which is then able to activate and amplify other tumor promoting pathways. On the other hand, PIN1 activity and oncogenic function are suppressed by tumor suppressors BRCA1 (Breast cancer type 1 susceptibility protein) [147] and DAPK1 (Death-associated protein kinase 1) [144]. DAPK1 is also linked to Notch signaling and it has been found that PIN1 is upregulated by Notch1 and Notch4 membrane-bound receptors in breast cancer [148, 149]. Notch receptors undergo a ligand-induced cleavage – firstly, by an extracellular metalloprotease and, secondly, by γ-secretase – that releases their Notch intracytoplasmatic domain (NICD), which then exerts its transcriptional activity in the nucleus [150, 151]. These receptors have been found deregulated in different carcinomas, including breast cancer. PIN1 interacts with Notch1, strengthening its cleavage by γ-secretase thus increasing NICD release and Notch1 transcriptional and carcinogenic activity [148]. In addition, Notch1 can directly induce PIN1 transcription, thus producing and establishing a molecular circuitry that may lead to PIN1 overexpression in a variety of cancer types, exerting a pivotal role in tumorigenesis and cancer progression [148]. Indeed, PIN1 and Notch1 are known as mediators of chemoresistance [152–154], since Notch1 is known to promote the expression of drug efflux transporter genes and cell survival genes [153, 155], suggesting that PIN1 and Notch1 altered regulation and expression in carcinomas promote tumor progression by fostering cancer stem cells (CSCs) self-renewal [149]. Noteworthy, several Notch1 targets – including cyclin D1, NF-κB and Survivin – were found to be also PIN1 substrates [156, 157].

Concerning the "Two-Hit Hypothesis", PIN1 exerts a dual role in cell cycle regulation, as it promotes G1/S transition by increasing Cyclin D1 expression and stabilization and, in S phase, it coordinates DNA synthesis and centrosome duplication [158, 159]. In this regard, PIN1 over-expression promotes not only oncogenesis by advancing central signaling pathways that increase Cyclin D1 expression, but also the production of an excess of centrosomes, thus leading to genomic instability [160–162]. Therefore, PIN1 has been suggested to be strictly regulated in cells with mitotic potential. On the other hand, in neurons, PIN1 has been found to be highly expressed in the first steps of neuronal differentiation, possibly indicating a diverse role in post-mitotic cells [163, 164]. In this regard, it has been shown that β-catenin is one of the major PIN1 substrates in neural progenitor cells (NPCs), suggesting its role in a post-phosphorylation signaling mechanism in regulating neuronal differentiation. Indeed, PIN1 appears as an important regulator of NPC differentiation due to its stabilizing activity on β-catenin. In fact, PIN1, through the Wnt/β-catenin molecular pathway, can promote NPCs proliferation and induce neuronal differentiation at early and late developmental stages respectively [165].

In contrast to cancer, PIN1 is inhibited in AD through downregulation [164], oxidation [166], phosphorylation [162] and sequestration [140]. Regarding the "Metabolic Deregulation Hypothesis", oxidized and inactivated PIN1 has been found in the hippocampus of MCI and AD patients [166–168], suggesting its role in the early response to oxidative stress. PIN1 has also been involved in limiting oxidative damage by negatively regulating CDK inhibitor $p27^{Kip1}$ (Cyclin-dependent kinase inhibitor 1B) through binding to FOXO4 (Forkhead box protein O4), a protein involved in mitochondrial and oxidative stress response and regulated by SIRT1-mediated deacetylation/acetylation cycle [169].

PIN1 may be identified as a novel key regulator preserving cellular integrity during aging. PIN-knockout mice display a series of premature aging-related hallmarks, including

AD-like feature – characterized by hyper-phosphorylated tau, neurodegeneration, pathogenic processing of APP and Aβ accumulation – osteoporosis and accelerated telomere shortening [161, 164, 170–172]. Interestingly, the same mice are resistant to breast cancer induced by oncogene Ras or Neu over-expression [173], reinforcing the idea of Pin at the crossroad between cancer and neurodegeneration. Regarding telomere maintenance, PIN1 can convert the telomeric binding protein TRF1 (Telomeric Repeat Factor 1) *cis*-conformation, which is stable and inhibits telomere elongation, to the TRF1 *trans*-conformation, susceptible to UPS-mediated degradation, thus allowing telomere elongation [174]. Concerning p53-PIN1 relationship, PIN1 enshrines p53 ability to respond to DNA damage by preventing its UPS-mediated degradation and by enhancing its DNA-binding ability to its targets [136, 175].

Noteworthy, PIN1 regulates central neuronal proteins like tau, APP, myeloid cell leukemia sequence-1 (MCL-1) and gephyrin [170, 176, 177]. PIN1 over-expression promotes oncogenesis by affecting several proteins, among which notably increasing levels of both functional tau and APP. Due to tau stabilizing activity on MTs required for the mitotic process, tau over-expression correlates with less sensitivity to taxane – a class of drugs that promote disruption of MT function [178] – and poor prognosis particularly in breast and ovarian cancer [179]. While normal APP function is suggested to promote developing neurons growth [180], its abnormal expression is correlated to a subset of cancer types, notably lung, breast, colon, prostate and pancreas [181]. It is important to note that *trans*-conformations of tau and APP are functional and "healthy", thus promoting their normal functions, while *cis*-conformations, usually triggered after phosphorylation, are pathogenic. In this regard, *cis*-phospho tau has been found to be resistant to binding to microtubules, protein phosphatases and degradation. By catalyzing the isomerization from *cis* to *trans* conformation, Pin1 facilitates tau binding to microtubules thus restoring its normal function. Concerning APP, the *cis* conformation represents the amyloidogenic APP processing. When Pin 1 catalyzes the isomerization from *cis* to *trans* conformation, a reduction in Aβ 1-42 levels and an increased release of soluble APP alpha have been observed. In addition, it has been revealed that in MCI and AD hyperphosphorylated *cis*-tau is the early pathologic species [182] and PIN1 activity may prevent this isomerization. Concerning the "Deregulated UPR System Theory", tau *cis*-conformation not only loses normal binding and MT assembly-promoting function, but also becomes resistant to degradation and dephosphorylation and prone to form aggregates, ultimately leading to cell structure destabilization and eventually cell death [183]. In addition, PIN1-mediated tau regulation is also exerted through GSK3 (Glycogen synthase kinase 3) inhibition, 3since when PIN1 function is inhibited GSK3 is hyperactivated, leading to tau hyperphosphorylation [184]. PIN1 binds specifically the phosphorylated Thr668-Pro motif on APP, accelerating its *cis*-to-*trans* isomerization that keeps APP in the plasma membrane, favoring the non-amyloidogenic pathway, preventing its accumulation and increasing its turnover [184]. Conversely, in the absence of PIN1-mediated reversion to APP *trans*-conformation, phosphorylated APP *cis*-conformation not only is resistant to UPS-mediated degradation, leading to its accumulation [184], but also internalizes in endosomes and is processed through the amyloidogenic pathway, which ultimately release Aβ [183]. Altogether, these data suggest that PIN1 may have a pivotal housekeeping role in maintaining tau, APP and other proteins in their healthy and functional conformation. This is supported by the evidence that in neurodegeneration the activity of GSK3 and CDK5, which phosphorylate tau, is upregulated [184, 185] and that PIN1 appears to colocalize with insoluble tau aggregates. Moreover, data collected from MCI and AD brain specimens have revealed a very low PIN1 expression, further suggesting its protective role against hyperphosphorylated tau [140].

Besides these molecular mechanisms, polymorphisms in PIN1 promoter have been recently reported and they correlate with PIN1 dysfunction. Polymorphism rs2287839, located in the consensus binding motif for the transcription factor AP4 (Activating Enhancer Binding Protein 4), is correlated with an increased PIN1 expression as it suppresses AP4 ability to bind and repress PIN1 promoter activity. This polymorphism is associated with a 3-year delay of sporadic AD age of onset, suggesting a PIN1 neuroprotective activity [184]. Conversely, functional polymorphism rs2233678 is related to a reduced PIN1 expression and associated with a decreased risk of multiple cancers due to an attenuated transcriptional activity [186], suggesting PIN1 cancer-promoting activity. These observations may be considered a part of an emerging iCAP (inverse Cancer-Alzheimer relationship through PIN1) hypothesis (Fig. 1) and may have implications for therapy. For example, due to the impact of PIN1 deregulation on the development of a variety of diseases, including cancer and AD [143, 187], its drug targeting may offer new therapeutic strategies. In fact, based on available data, PIN1 inhibition may be pivotal to effectively suppress oncogenesis. The possibility to selectively target PIN1-hypothesized deficits in AD is still largely unexplored. In both cases it will be important to contrast PIN1 alterations in the pathological tissue without altering its equilibrium in the other tissues.

Our view is further strengthened by data published by Sherzay et al. [188], who were able to establish the inverse relationship between cancer and AD based on a nationally representative database. Moreover, the authors observed that cancer types overexpressing Pin1 (prostate, lung,

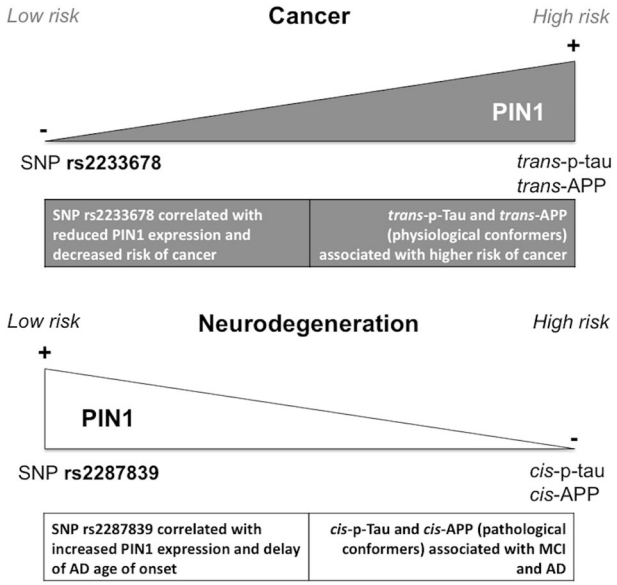

Fig. 1 Emerging role of PIN1 as culprit governing the inverse relationship between cancer and Alzheimer's disease (iCAP – inverse Cancer-Alzheimer correlation through PIN1- hypothesis). When PIN1 activity is prevailing, the system favors the proliferation processes and, in neuronal progenitor cells, the differentiation acting upon microtubule assembly, cell cycle regulation, the Wnt/β-catenin system and p53 sustained cell survival. In the case of PIN1 failure the system favors cell degeneration and removal because of unsupported survival activities and accumulation of pathogenic protein conformers (abbreviations used as follows:"*trans*-p-tau" for *trans*-conformation hyperphosphorylated tau; "*trans*-APP" for *trans*-conformation APP; "*cis*-p-tau" for *cis*-conformation hyperphosphorylated tau; "*cis*-APP" for *cis*-conformation APP).

ovarian) were those associated with the lowest prevalence of AD diagnosis, making Pin1 an interesting potential target for further investigation.

Conclusions

The analyzed literature suggests some relevant points to be considered encompassing the fields of aging, neurodegenerative diseases and cancer. In particular, it appears that:

- In some cases, the biological trajectory of an individual organism may take one of two alternative pathways toward a neurodegenerative disease or cancer.
- The crossroad point is set at an advanced age; therefore, it can be hypothesized an age-associated deregulation of a control mechanism.
- These events occur at systemic level but with distinct effects in periphery and in brain. Accordingly, specific organ characteristics should play a role.

The choice is, sadly, between two deadly and frightening end of life paths, even if more and more patients survive cancer as the examined literature documents. Moreover, epidemiology data indicate that in the case of centenarians there is a third "winning" possibility: to live up to the end of life maintaining the ability to buffer the full expression of the cancerous or dementing diseases. Indeed, decreased cancer prevalence, mortality and cancer-related deaths are reported in very advanced age groups (reviewed in [189]). Incidence of most cancers, cancer prevalence and tumor spreading increase with age until age 80, whereas decrease thereafter and tend toward zero among centenarians [190]. In addition, metastasis formation is less frequent in non-agenarians and centenarians [191], suggesting that in the oldest old cancer displays a less aggressive behavior, characterized by a slower growth rate and a reduced life-threatening potential. Notably, not only a high rate of clinically undetected cancers in the oldest old – mostly due to low diagnostic accuracy – is reported, but also double or triple cancers have been found in almost 8% after age 90 [191–195]. Although frequencies of disease-associated genetic variants are similar in centenarians and in the general population [196, 197], the former group tends to avoid, delay or offset the phenotype of the gene/age-related pathologies [198]. Ganz et al. [199] reported that the centenarian cohort included in their study revealed, at different extents, some disease-associated neuropathological hallmarks – including Aβ and Tau pathology – not associated with consistent cognitive impairment, indicating that AD-like neuropathology may not be inevitable in the oldest old [200]. This suggests that the extreme old population may exhibit the existence of offsetting mechanisms that play a role in escaping the full expression of a variety of gene/age-related pathologies [201]. Even though environment and lifestyle have a strong influence on both lifespan and healthspan, these traits appear to have a certain degree of heritability. In fact, it has been reported that heritability of age of death in adults is about 25% [202] and that offspring of centenarian parents display lower prevalence of age-related diseases [203]. In this regard, several linkage and gene association studies have been performed to investigate quantitative trait loci (QTLs), single-nucleotide polymorphisms (SNPs), gene variants and epigenetic modifications that could be linked to healthy aging. Concerning epigenetics, as an example, a mechanistic view provided by the LEARn (epigenome-based latent early-life associated regulation) model suggests an interactive influence of gene and environment in the determination of sporadic disorders [204]. Following this model, a *sequela* of multiple hits may affect biochemical pathways thus gradually changing a normal healthy state in a dysfunctional one. Furthermore, it has been hypothesized a mechanism buffering disease risk variants [205] and consequently not expressing the full potential of the disease [206]. These observations may provide some cues in the chase of gene targets for

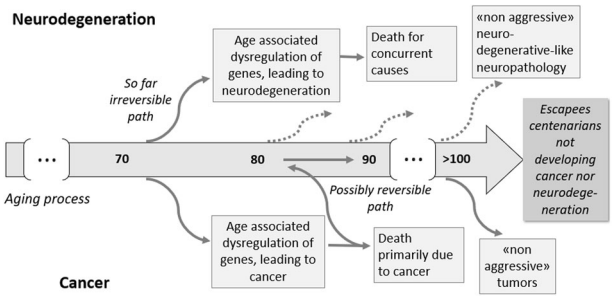

Fig. 2 Hypothesis on the age-related diverging derailment of pathways at the crossroads between cancer and neurodegeneration. The figure illustrates the hypothesis of age-associated derailments of pathways that may lead either to cancer or to neurodegeneration. So far, it appears that once the derailment has taken place in either direction that pathway cannot derail towards the other one. There is an important difference: the pathway leading to neurodegeneration is irreversible, the patient will be less prone to develop cancer (or at least certain types of cancer) but at the cost of a devastating neurodegenerative disease for which, at the moment, there is no cure. On the other hand, the pathway leading to cancer is amenable to treatment and cure, and in the survivors the opposite derailment towards neurodegeneration seems to be permanently inhibited. A possible example of one of such pathways is that linked to PIN1 (see text for details). Such perhaps over simplistic hypothesis raises several questions amenable to research. Few examples: What is the critical age at which these events occur? Considering the most common age of onset of AD one would speculate on a decade between 70 and 80. The assumption of an inverse association with cancer is true only for AD, for every neurodegenerative disease or for late onset subgroup/diseases? Accordingly, early onset and familial cases with well described genetic causes of neurodegenerative diseases should not display the described inverse relationship with cancer. A survivor of a cancer at young age will still be "protected" against neurodegeneration while he/she ages? What is the regulation of the candidate genes involved in the mutually exclusive pathways in very old people escaping both neurodegenerative diseases and cancer?

molecules useful to prevent diseases while aging. Therefore, if the theories here discussed have a biological plausibility, in a significant number of cases cancer and AD are mutually exclusive, but also there is the possibility of maintaining the equilibrium, not derailing towards one of the two (Fig. 2).

Accordingly, further and more detailed studies of these biological pathways may offer new therapeutic strategies aimed at maintaining such an equilibrium. In the case of dementias, in particular of Alzheimer's disease, new biological markers and targets based on the discussed players can be developed based on a theoretical approach relying on different grounds compared to the past. An unbiased expansion of the rationale and of the targets may help to achieve in the field of neurodegenerative dementias similar advances as those attained in the case of cancer treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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