Advances in Cancer Biology - Metastasis 4 (2022) 100034

Contents lists available at ScienceDirect

Advances in Cancer Biology - Metastasis

journal homepage: www.journals.elsevier.com/advances-in-cancer-biology-metastasis

The cause of cancer: The unifying theory

Marie-Ange Majérus

Freelance Cell Biologist, Lunimam, Amsterdam, 1082MC, the Netherlands

ARTICLE INFO

Keywords:
Cancer cells
Mitochondria
iMM reprogramming
Oxidative phosphorylation
ANT1

ABSTRACT

Nowadays, still, the exact etiology of cancer remains to be uncovered. The understanding that cancer results from uncontrolled proliferation of cells does not provide a solution to curing cancer. Although several irreconciliable theories on the cause of cancer have been proposed, none explain the overall complexity of the disease. Yet, there is the remarkable discovery that the Egg Cell's Genetic Program (ECGP) has the potentiel to produce cancer. Based on this first and only experimental model created in the mid-20th century where cancer can be observed *in statu nascendi*, I hypothesized that cancer arises from a cell reprogrammed with the ECGP as a plausible model that brings together all the pieces of the cancer puzzle.

Today, the experimental production of induced Pluripotent Stem Cells (iPSC's) and their differentiated derivatives, together with their risk of cancer formation validated this theory.

This is of prime importance as it opens a non-existing line of research with high potential for the fight against cancer. We can transpose the knowledge of the ECGP to facilitate the study of a selective treatment for cancer. Instead of basing therapeutic strategies on the fate of cancer cells, we should consider the potential of the ECGP to produce cancer as the key factor to devise an effective therapeutic strategy that selectively targets cancer cells. I then propose a non-toxic metabolic approach to treating cancer which, instead of killing cancer cells, gives them respiration.

1. Background

Cancer is a complex biological phenomenon with more than a hundred types, depending on the original site of proliferation and cell type. Regardless of the type of cancer, it is recognized that all cancers follow the same principles regarding its genesis and its development. Cancerous cells are defined by two dogmas that postulate that they ignore the signals and mechanisms that normally control cell proliferation and death and they are also able to escape the immune system leading to this aberrant, complex, and efficient autonomous cell proliferation, known as cancer. This is the model which has been used to describe cancer since the 1970s, even though research has shown that these dogmas are not true (Fig. 1). Therefore, the 2 main issues in our understanding of cancer are:

1. When a spontaneous cancer is clinically detected, we can only focus on the abnormal cellular characteristics rather than on the causal mechanism. When diagnosing cancer, it is very difficult to identify precisely which anomaly or which mutation within a cell can produce such a biological complex phenomenon.
2. Furthermore, by the absence of *in vivo* models where cancer is initiated from a normal cell, cancer retains all its mystery as to its genesis.

The complexity of cancer biology is also reflected in the multiple theories attempting to explain its origin and development.

The Somatic Mutation Theory (SMT) [11,56,57,108] explains that cancer occurs due to the accumulation of a series of mutations within oncogenes or tumor suppressor genes resulting in increased proliferation and decreased cell death. If modern molecular biology has documented the many defects of cancer cells, it is hard to imagine that this model of cancer evolution, simply through the accumulation of mutations in both oncogenes and tumor suppressor genes, can explain the systematic and predictable behavior of cancer cells and the hallmarks of cancer [14,79,134].

Other alternative models, given below, explain cancer based on the various defective normal processes that underlie cancer.

The Tissue Organization Field Theory (TOFT) considers that proliferation is the default state of all cells and carcinogenesis is a disease of tissue organization comparable to organogenesis [135].

The Atavistic Theory of Cancer (ATC) postulates that the hallmark capabilities of cancer pre-exist in normal human cells. They represent a

E-mail address: lunimam944@gmail.com.

https://doi.org/10.1016/j.adcanc.2022.100034
Received 12 January 2022; Received in revised form 21 February 2022; Accepted 21 February 2022
Available online 25 February 2022

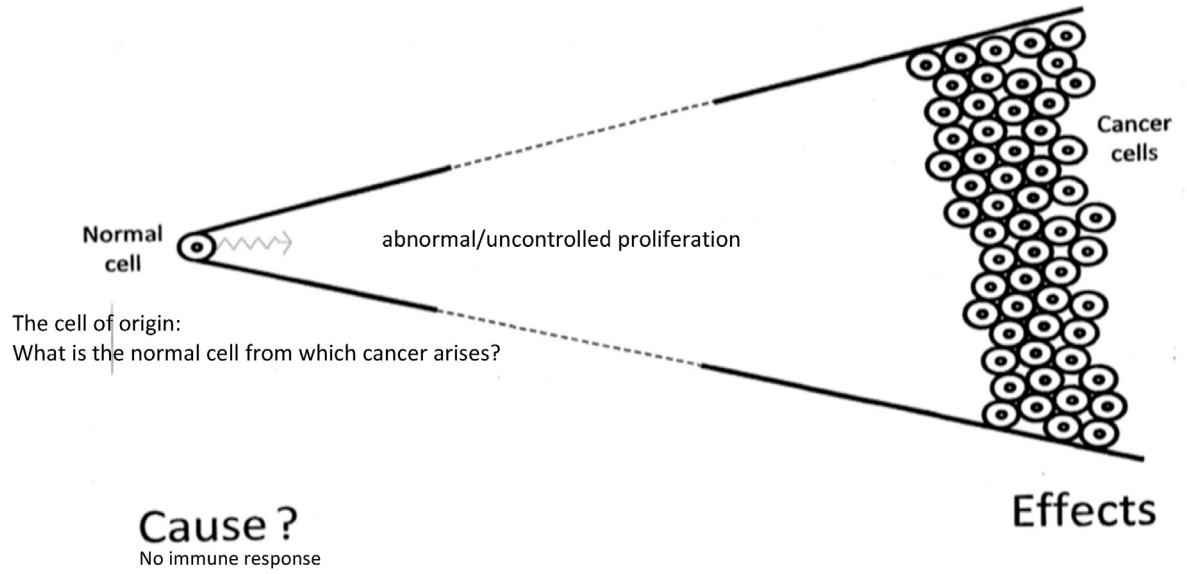

Fig. 1. Cancer defined by 2 dogmas:
1st dogma
cancer cells no longer respond to the mechanisms that regulate cell proliferation. Contrary to the 1st dogma, cancer cells are susceptible to the action of rigorous regulations and can participate in normal embryogenesis [12,65,100,112].
- 2nd dogma: when cancer cells escape the immunological surveillance, a cancer develops. Contrary to the 2nd dogma, cancer cells are protected by our immune system [33] and « in contrast to our expectations, the immune system seems to foster teratocarcinogenesis and to promote the proliferation of undifferentiated cells » [31,133].

reversion to an ancient program of survival (cell versus organism) triggered by mutations, a reactivation of an ancient genetic toolkit of pre-programmed behaviors [34].

The Cancer Stem Cell Theory defined a Cancer Stem Cell (CSC) as a tumor-initiating cell that possesses stem-like characteristics: the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor. It suggests that cancer initiates from tissue stem, progenitor or dedifferentiated cells that acquired tumor-initiating mutations [128].

Work by Otto Warburg claimed that tumor cells have an altered energy metabolism on its fundamental statement that insufficient respiration is responsible for aerobic fermentation and the origin of cancer [161]. Based on this work, cancer is reconsidered as a metabolism disease in which mitochondria play a key role in tumorigenesis and cancer [3,129].

Even if these theories, based on the most fundamental and significant properties of cancer cells, are fundamentally different, they are not mutually exclusive. I propose a plausible unifying model which integrates all the pieces of the cancer puzzle based on a forgotten discovery and in light of the most recent biotechnological advances.

2. Cancer viewed as a reprogrammed cell with the ECGP

Throughout cancer research studies, cancer cells have repeatedly been compared to embryonic stem cells to describe their growth and phenotypes. It is the ambiguous status of embryonic stem cells argued by A.H.Maehle as representing common heritage and normal development as well as potential sources of cancer [90]. The hypothesis that cancer originates from a small population of embryonic cells dates to the 19th century, with the embryonal rest theory of Cohnheim, suggesting that cancers arise from the activation of dormant embryonic stem cells present throughout the human body [90]. In the 20th century, Stevens and Pierce provided solid evidence to support Cohnheim's theory. By transplanting mouse embryos (ranging from zygote to preterm fetus) to extrauterine sites, they could experimentally induce benign teratoma cancers whereas only early embryos could induce malignant teratoma cancers (teratocarcinomas), similar to the corresponding spontaneous forms. Grafting embryos were used to identify the population of cells, e.g., malignant undifferentiated cells that initiate teratomas [115,136,137]. Futhermore, direct evidence was provided that teratomas developed in the ovaries arise from oocytes that develop parthenogenetically [138]. With the insights of these investigations on teratomas, these malignant undifferentiated cells are now regarded as essentially normal early embryonic cells which retain their undifferentiated embryonic phenotype, with the peculiar property of being able to differentiate following the normal pathways of development. Furthermore, in mice, the same malignant undifferentiated cells (teratocarcinoma cells) that produced teratomas in the experimental setting of the teratoma model created by Stevens, when placed back into the developing blastocyst, integrate into the embryo and take part in the normal development of the whole mouse as a chimera contributing to the formation of all tissues [100]. This reversion to normalcy demonstrates the functional normality of these cells and illustrates the progression of the autonomous ECGP program that develops in these cells.

Based on the first *in vivo* model initiated from normal cells where we can observe a cancer *in statu nascendi*, e.g., aberrant teratoma cancer growths that originate from a group of normal embryonic cells developing the autonomous ECGP, I hypothesized that cancer originates from a cell reprogrammed with the ECGP [93]. By showing the ECGP has the potential to produce cancer, under permissive conditions, the teratoma model identifies a normal biological event as the causal mechanism of cancer. That ECGP development takes place is what is most remarkable about this model. Instead of aborting, the grafted embryo disorganizes and permissive conditions exist enabling the autonomous proliferation and development of embryonic stem cells resulting in this aberrant efficient complex growth known as cancer.

The ECGP contains in its repertoire everything that a cancer cell can be (Table 1). In summary, a cell reprogrammed with the ECGP supports:

- Firstly, that cancer cells manage to escape immunological control and develop as the mechanisms at work to induce the immunotolerance that protects the egg and the embryonic cells [47] are similar to those

Table 1
ECGP potential to produce cancer. How the pathogenesis of cancer governed by the ECGP is representative of the complex cancer biology.

1. Teratoma model: the possibility for the 1st and only time of observing a cancer *in statu nascendi* initiated from normal cells: -The ECGP program has the potential to produce cancer -There are only 2 types of cells capable to transfer cancer after injection into an adult host: malignant undifferentiated cancer cells, embryonic and induced pluripotent stem cells. -The site of embryo graft influences the pattern of differentiation and growth. -With time, on successive transplant generations, there is a selection for cells with rapid growth with restricted developmental capacities. - similarities of immunotolerance between cancer and embryo	6. Cancer is a proliferation of cells, which, at any time during its progression, acquire dangerous biological properties for the host: to self-renew, to proliferate without limits, different rates of cell division, to resist growth inhibitory signals, to evade apoptosis (resistance to death), to undergo angiogenesis, to metastasize (new adhesive properties of their cell membranes that determine their capacity to migrate), biochemical activity (harmful secretion of metabolites lethal to the host). The ECGP program contains all the different orderly sequences, all the mechanistic processes to provide cells with all these new biological capabilities (autonomous proliferation, resistance, vascularization …) during normal embryo development.
2. Different factors can condition the transformation of a normal cell into a cancer cell during any cell's aggression: physical (radiations), chemical, viral, bacterial … The ECGP program is launched the normal way by fertilization and can also be activated by different means: experimental parthenogenesis	**7.** Cancers are commonly classified as benign or malignant. This is the same ECGP program which gives rise, out of context, to cells fates to contribute to benign cancers (teratoma) or cells fates to contribute to malignant cancers (teratocarcinoma) It has been shown that embryonic and metastatic cells share several properties.: - the requirement of a specific microenvironment to support growth. -The use of specific fetal pathways for migration to target sites -Enhanced resistance to cell death -Increased capacity for drug resistance
3. The development of cancer is autonomous, independent of the normal processes in the body The ECGP program has cellular regulatory circuits operating on a cell-autonomous basis to produce the autonomous proliferation of embryonic cells.	**8.** Cancers contain heterogeneous cell populations with diverse biological characteristics, capabilities and various degrees of differentiation and growth. The ECGP program is a source of efficiency, complexity, and heterogeneity as soon as the egg cleaves which gives rise to differences between the successive generation of blastomeres (cells fixed in position or migrating with the production of non-adhesive membranes in coupling with continued cell division)
4. Cancer, whatever the factor conditioning the transformation of a normal cell into a cancer cell, is always an autonomous proliferation of cells. The 1st manifestation of the ECGP program is a succession of DNA synthesis and mitoses to produce an autonomous proliferation of embryonic cells.	**9.** Occasionally, cancers exhibit a remarkable and rare phenomenon *in vivo* known as spontaneous regression. Apoptosis might be involved in mediating spontaneous regression. The ECGP program contains sequences of cell differentiation during embryonic development leading to cell death too: the programming for cell death, essential for normal morphogenesis of the embryo, occurs and plays a fundamental role as early as the formation of the proamniotic cavity in the mammalian embryo (post-implantation)
5. Cancer is an autonomous proliferation of cells which is progressive, purposeless (with individual cells exhibiting functions but with no purpose), regardless of surrounding tissue, not related to the needs of the body, producing unneeded cells, parasitic (cancer draws its nourishment from the body while contributing nothing to its function, it induces the body to provide a blood supply and in the case of epithelial cancer, a supporting stroma …) The ECGP program is an autonomous proliferation of cells which is progressive, regardless of surrounding tissue, not related to the needs of the body, parasitic, induces a blood supply …	**10.** All these properties acquired by the cancer cells are attributed to an aberrant programming of gene function but rather than genes coding for cancer per se, it is a gene activity programmed by epigenetic changes to produce the cancer pattern (turning on/off genes, modulating synthesis …) The epigenetic modifications associated with differentiation play an important role during normal embryo development by regulating gene expression (activating or silencing genes …): in the ECGP program, the gene-specific methylation patterns are established by epigenetic changes in early embryo by a process that involves genome-wide demethylation in the morula stage and methylation in the pre-gastrula stage.

that induce an active immunotolerance that protects cancer cells at the stage of cancer emergence [33,93].
- the fundamental characteristics of cancer cells that can vary quantitatively and exist in many different combinations. In particular, the rate of cell division, the adhesive properties of the cell membrane that determine the capacity of the cell to migrate or metastasize and specific patterns of cellular metabolism (Fig. 2).

The aberrant metabolism of cancer cells is often attributed to their dependence on glycolysis to produce their energy, even in the presence of oxygen. However, what Otto Warburg has shown is that this glycolytic contribution never exceeded 50% meaning that cancer cells can also get up to 50% of energy from respiration [114]. Beyond the variation of the percentage of energy obtained from glycolysis/respiration, due to the high metabolic diversity of cancer cells [32,50,75,101,144], we can infer from Warburg's finding that 2 mitochondrial populations co-exist within cancer cells, one immature, one mature. These 2 mitochondrial populations are at the origin of metabolic heterogeneity, variability and plasticity of cancer cells and contribute to their adaptation to local hypoxic conditions like within embryonic cells during embryogenesis, where one abundant population of immature mitochondria regulates anaerobic metabolism and a reduced population of mitochondria contributes efficiently to aerobic metabolism [39,97,148,172]. Such mitochondrial heterogeneity and metabolic variations are well illustrated when we follow the structural and functional journey of mitochondria during development [8,99,105]. It shows that mitochondrial activity is important for embryonic development and embryo survival [36], as well as the importance of two mitochondrial subpopulations contributing to the metabolic changes during ECGP development [72,154,166] and the involvement of mitochondria beyond their role in generating ATP [59]. The mitochondrial heterogeneity and metabolic variations of cancer cells would agree with the postulate of a cell reprogrammed with the ECGP as the cause and development of cancer.

The ECGP potential to produce cancer was rediscovered when scientists produced induced Pluripotent Stem Cells (iPSC) and their differentiated derivatives for the use of pluripotent stem cell-derived tissue for therapeutic purposes. Through these nuclear and cellular reprogramming of somatic cells, scientists produced cancers other than teratomas and like the corresponding spontaneous cancer forms. Therefore, the risk of cancer formation remains the main concern in the use of such cells for therapeutic cloning [77,140,170].

Whether generated by the reprogramming of somatic cells or generated from parthenogenesis (artificial activation of oocytes), iPSCs and human parthenogenic Embryonic Stem Cells (pESC) show the same characteristics as Embryonic Stem cells (ESC) [44], including pluripotent marker expression, self-renew potential and multi-differentiation potential through teratoma formation in mice [58,140]. This supports the concept that reprogramming of somatic cells to pluripotency corresponds to the activation of the ECGP and is in good agreement with the postulate of a cell reprogrammed with the ECGP that initiates cancer.

From these studies on nuclear reprogramming, scientists have demonstrated that any cell can be reprogrammed into pluripotency in the artificial environment of the Petri dish, by manipulating only a few factors. Furthermore, by using the ECGP properties (Table 2), one can derive various differentiated cells, replicating what any cell may be able to do, in a much more complex *in vivo* environment under influences of multiple factors and variables. The ability to produce such reprogrammed cells (iPSCs) and their differentiated derivatives validates the mechanism of a cell reprogrammed with the ECGP that sustains cancer and all types of

Table 2
The fate: What cells actually do under specific internal and external influences to direct specific cell differentiation How the pathogenesis of cancers governed by the ECGP properties can apply to the range of cancers.

1 Studies on nuclear reprogramming have shown: -A low percentage of successes that make reprogramming difficult to achieve: cancer is a relatively rare cellular event, e.g., the permissive conditions *in vivo* potentially leading to ECGP reprogramming have to be exceptionally gathered - Any cell from the less to the most differentiated can be reprogrammed to pluripotency: cancer transformation can occur at any step in cell differentiation, from the less to the most differentiated cell - It involves a great number of variables: source of the heterogeneity of cancers - It often leads to chromosomal defects stably inheritable: source of genetic abnormalities of cancers - Even if certain genomic modifications are efficient, most DNA modifications are aberrantly reprogrammed, resulting in the dysregulation of many genes: source of chromosomal abnormalities in cancers -Specific experimental conditions are needed to obtain somatic cell reprogramming to pluripotency: . The prior step to induce the donor cells to become quiescent .and metabolic shifting from oxidative phosphorylation to glycolysis	2. Even if the ECGP has circuits functioning on an autonomous-basis, the teratoma model and the experimental studies on reprogramming have shown that the ECGP can also be under influences of factors which can direct the pattern of differentiation. a. The ECGP can be influenced by intrinsic factors: -The reprogrammed cell retains the specific DNA characteristics of the cell of origin [61,62] Scientists have demonstrated that reprogramming the nucleus of a fully terminally differentiated cell's nucleus to pluripotency does not modify the specific-genomic rearrangements which characterize the terminally differentiated cell, with its specific DNA-markers being in all tissues of the cloned animal. The specific DNA markers of a cell -the original potency of the cell of origin- are retained during the process of reprogramming leading to the co-expression of pluripotency and the lineage-specific markers of the cell. b. The ECGP can be influenced by extrinsic factors: -The differentiation towards a specific cell lineage from iPSC is accompanied *in vivo* by the homing capacity of the differentiated cells in the target organ [139] Scientists have shown that their teratoma system under the influences of specific extrinsic factors can select and direct the differentiation of the corresponding specific lineage cells, in addition with homing capacity. The reprogrammed cells respond to environmental stimuli from their microenvironment and are subjected to developmental changes and clonal selection. Consequently, the co-expression of pluripotency combined to the potency of the cell of origin together with the influences of its microenvironment can be representative of what any cell can do, *in vivo*, to produce any types of cancers

cancers. Moreover, it supports that carcinogenesis can occur in any cell from the less to the most differentiated cell and that the particular stage in differentiation at which carcinogenesis occurs has an effect on the specific characteristics of the cancer cells. Additionally, after reprogramming, the cancer cells can be subject to further developmental changes as they respond to changing environmental stimuli elaborated by adjacent cancer or normal cells. The consequences of such interaction affect the path of each cancer cell differentiation, therefore diversifying the types of cancers.

Studies on nuclear cell reprogramming into pluripotency have also shown the specific experimental conditions needed to achieve such a reprogramming, these being induction of quiescence [17,165] and metabolic shifting from OXPHOS to glycolysis [45,160,167]. It supports the idea that various cancer-prone situations occur from cells in a growth arrested state with a shift to a more glycolytic metabolism like senescent cells [164] or stem cells [131], while any cell aggression (physical, chemical, viral, bacterial) causes the cells to maintain themselves in a survival quiescent and glycolytic adaptation state. This is also demonstrated by the spontaneous transformation of cultured cells [82], where the commonality shared by any of these cells is the survival state. The survival state is a decision-making process where the cell can die, differentiate, repair or rescue itself by anastasis; a process where cells can recover by reversal of apoptosis, a phenomenon that has the potential of becoming carcinogenic [52,142].

The complexity of such a reprogramming mechanism at the origin of cancer also stems from the key part played by mitochondria prior, during and after the somatic nucleus reprogramming of a cell with the ECGP. Mitochondria are indeed not only dynamic organelles that display structural and functional heterogeneity in cells but exist also as heterogeneous mitochondria population found not only in different tissues at one developmental stage [26], but also in the one cell type during different developmental stages [72,120,130,154].

For example, the numerous studies carried out on rat liver mitochondria make it possible to suggest and develop a plausible scenario of the cancer-causing process which is as follows:

Two mitochondrial populations with different morphological and functional characteristics have been identified in adult liver and other tissues representing mature forms of mitochondria that predominate over immature forms of mitochondria as alternate stages of division and maturation in a cyclic process of mitochondria biogenesis [85,118].

The mitochondrial maturation process has been shown to be influenced by hormones [15,16,122] and sex-related differences existing in mitochondrial morphological features; females contain more highly differentiated mitochondria compared with males [73]. This may explain why hormone-dependent cancers exist, but also the role of hormones in the development and progression of these cancers as well as their inherent or acquired resistance to hormonal therapy [81].

In rat liver, ethanol has been shown to induce a redistribution of the immature/mature mitochondrial populations leading to an increase in immature forms of mitochondria [95] and a reduced OXPHOS capacity [41]. This supports a common property of cancer, whereby aetiologic agents target mitochondria demonstrating that it is through functional alterations of mitochondria, potentially resulting in inducing a metabolic shift.

Upon removing ethanol, the normal mature/immature ratio is restored, as the increase in immature mitochondria is reversed by returning to the normal functional and morphological mature state [95]. The ultimate consequence of chronic alcohol abuse is cancer, in liver and other organs [10,123], with reversion to a fetal type metabolism observed in fast-growing and highly glycolytic hepatoma cells [28].

Whether it be after transient treatment with lethal doses of ethanol [142], or maintained in survival state in long-term primary cultures without any treatment or even with biliverdin-treated primary culture that triggers DNA synthesis [82], only a few primary liver cells undergo cancer transformation. These cells then display DNA damages, chromosomal aberrations [82,142]; and high tumorigenicity when injected into nude mice [82]. It supports that whatever the aetiologic agent is, it leads to the same effect, carcinogenesis but also that there is only one prime cause for cancer [162].

One of the earliest manifestations of the effects of chronic ethanol consumption on the liver is alterations in mitochondrial structure and function, resulting in a generalized decrease in hepatic mitochondrial ADP-stimulated respiration and OXPHOS [30,63]. Metabolism shifting in a cell may possibly occur via a mechanism based on a threshold effect such as the following: the mature to immature mitochondrial transition reduces the number of mature mitochondria to a low level but still sufficient to maintain an efficient OXPHOS activity and increases the immature mitochondria number. Metabolism shifting would occur only when a threshold level of mature mitochondria has been passed and consequently, an appropriate number of immature mitochondria has been reached that changes the mature/immature distribution ratio in the cell. Therefore, resulting in shifting from oxidative to glycolytic

metabolism as the prior step before reprogramming the nuclear genome of the cell with ECGP.

Anyway, this is the setting replicated in the experimental studies on somatic cell reprogramming to pluripotency. Therefore, in such a setting, glycolytic shift in a survival state could also promote in that cell *in vivo* ECGP reprogramming. This is like a parthenogenetic activation of the ECGP program with the difference that both maternal and paternal genomes are present.

Studies have shown that developmental competence of parthenogenetically activated oocyte reflects the one of normal fertilized oocytes as successful parthenogenetic activation of the ECGP can be induced in human oocytes, essentially mimicking the activation of ECGP and early embryo development with normal fertilization [74,110,111]. Even if parthenogenesis only initiates the early embryonic development in mammals, some development proceeds as far as the blastocyst stage [110]. As a source of stem cells, it is sufficient to originate cancer growth and development as demonstrated by the teratoma model that shows that disorganised clusters of ESCs and even one of them [76] can lead to both benign differentiated cells and malignant undifferentiated cells [137].

Other studies have revealed the role of mitochondria in developmental competence and their bioenergetics contribution to the fertilized oocyte and early embryo development competence. This contribution stems from two distincts populations of mitochondria; a major low-polarized immature mitochondria (LPM) and a small fraction of high-polarized mitochondria (HPM) with responses and characteristics similar to their fully developed somatic cell counterparts [36,37,103,152–156].

Nuclear reprogramming into pluripotency in a cell with 2 populations of mitochondria, one predominantly immature and one small fraction mature, could then occur through the establishment of the energetic and dynamic relationship between the nucleus and mitochondria that allows ECGP to be launched and produce ESC metabolically bivalent. Then, to produce hESC almost exclusively glycolytic, corresponding to the stage where metabolic switch occurs during early stem-cell development. The reversion to a fetal type metabolism observed in fast-growing and highly glycolytic hepatoma cells [18,28]; and the functional similarity of human embryonic stem cells (hESC) with the glycolytic phenotype in cancer [172] concludes my plausible scenario of cancer-causing process.

The uterus constituates a hypoxic environment for the embryo. Prior to embryo implantation, embryonic cells, in this hypoxic environment, rely on a bivalent anaerobic/aerobic metabolism to develop the ECGP. Therefore, carcinogenesis could be like embryogenesis, implying that glycolysis is not regulated like in aerobic environment. Anaerobic glycolysis could elucidate the Warburg paradox and better explain the Warburg effect achieved within cancer cells. Metabolic reprogramming associated with the development and progression of cancer and its subsequent important role played to attenuate cell death support a cell reprogrammed with the ECGP as the origin of cancer.

From a re/programmed cell with the ECGP emerges a bivalent metabolic state: preponderantly anaerobic glycolytic from a predominant population of immature mitochondria configurated to resist apoptosis and efficiently oxidative from a reduced number of active mitochondria. The cancer cells metabolic plasticity to adapt to various microenvironments (such as hypoxic conditions), to promote, under internal and external influences, cancer progression and metastasis, to benefit from selective advantages in multiple circumstances (proliferation, survival, metabolic changes, protection against cell death and toxic drugs), is in good agreement with the hybrid metabolic remodeling where both anaerobic and aerobic pathways are active, adapted to hostile hypoxic conditions that arise during nuclear programming or reprogramming by ECGP and the early fermentative stages of embryogenesis [39,44,78,83,97,148,163,171,172].

So, the proposed model of a cell reprogrammed with the ECGP as the prime cause of cancer:

1. As a source of mutagenesis and chromosomal abnormalities,
2. As a source of stem cells and tissue-differentiated derivatives,
3. As a reversion to a fetal metabolism programming,
4. As involving the multifaceted influence of mitochondrial metabolism and the role of mitochondrial function before, during and after reprogramming,
5. As supporting cancer origin, growth, development, and progression,
6. And as a source of autonomously proliferative cells with bivalent anaerobic/aerobic metabolism is a plausible unifying model as the “only one prime cause of cancer” [162] which explains the overall complexity of the disease.

3. An anticancer strategy based on a developmental sequence of the ECGP

Cancer treatments have limited selectivity with risk of therapeutic toxicity, resistance and/or relapse. The proposed model of carcinogenesis explains the failure of strategies to force cancer cells into the apoptotic process [51,66] and the more promising results of strategies that target the cancer cells metabolism, especially those which can effectively induce a metabolic switch from glycolysis to oxidative metabolism, rendering cancer cells sensitive to apoptosis induction [143]. However, the recurrent problem with anti-glycolytic therapies is the high prevalence of dose-limiting toxicities with the class of drugs used, therefore limiting their clinical use [1].

The proposed model of carcinogenesis identifies the mitochondrial maturation, such as, the acquisition of the ultrastructural, molecular, and functional features of adult mitochondria, as the process to be targeted in cancer cell metabolism. Therefore, a non-toxic metabolic strategy, not based on glycolysis inhibition but on cancer cell oxidative metabolism restoring as a strategy for cancer treatment can be designed to target cancer cell hybrid metabolic phenotype selectively by shifting their primarily anaerobic glycolytic to primarily oxidative (OXPHOS) metabolism as the main aerobic pathway that provides cell energy. Once a threshold of fully functional mature mitochondria is restored, cancerous cells could regain their death-mediating abilities (Fig. 3b).

In the ECGP there are development sequences where metabolism transitions from anaerobic glycolytic to oxidative (OXPHOS) can occur [8]. These are early transitions from embryonic stem cells (heart, brain) in utero or, transitions from stem cells in hypoxic niches and the main developmental switch at birth, involving profound hormonal, physiological and metabolic changes. Indeed, postnatal switch of glycolytic to oxidative metabolism is of crucial importance for all mammalian neonates and it is essential for successful adaptation to extra-uterine life. The shift from fetal to neonate liver provides a good model as the classic example and the understanding of the process of OXPHOS development (Fig. 3a).

3.1. Perinatal mitochondrial maturation

The fetal liver is hypoxic and its oxygenation occurs in the first hour after birth. Despite this, two distinct populations of mitochondria have also been isolated from fetal rat liver; the predominant population consists of non-functional immature mitochondria that rely on anaerobic metabolism, owing to hypoxia, and a reduced mature mitochondria population capable of OXPHOS [86,117,119,124]. Adaptation to the aerobic extrauterine environment requires an appropriate number and functional activity of the mitochondria present in neonate and adult liver. Mitochondrial biogenesis, during development, consists of 2 processes that differ in time and do not share the same molecular mechanisms: the increase in the number (proliferation) of mitochondria is a continuous process throughout the liver development controlled at the level of transcription/post-transcription and the increase in the functional capability (maturation) of pre-existing mitochondria is a process that occurs very rapidly in the first hour after birth and controlled at post-transcriptional levels of gene expression [28,87].

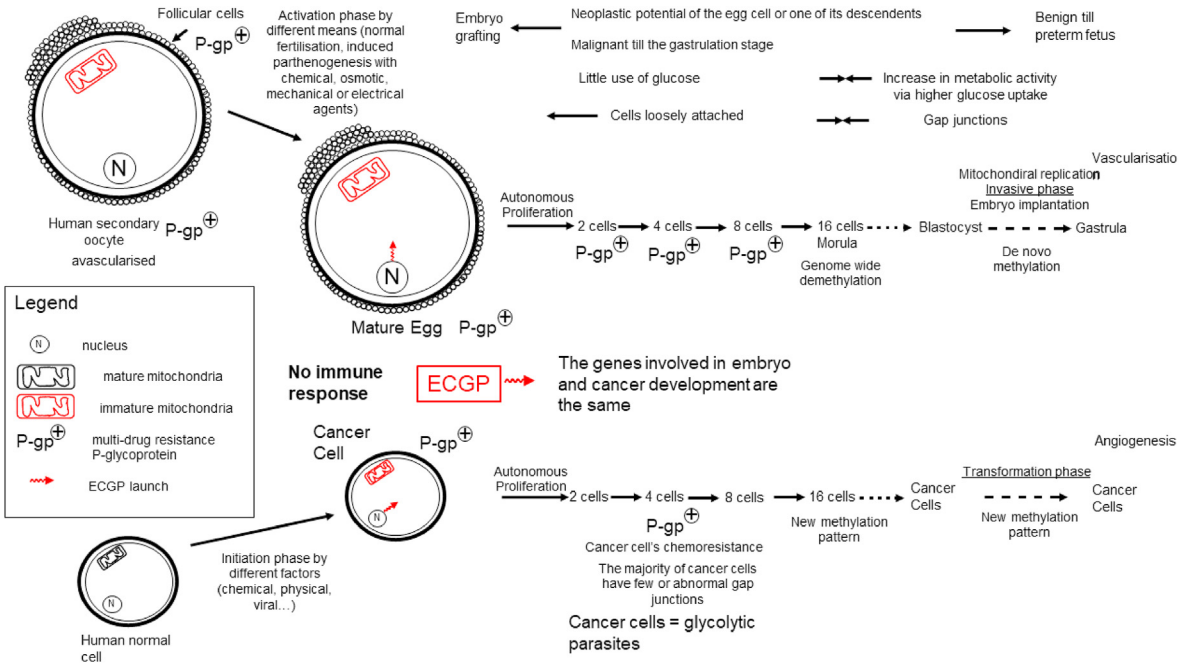

Fig. 2. *The potential of the ECGP repertoire representative of the complex cancer biology:*
ECGP program of differentiation is characterized by the rate of cell division, the adhesive properties of the cell membrane and specific patterns of cellular metabolism; specific cellular pathways for migration, enhanced resistance to cell death and increased capacity for drug resistance.
Cancer is an autonomous proliferation of cells, with phenotype and proliferative potential heterogeneity, progressive, independent of the surrounding tissues, unrelated to the needs of the organism, parasitic, which can acquire dangerous biological properties for the host; the ability to evade apoptosis, support of angiogenesis, to invade tissues, to metastasize.

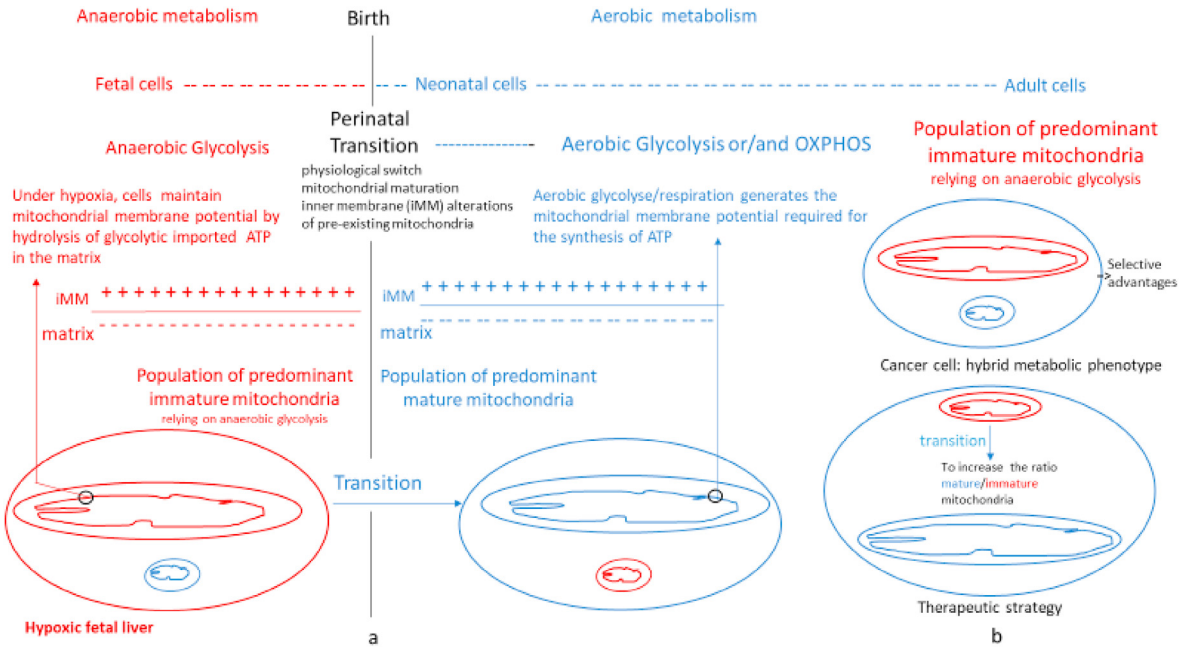

Fig. 3. a: Anaerobic/aerobic transitions during development for adaptation to the extrauterin aerobic environment through maturation of inner mitochondrial membrane (iMM) for the acquisition of fully developed mature mitochondria.
b: *Therapeutic strategy: to shift the cancer cell hybrid state to oxidative metabolism by replicating the developmental switch to aerobic metabolism at birth: within cancer cells, the transition to a threshold mature mitochondria population compatible with aerobic environment as the prior step to shift stemness to cell differentiation, before cancer cells could restore their death-mediating abilities.*

The maturation of pre-existing mitochondria is a mechanism of rapid adaption to respiratory demands of a cell during postnatal switch of the predominant fetal anaerobic glycolytic to the efficient neonatal oxidative metabolism (OXPHOS) that develops ADP-stimulated respiration. It is the acquisition of ultrastructural, molecular and functional features of adult mitochondria via changes in the properties of their inner mitochondrial membrane (iMM), such as in permeability [116], in enzymatic activities by changes in membrane composition as, for example, in the case of

membrane-bound Hexokinase (In this example, the attachment of Hexokinase to the mitochondria may not be just a property of the Hexokinase isoenzyme that changes but may also depend on a specific property of the mitochondrial membrane that changes its characteristics during the developmental transition) [21,23,24], in proton conductance [150,151]; and in calcium flux [122].

As a key process for the acquisition of fully developed mitochondria, the maturation of pre-existing mitochondria represents a valid approach in the strategy of shifting cancer cell predominant anaerobic glycolytic to mainly oxidative metabolism.

3.2. *ANT1 candidate to switch a non-electrogenic to an electrogenic mitochondrial ATP/ADP exchange*

The primary mechanism that controls the pre-existing mitochondria maturation process is a rapid, sharp redistribution of the adenine nucleotides pool, which are specific to ATP and ADP, from the cytosolic to the mitochondrial compartment simultaneously with a reduction of the matrix volume. The rapid intra-mitochondrial enrichment in ATP/ADP is mainly due to the increase of ADP [106], essential for mitochondrial contraction and responsible for the ultra-structural changes of iMM [125]. This results in a stimulating effect on respiration and is a mechanism independent of protein synthesis [149]. The marked increase of the level of the intra-mitochondrial ATP/ADP content over a certain range promotes changes on the mitochondrial ultrastructure (as the transport of these two large and charged nucleotides through the mitochondrial membrane leads to modifications of the structure of their protein carriers inducing important conformational iMM changes) and when an ATP/ADP threshold effect is reached from the first hour after birth, it then develops ADP-stimulated respiration in about one day in the liver.

Increase and decrease in the mitochondrial adenine nucleotide content is completely reversible and promotes, through a threshold effect, the many mitochondrial changes with respect to both their morphology and their metabolism.

The mechanism requires the presence of 2 specific systems for each inclusion in the mitochondria capable of discerning ATP from ADP and in different proportions. Two distinct reversible transport pathways across the inner mitochondrial membrane allow the net increase or decrease [5,6] of ATP/ADP in the mitochondrial matrix and are responsible for alterations of the matrix adenine nucleotide content (Fig. 4):

The 1st transport is a divalent electroneutral exchange of (ATP-Mg) 2- for HPO2- [107]. SCaMC is the protein carrier for this ATP-Mg/Pi electroneutral exchange. Under physiological conditions ATP-Mg is the preferred substrate of this protein.

3 isoforms exist for the ATP-Mg/Pi carrier, SCaMC 1–3 [42]. SCaMC1 and 3 are all co-expressed in early embryonic and postnatal liver. SCaMC-3 is the major carrier in adult mouse liver [2].

Studies have shown that:

1. In *Saccharomyces cerevisiae*, the ATP-Mg/Pi mitochondrial carrier is not necessary for OXPHOS [20].
2. All SCaMC1-3 isoforms have high levels of expression in cancers [89,146], giving their cells a selective advantage, especially against cell death.

Therefore, the use of this protein carrier-mediated electroneutral transport presents no interest to trigger the changes in the properties of the iMM whereby the fetal to neonatal metabolism switch occurs.

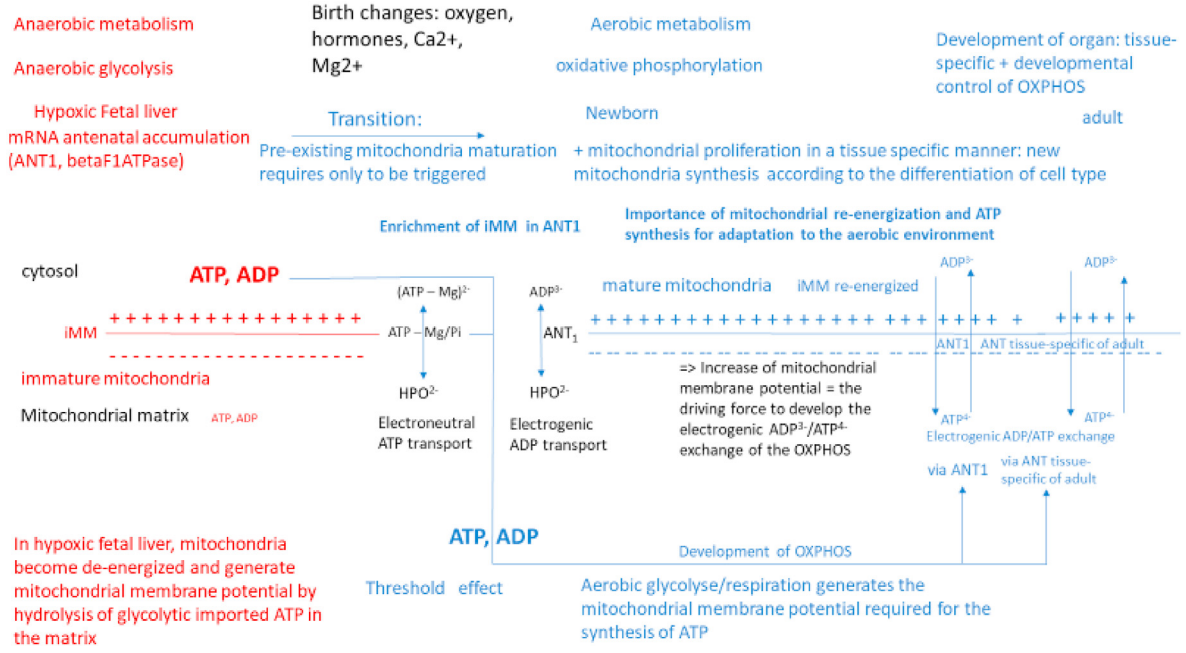

Fig. 4. The physiological switch from anaerobic to aerobic metabolism depends on the mitochondrial maturation of pre-existing mitochondria: a key regulatory process for successful neonatal adaptation to extrauterine aerobic life via a mechanism of ATP/ADP recompartmentalization in the mitochondrial matrix at the origin of iMM alterations and development of OXPHOS. During the post-natal development of immature mitochondria to fully developed active phosphorylating mitochondria, the enrichment of ANT1 contributes mainly to the maturation of mitochondria through the re-energization of their inner membrane, as the electrogenic nature of the carrier provides a means of injecting ADP3- in the matrix.
Selective metabolic anticancer strategy: At birth, the liver model demonstrates a physiological role for ANT1 in switching from a non-electrogenic to an electrogenic mitochondrial ATP/ADP exchange, contributing to the metabolic phenotype of aerobic glycolysis/respiration compatible with aerobic environment. As such, ANT1 could be a candidate to trigger the mechanism of acquisition of fully developed active phosphorylating mitochondria within cancer cells (*as all the ATP-Mg/Pi electroneutral mitochondrial carrier isoforms are over expressed in cancer cells with a low ATP/ADP intramitochondrial content whereas ANT1 electrogenic mitochondrial carrier expression is non-existent in cancer cells).*
The maturation of cancer cells mitochondria through their iMM enrichment with ANT1 could shift stemness to differentiation, the prior step before cancer cells could restore their death-mediating abilities and trigger their spontaneous death, the cancer cells being revealed in excess and eliminated as unneeded cells by the body.

The 2nd pathway is the transport of ADP. In parallel with the increase in the matrix adenine content, the Adenine Nucleotide Translocase isoform 1 (ANT1) also increases strongly at birth [53,127]. The main function of ANT1 is to electrogenically exchange cytosolic free ADP3- with matrix free ATP4- in OXPHOS. The liver model demonstrates that the increase in ANT1 contributes to the maturation of the pre-existing mitochondria, but it cannot be through its translocase activity at birth, at a time even before the mitochondrial OXPHOS can contribute significantly to cytoplasmic concentration in ATP. An additional indication of the importance of the ANT1 specific fundamental activity, other than its translocase activity at birth, comes from the demonstration of a change in expression of the ANT isoform during perinatal liver development. It is ANT1, the heart/muscle specific isoform, which is transiently expressed in the neonatal liver whereas ANT1 is not expressed in the adult liver [43,53]. This developmental change, in the expression of the ANT1 isoform, as in its quantity in relation with an increased activity, demonstrates the physiological key role of ANT1 in maturation of pre-existing mitochondria and in postnatal development of OXPHOS at birth. The iMM enrichment in ANT1 as a carrier-mediated electrogenic transport at birth corresponds to an increase of a specific activity for this protein. This protein mediates a unidirectional ADP electrogenic transport, where the electrogenic nature of the ANT1 carrier provides a means of injecting ADP3- in the mitochondrial matrix.

The predominantly distinct transient expression of ANT1, during postnatal development, followed by the decline in control of this protein on respiration during the subsequent development of the newborn to the adult, strongly binds this protein with the acquisition of fully developed mitochondria. This is done via a mechanism independent of protein synthesis that triggers a unique and common non-specific iMM maturation mechanism to all cells.

Just like the depletion of ATP/ADP intramitochondrial content, beyond a certain threshold, affects OXPHOS [4–6], an increase in ATP/ADP matrix content beyond a certain threshold:

1. Promotes the changes in the mitochondrial ultrastructure with the consequence that the hexokinase isoform is changed and displaced and could interact with ANT1 by a direct or indirect mechanism [60].
2. Develops ADP-stimulated respiration: While ATP-Mg/Pi generates an electroneutral ATP transport, ANT1 can generate an ADP electrogenic transport, ADP3- versus HPO2- that results in a charge imbalance. It results in a net import of a negative charge for each molecule of ADP, acting as an incoming current that re-energizes the iMM [132] in a negative potential gradient across the iMM that can account for the increase of mitochondrial membrane potential; the driving force to develop for the electrogenic ADP3-/ATP4- exchanges of the OXPHOS [13].
3. Reduces passive conductance to H + protons [150,151].
4. Increases the protomotive force which can increase the F1ATPase activity by release of the IF1 inhibitor [68,69,80,84,87].
5. And stimulates the synthesis of matrix proteins [71].

Such mobilization of ANT1 has been reported as molecular bases of the biochemical threshold effect observed in mitochondrial diseases and could occur through the assembly of inactive ANT1 subunits into active carriers or conformational changes in the ANT1 [40]. As ANT functions are related to their conformation in the iMM [7,109,147], we may suppose that the transient overexpression of ANT1 in the liver at birth, which does not disrupt the iMM, may occur through a specific ADP-induced conformational change of ANT1 to trigger the iMM changes and development of OXPHOS.

The fetal liver at birth highlights ANT1 as the necessary, fundamental, and essential factor assigned to the development of OXPHOS, with the appearance of an electrogenic ADP/ATP mitochondrial exchange.

The fetal liver model shows that:

1. A fundamental function for ANT1 carrier other than its translocase activity is responsible for the net uptake or efflux of ADP into or from the mitochondria and hence for the reversible variation in the matrix adenine nucleotide content which has been found to change in cancer [9].
2. ANT1 is the isoform expressed, transiently, even in cells where ANT1 is not the expressed isoform, in a compartmentalization regulatory mechanism that has the effect of developing the structural and functional abilities of pre-existing mitochondria and of triggering the development of OXPHOS.
3. The rapid mechanism of mitochondrial maturation requires only non-functional pre-existing mitochondria and mobilization of ANT1.
4. The mechanism that triggers the conformational changes in fetal iMM is sufficient to rapidly trigger cell adaptation to oxidative metabolism, independent of protein synthesis. Such a compartmentalized regulatory mechanism allows cells to respond to environmental changes more rapidly than a transcriptionally controlled biogenesis (proliferation) [121].

The hypoxic fetal liver has many manifestations in common with highly glycolytic tumor cells [28,29]. Its cells express isoforms of glycolytic enzymes different from those present in adult liver cells [28,29]. For instance, the fetal liver [70], like cancer cells [96] shows high hexokinase activity (I and II). Fetal liver is like cancer, implying that glycolysis is not regulated as in adult liver. Under hypoxia, their mitochondria become de-energized and cells generate mitochondrial membrane potential by glycolytic imported ATP hydrolysis. They rely on primarily anaerobic metabolism. As such, cancer cell mitochondria, just like embryonic stem cell mitochondria [19] are configurated to regulate anaerobic glycolysis and resist apoptosis [30,41,63]. Therefore, they differ from normal cells mitochondria configured to regulate aerobic glycolysis [157] and to contribute to apoptosis in immune cells for instance [48,88,91,92].

Following the transition from the pre-to the postnatal environment, fetal liver cells undergo a shift from primarily anaerobic glycolytic to primarily aerobic energy metabolism, where the aerobic glycolysis/respiration generates the mitochondrial membrane potential required for the synthesis of ATP.

The liver model, at birth, shows the physiological importance of mitochondrial re-energization and ATP synthesis for adaptation to the aerobic environment:

1. ANT1, by injecting ADP3-, demonstrates its role in switching from a non-electrogenic to an electrogenic mitochondrial ATP/ADP exchange.
2. The necessary mitochondrial maturation through iMM alterations which preceds cell differentiation.
3. And the subsequent metabolic shift from a change of a preponderant immature to mature mitochondrial population compatible with aerobic environment.

The liver model at birth shows that the modifications triggered by ECGP reprogramming within a cell leading to its conversion to cancer, could be physiologically reversed (Figs. 3b and 4).

Although ANT2 and ANT3 are overexpressed in many cancers [64], cancer cells could use the non-electrogenic ATP/Mg-Pi carrier that could take over exchange of ATP and ADP in cancer cells [94]. While ATP-Mg/Pi isoforms are over expressed in cancer cells [89,146] with a low ATP/ADP intramitochondrial content [9], ANT1 expression is non-existent in cancer cells [94].

The enrichment of ANT1 in the liver contributes mainly to the maturation of pre-existing mitochondria through the re-energization of their inner membrane. ANT1 thus appears to be the necessary and sufficient factor to reprogram mitochondria for aerobic metabolism. ANT1

as such could be of interest as a non-toxic metabolic tool to manipulate immature mitochondria of cancer cells for therapeutic benefit by switching from a non-electrogenic to an electrogenic mitochondrial ATP/ADP exchange. A potential candidate to develop an oxidative metabolism from a preponderant population of mature mitochondria within cancer cells that would shift stemness to differentiation, the prior step before cancer cells could restore their death-mediating abilities [159].

3.3. Implications in designing effective therapies

Despite the enormous efforts to improve cancer treatments, basic research remains essential, particularly to decipher the tactics of metastasis responsible for most cancer deaths due to intrinsic or acquired tumor resistances. In the last years, the well recognized metabolic reprogramming associated with the development, progression and chemoresistances of cancer, has attracted a boom research to develop innovative and new avenues [22,25,38,46,49,50,55,67,98,104,113,145,158,168,169].

With the view of cancer as a cell reprogrammed with the ECGP which is valuable in understanding cancer transformation, we might be able to apply ECGP knowledge selectively to devise effective therapies to deal with such transformation.

In support of this view, computational modelling of cancer metabolism shows that cancer cells can acces a hybrid state with both glycolytic/OXPHOS metabolic modes coexisting, contributing to metabolic plasticity of cancer [168].

Studies performed by using grafting human p0 tumor cells exemplify the hybrid metabolic phenotype of cancer cells. The p0 tumor cells devoid of mitochondrial DNA preserve intact immature mitochondria that localize around the nucleus, can still generate mitochondrial membrane potential, relie on glycolysis and are able to form tumors in athymic nude mice with delayed appearance as compared to the parental tumor cells ([27,35,141]. It has been shown that delayed tumor growth was associated with the acquisition of mitochondrial DNA [141] or active mitochondria [35] from surrounding cells resulting in stepwise recovery of respiration from primary to metastatic tumor cells. These data strongly point to respiration recovery as essential for driving efficient tumor transformation [35,54]. In addition, one other study evaluating the uptake of active mitochondria by cancer cells has shown that these cells could receive 5 to up to 16 mitochondria which could represent at most an increase of 14% of their total mitochondrial mass (mean 124 mitochondria per cancer cell) resulting in a very efficient increase in ATP produced by these active mitochondria [102].

Together, these results demonstrate that, in these recipient cancer cells, low mature/immature ratios of mitochondria maintain survival, resistance and progression of these cells supporting the hybrid metabolic state of cancer cells with both anaerobic glycolytic metabolism from a predominant immature population of mitochondria configurated to resist apoptosis and efficient oxidative metabolism from a reduced number of mature mitochondria coexisting. It also shows the essential role of a reduced population of functional mitochondria in the tumorigenic potential of cancer cells, in the same way that murine embryonic stem cells with high mitochondrial membrane potential show an ability to form teratomas [126]. This transformation resulting in the reversion of the cellular energy metabolism is indeed reminiscent of the metabolic properties of pre-implantation embryonic cells fuelled by anaerobic glycolysis and a reduced efficient mitochondrial oxidative phosphorylation [39,97,126,148,172].

An efficient anticancer strategy would then be to drive cancer cells away from the hybrid state [168].

The mitochondrial developmental sequence of the ECGP described, at birth, in the liver model, could have the potential to target the hybrid state of cancer cells by changing a low mature/immature mitochondrial ratio to a high mature/immature mitochondrial ratio. Therefore, iMM cancer cells appear to be the pertinent target to be altered to devise specific therapies which would exploit the unique metabolic coupling that promotes cancer cells' growth, resistances, and metastasis. Therefore, it would be of interest to evaluate the ANT1 function described in the liver model for its therapeutic usefulness in the field of cancer, for its targeted and limited action which target the specific mechanism of energy switching at birth. That could restore a high mature/immature ratio population of mitochondria within cancer cells adapted to aerobic metabolism, the prior step to reorient the response of cancer cells towards their bioenergetics death. Metabolism's shifting by forcing the inactive cancer cells'mitochondria to actively engage in energy production by oxidative metabolism using the chemical drug DiChloroAcetate (DCA), has indeed proved effective in the recovery of the suppressed mitochondrial Apoptosis in cancer cells [143].

To restore a threshold population of mature mitochondria to achieve a high mature/immature mitochondria ratio compatible with aerobic environment within cancer cells could have general applicability:

1. Because decreased aerobic capacity and increased anaerobic glycolysis are universal features of primary and metastatic tumors.
2. Because any type of cancer has the ability to metastasize or develop death/drug resistances.
3. Because most of normal differentiated cells rely primarily on OXPHOS to generate their energy therefore alteration of cancer cells iMM through enrichment in ANT1 could shift stemness to differentiation, the prior step before cancer cells could reorient their response towards their death-mediating abilities as demonstrated in teratocarcinoma where only cancer stem cells with active mitochondrial metabolism are more susceptible to DCA [159].

4. Conclusion

Depending on the entry point into the cancer cell and the differences observed with the normal cell, multiple theories on carcinogenesis lead to different causes without modeling the entire process of carcinogenesis. Otto Warburg stated: "Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause" [162]. Yet the only prime cause identified so far is the one demonstrated by the ECGP potential to produce cancer, under permissive conditions, revealing the similarities between normal cells and cells developing as cancerous. Although this does not make cancer any less complex, due to the involvement of such pleiotropic dynamic organelles and mitochondria all along the process, it opens up the possibility to model and treat cancer cells from a different perspective and potentially provides a new target in the battle against cancer; mitochondria reprogramming/remodeling.

This view of cancer as a cell reprogrammed with the ECGP leads to avenues for treating cancer and identifies a new therapeutic strategy in a multidisciplinary approach.

Such an etiology of carcinogenesis with the understanding of the ECGP program of differentiation, only aberrant because developing inappropriately, has implications for cancer research as we can potentially apply ECGP knowledge selectively to kill cancer cells. O. Warburg found that a unique metabolism characterizes cancer cells and can distinguish between cancer and normal cells. The famous Warburg paradox is resolved if we consider a bivalent anaerobic glycolytic/aerobic metabolism. The proposed model highlights that the cancer cell metabolism modifications are physiologically reversible, as the fundamental mechanism switching between anaerobic glycolytic and oxidative metabolisms occurs through a threshold effect mechanism at least at two levels. The fundamental first level which triggers the switching metabolic pathways, is a redistribution of the pool of adenine nucleotides. The second level is observed in the mitochondrial metabolism because of increases or decreases of the ratio immature/mature mitochondria.

Metabolic changes are associated with alterations in the mitochondrial structure, dynamics, and function. Given the fundamental role of ANT1 in these iMM alterations and the subsequent metabolic shift associated with the ADP-stimulated respiration and the development of OXPHOS in the cell, it would be of great interest to exploit this

fundamental function of ANT1 to develop a successful anticancer strategy. In that cancer cells restore their death-mediating abilities by replicating, within cancer cells, the mechanism of acquisition of fully developed mitochondria from pre-existing immature mitochondria.

The ECGP potential to produce cancer is the discovery that should have shaken our way of understanding cancer and open new ways to fight it. Today, we can quickly provide an answer to this theory which leads to a more appropriate and medically sound approach to cancer therapy. The ANT1 function which triggers the mechanism of acquisition of fully developed active phosphorylating mitochondria within cancer cells is the prior step to make it possible to reorient the response of cancer cells towards their bioenergetic death. Among all the laboratories devoted to fight cancer, it only takes one to explore and exploit this avenue to bypass cancer cell resistances.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Not applicable.

Competing interests

The author declares that she has no competing interests.

Funding

The author declares no source of funding

Authors' contributions

Majérus M.A. is the only author who contributed to and wrote the whole paper. Chantreau Zoé, Chantreau Raphaël, Foisor V. and Whittock A. reviewed the manuscript for English writing.

Declaration of competing interestDoCI

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Dedication.

This work is dedicated to Virginie Majérus.

Acknowledgements

I heartily thank Z. Chantreau, R. Chantreau, M. Chantreau and A. Chantreau for their kindly support. I thank R. Chantreau for the technical support he provided for this paper. And I greatly acknowledge valuable support from Z. Chantreau for assisting with the preparation of this manuscript and R. Chantreau, V. Foisor and A. Whittock for editing the article.

References

[1] A.F. Abdel-Wahab, W. Mahmoud, R.M. Al-Harizy, Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy, Pharmacol. Res. 150 (2019) 104511, https://doi.org/10.1016/j.phrs.2019.104511.

[2] I. Amigo, J. Traba, M.M. González-Barroso, C.B. Rueda, M. Fernández, E. Rial, A. Sánchez, J. Satrústegui, A. Del Arco, Glucagon regulation of oxidative phosphorylation requires an increase in matrix adenine nucleotide content through Ca2+ activation of the mitochondrial ATP-Mg/Pi carrier SCaMC-3, J. Biol. Chem. 288 (2013) 7791–7802, https://doi.org/10.1074/jbc.M112.409144.

[3] V.D Appanna, T.N Seyfried, Cancer as a mitochondrial metabolic disease, Front. Cell Dev. Biol. 3 (2015) 43.

[4] J.R. Aprille, Regulation of the mitochondrial adenine nucleotide pool size in liver: mechanism and metabolic role, Faseb. J. 2 (1988) 2547–2556, https://doi.org/10.1096/fasebj.2.10.3290024.

[5] J.R. Aprille, J. Austin, Regulation of the mitochondrial adenine nucleotide pool size, Arch. Biochem. Biophys. 212 (1981) 689–699, https://doi.org/10.1016/0003-9861(81)90413-6.

[6] G.K. Asimakis, J.R. Aprille, In vitro alteration of the size of the liver mitochondrial adenine nucleotide pool: correlation with respiratory functions, Arch. Biochem. Biophys. 203 (1980) 307–316, https://doi.org/10.1016/0003-9861(80)90181-2.

[7] V. Azzu, N. Parker, M.D. Brand, High membrane potential promotes alkenal-induced mitochondrial uncoupling and influences adenine nucleotide translocase conformation, Biochem. J. 413 (2008) 323–332, https://doi.org/10.1042/BJ20080321.

[8] C. Baker, S. Ebert, Development of aerobic metabolism in utero: requirement for mitochondrial function during embryonic and fetal periods, OA Biotechnol. 2 (2013), https://doi.org/10.13172/2052-0069-2-2-571.

[9] R.L. Barbour, S.H.P. Chan, Adenine nucleotide transport in hepatoma mitochondria and its correlation with hepatoma growth rates and tumor size, Cancer Res. 43 (1983) 1511–1517.

[10] P. Boffetta, M. Hashibe, Alcohol and cancer, Lancet Oncol. 7 (2006) 149–156, https://doi.org/10.1016/S1470-2045(06)70577-0.

[11] T. Boveri. Zur Frage der Entstehung Maligner Tumoren [Origin of malignant tumors], Gustav Fisher, Jena, 1914.

[12] R.L. Brinster, The effect of cells transferred into the mouse blastocyst on subsequent development, J. Exp. Med. 140 (1974) 1049–1056, https://doi.org/10.1084/jem.140.4.1049.

[13] N. Brustovetsky, A. Becker, M. Klingenberg, E. Bamberg, Electrical currents associated with nucleotide transport by the reconstituted mitochondrial ADP/ATP carrier, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 664–668, https://doi.org/10.1073/pnas.93.2.664.

[14] L.-T.R. Busund, 10. Hypotheses of carcinogenesis—the AtavisticTheory, in: Advancing Systems Epidemiology in Cancer, Universitetsforlaget, 2020.

[15] F.L. Bygrave, T.P. Heaney, C. Ramachandran, Submitochondrial location of ruthenium red-sensitive calcium-ion transport and evidence for its enrichment in a specific population of rat liver mitochondria, Biochem. J. 174 (1978) 1011–1019, https://doi.org/10.1042/bj1741011.

[16] F.L. Bygrave, G.R. Ash, Development of mitochondrial calcium transport activity in rat liver, FEBS Lett. 80 (1977) 271–274, https://doi.org/10.1016/0014-5793(77)80455-9.

[17] K.H.S. Campbell, J. McWhir, W.A. Ritchie, I. Wilmut, Sheep cloned by nuclear transfer from a cultured cell line, Nature 380 (1996) 64–66, https://doi.org/10.1038/380064a0.

[18] C.W. Chang, J.F. Lo, X.W. Wang, Roles of mitochondria in liver cancer stem cells, Differentiation 107 (2019) 35–41, https://doi.org/10.1016/j.diff.2019.04.001.

[19] C.T. Chen, S.H. Hsu, Y.H. Wei, Mitochondrial bioenergetic function and metabolic plasticity in stem cell differentiation and cellular reprogramming, Biochim. Biophys. Acta Gen. Subj. 1820 (2012) 571–576, https://doi.org/10.1016/j.bbagen.2011.09.013.

[20] X.J. Chen, Sal1p, a calcium-dependent carrier protein that suppresses an essential cellular function associated with the Aac2 isoform of ADP/ATP translocase in Saccharomyces cerevisiae, Genetics 167 (2004) 607–617, https://doi.org/10.1534/genetics.103.023655.

[21] F. Chiara, D. Castellaro, O. Marin, V. Petronilli, W.S. Brusilow, M. Juhaszova, S.J. Sollott, M. Forte, P. Bernardi, A. Rasola, Hexokinase II detachment from mitochondria triggers apoptosis through the permeability transition pore independent of voltage-dependent anion channels, PLoS One 3 (2008) e1852, https://doi.org/10.1371/journal.pone.0001852.

[22] F. Chiaradonna, D. Scumaci, Cancer metabolism as a new real target in tumor therapy, Cells 10 (2021) 1393, https://doi.org/10.3390/cells10061393.

[23] S. Chung, D.K. Arrell, R.S. Faustino, A. Terzic, P.P. Dzeja, Glycolytic network restructuring integral to the energetics of embryonic stem cell cardiac differentiation, J. Mol. Cell. Cardiol. 48 (2010) 725–734, https://doi.org/10.1016/j.yjmcc.2009.12.014.

[24] S. Chung, P.P. Dzeja, R.S. Faustino, C. Perez-Terzic, A. Behfar, A. Terzic, Mitochondrial oxidative metabolism is required for the cardiac differentiation of stem cells, Nat. Clin. Pract. Cardiovasc. Med. 4 (2007) S60–S67, https://doi.org/10.1038/ncpcardio0766.

[25] H.A. Coller, Is cancer a metabolic disease? 9582978472, Am. J. Pathol. 184 (2014) 4–17, https://doi.org/10.1016/j.ajpath.2013.07.035.

[26] T.J. Collins, M.J. Berridge, P. Lipp, M.D. Bootman, Mitochondria are morphologically and functionally heterogeneous within cells, EMBO J. 21 (2002) 1616–1627, https://doi.org/10.1093/emboj/21.7.1616.

[27] C.C. Cook, M. Higuchi, The awakening of an advanced malignant cancer: an insult to the mitochondrial genome, Biochim. Biophys. Acta Gen. Subj. 1820 (2012) 652–662, https://doi.org/10.1016/j.bbagen.2011.08.017.

[28] J.M. Cuezva, L.K. Ostronoff, J. Ricart, M.L. De Heredia, C.M. Di Liegro, J.M. Izquierdo, Mitochondrial biogenesis in the liver during development and oncogenesis, J. Bioenerg. Biomembr. 29 (1997) 365–377, https://doi.org/10.1023/A:1022450831360.

[29] J.M. Cuezva, M. Sánchez-Aragó, S. Sala, A. Blanco-Rivero, Á.D. Ortega, A message emerging from development: the repression of mitochondrial β-F1-ATPase

expression in cancer, J. Bioenerg. Biomembr. 39 (2007) 259–265, https://doi.org/10.1007/s10863-007-9087-9.
[30] C.C. Cunningham, W.B. Coleman, P.I. Spach, The effects of chronic ethanol consumption on hepatic mitochondrial energy metabolism, Alcohol Alcohol 25 (1990) 127–136, https://doi.org/10.1093/oxfordjournals.alcalc.a044987.
[31] I. Damjanov, D. Solter, Maternally transmitted factors modify development and malignancy of teratomas in mice, Nature 296 (1982) 95–96, https://doi.org/10.1038/296095a0.
[32] P. Danhier, P. Bański, V.L. Payen, D. Grasso, L. Ippolito, P. Sonveaux, P.E. Porporato, Cancer metabolism in space and time: beyond the Warburg effect, Biochim. Biophys. Acta Bioenerg. 1858 (2017) 556–572, https://doi.org/10.1016/j.bbabio.2017.02.001.
[33] G. Darrasse-Jèze, A.S. Bergot, A. Durgeau, F. Billiard, B.L. Salomon, J.L. Cohen, B. Bellier, K. Podsypanina, D. Klatzmann, Tumor emergence is sensed by self-specific CD44hi memory Tregs that create a dominant tolerogenic environment for tumors in mice, J. Clin. Invest. 119 (2009) 2648–2662, https://doi.org/10.1172/JCI36628.
[34] P.C.W. Davies, C.H. Lineweaver, Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors, Phys. Biol. 8 (2011) 015001, https://doi.org/10.1088/1478-3975/8/1/015001.
[35] L.F. Dong, J. Kovarova, M. Bajzikova, A. Bezawork-Geleta, D. Svec, B. Endaya, K. Sachaphibulkij, A.R. Coelho, N. Sebkova, A. Ruzickova, A.S. Tan, K. Kluckova, K. Judasova, K. Zamecnikova, Z. Rychtarcikova, V. Gopalan, L. Andera, M. Sobol, B. Yan, B. Pattnaik, N. Bhatraju, J. Truksa, P. Stopka, P. Hozak, A.K. Lam, R. Sedlacek, P.J. Oliveira, M. Kubista, A. Agrawal, K. Dvorakova-Hortova, J. Rohlena, M.V. Berridge, J. Neuzil, Horizontal transfer of whole mitochondria restores tumorigenic potential in mitochondrial DNA-deficient cancer cells, Elife 6 (2017), https://doi.org/10.7554/eLife.22187.
[36] R. Dumollard, M. Duchen, J. Carroll, The role of mitochondrial function in the oocyte and embryo, Curr. Top. Dev. Biol. 77 (2007) 21–49, https://doi.org/10.1016/S0070-2153(06)77002-8.
[37] R. Dumollard, M. Duchen, C. Sardet, Calcium signals and mitochondria at fertilisation, Semin. Cell Dev. Biol. 17 (2006) 314–323, https://doi.org/10.1016/j.semcdb.2006.02.009.
[38] P.B. Esparza-Moltó, J.M. Cuezva, Reprogramming oxidative phosphorylation in cancer: a role for rna-binding proteins, Antioxidants Redox Signal. 33 (2020) 927–945, https://doi.org/10.1089/ars.2019.7988.
[39] J.M. Facucho-Oliveira, St John J.C., The relationship between pluripotency and mitochondrial DNA proliferation during early embryo development and embryonic Stem Cell differentiation, Stem Cell Rev. Reports 5 (2009) 140–158, https://doi.org/10.1007/s12015-009-9058-0.
[40] B. Faustin, R. Rossignol, C. Rocher, G. Bénard, M. Malgat, T. Letellier, Mobilization of adenine nucleotide translocators as molecular bases of the biochemical threshold effect observed in mitochondrial diseases, J. Biol. Chem. 279 (2004) 20411–20421, https://doi.org/10.1074/jbc.M314259200.
[41] J.C. Fernández-Checa, T. Hirano, H. Tsukamoto, N. Kaplowitz, Mitochondrial glutathione depletion in alcoholic liver disease, Alcohol 10, Alcohol Web, (1993) 469–475.
[42] G. Fiermonte, F. De Leonardis, S. Todisco, L. Palmieri, F.M. Lasorsa, F. Palmieri, Identification of the mitochondrial ATP-Mg/Pi transporter, J. Biol. Chem. 279 (2004) 30722–30730, https://doi.org/10.1074/jbc.m400445200.
[43] V. Florian, P. Schönfeld, Alteration of the ADP/ATP translocase isoform pattern improves ATP expenditure in developing rat liver mitochondria, FEBS Lett. 433 (1998) 261–264, https://doi.org/10.1016/S0014-5793(98)00925-9.
[44] C.D.L. Folmes, H. Ma, S. Mitalipov, A. Terzic, Mitochondria in pluripotent stem cells: stemness regulators and disease targets, Curr. Opin. Genet. Dev. 38 (2016) 1–7, https://doi.org/10.1016/j.gde.2016.02.001.
[45] C.D.L. Folmes, T.J. Nelson, A. Martinez-Fernandez, D.K. Arrell, J.Z. Lindor, P.P. Dzeja, Y. Ikeda, C. Perez-Terzic, A. Terzic, Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming, Cell Metabol. 14 (2011) 264–271, https://doi.org/10.1016/j.cmet.2011.06.011.
[46] L. Frattaruolo, M. Brindisi, R. Curcio, F. Marra, V. Dolce, A.R. Cappello, Targeting the mitochondrial metabolic network: a promising strategy in cancer treatment, Int. J. Mol. Sci. 21 (2020) 1–21, https://doi.org/10.3390/ijms21176014.
[47] B. Fu, Y. Zhou, X. Ni, X. Tong, X. Xu, Z. Dong, R. Sun, Z. Tian, H. Wei, Natural killer cells promote fetal development through the secretion of growth-promoting factors, Immunity 47 (2017) 1100–1113.e6, https://doi.org/10.1016/j.immuni.2017.11.018.
[48] B. Geering, H.U. Simon, Peculiarities of cell death mechanisms in neutrophils, Cell Death Differ. 18 (2011) 1457–1469, https://doi.org/10.1038/cdd.2011.75.
[49] I. Genovese, M. Carinci, L. Modesti, G. Aguiari, P. Pinton, C. Giorgi, Mitochondria: insights into crucial features to overcome cancer chemoresistance, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22094770.
[50] G. Gentric, V. Mieulet, F. Mechta-Grigoriou, Heterogeneity in cancer metabolism: new concepts in an old field, Antioxidants Redox Signal. 26 (2017) 462–485, https://doi.org/10.1089/ars.2016.6750.
[51] V. Gogvadze, B. Zhivotovsky, S. Orrenius, The Warburg effect and mitochondrial stability in cancer cells, Mol. Aspect. Med. 31 (2010) 60–74, https://doi.org/10.1016/j.mam.2009.12.004.
[52] Y.N. Gong, J.C. Crawford, B.L. Heckmann, D.R. Green, To the edge of cell death and back, FEBS J. 286 (2019) 430–440, https://doi.org/10.1111/febs.14714.
[53] A. Grado, C. Manchado, R. Iglesias, M. Giralt, Francesc Villarroya, T. Mampel, O. Viñas, Muscle/heart isoform of mitochondrial adenine nucleotide translocase (ANT1) is transiently expressed during perinatal development in rat liver, FEBS Lett. 421 (1998) 213–216, https://doi.org/10.1016/S0014-5793(97)01563-9.
[54] C. Grasso, D.A. Eccles, S. Boukalova, M.S. Fabre, R.H. Dawson, J. Neuzil, P.M. Herst, M.V. Berridge, Mitochondrial DNA affects the expression of nuclear genes involved in immune and stress responses in a breast cancer model, Front. Physiol. 11 (2020), https://doi.org/10.3389/fphys.2020.543962.
[55] F. Guerra, A.A. Arbini, L. Moro, Mitochondria and cancer chemoresistance, Biochim. Biophys. Acta Bioenerg. 1858 (2017) 686–699, https://doi.org/10.1016/j.bbabio.2017.01.012.
[56] W.C. Hahn, R.A. Weinberg, Rules for making human tumor cells, N. Engl. J. Med. 347 (2002) 1593–1603, https://doi.org/10.1056/nejmra021902.
[57] D. Hanahan, R.A. Weinberg, Weinberg RA, Hanahan D. The hallmarks of cancer, 2000 Jan 7, Cell 144 (2011) 646–674. Cell.
[58] J. Hao, W.W. Zhu, C. Sheng, Y. Yu, Q. Zhou, Human parthenogenetic embryonic stem cells: one potential resource for cell therapy, Sci. China Ser. C Life Sci. 52 (2009) 599–602, https://doi.org/10.1007/s11427-009-0096-2.
[59] A.J. Harvey, Mitochondria in early development: linking the microenvironment, metabolism and the epigenome, Reproduction 157 (2019) R159–R179, https://doi.org/10.1530/REP-18-0431.
[60] M. Hashimoto, J.E. Wilson, Membrane potential-dependent conformational changes in mitochondrially bound hexokinase of brain, Arch. Biochem. Biophys. 384 (2000) 163–173, https://doi.org/10.1006/abbi.2000.2085.
[61] K. Hochedlinger, W.M. Rideout, M. Kyba, G.Q. Daley, R. Blelloch, R. Jaenisch, Nuclear transplantation, embryonic stem cells and the potential for cell therapy, Hematol. J. 5 (2004) S114–S117, https://doi.org/10.1038/sj.thj.6200435.
[62] K. Hochedlinger, R. Jaenisch, Monoclonal mice generated by nuclear transfer from mature B and T donor cells, Nature 415 (2002) 1035–1038, https://doi.org/10.1038/nature718.
[63] J.B. Hoek, A. Cahill, J.G. Pastorino, Alcohol and mitochondria: a dysfunctional relationship, Gastroenterology 122 (2002) 2049–2063, https://doi.org/10.1053/gast.2002.33613.
[64] S. Hyun Baik, J. Lee, Adenine nucleotide translocase 2: an emerging player in cancer, J. Stem Cells Regen. Med. 1 (2016), https://doi.org/10.15761/jscrm.1000111.
[65] K. Illmensee, B. Mintz, Totipotency and normal differentiation of single teratocarcinoma cells cloned by injection into blastocysts, Proc. Natl. Acad. Sci. U.S.A. 73 (1976) 549–553, https://doi.org/10.1073/pnas.73.2.549.
[66] I.R. Indran, G. Tufo, S. Pervaiz, C. Brenner, Recent advances in apoptosis, mitochondria and drug resistance in cancer cells, Biochim. Biophys. Acta Bioenerg. 1807 (2011) 735–745, https://doi.org/10.1016/j.bbabio.2011.03.010.
[67] A.M. Intlekofer, L.W.S. Finley, Metabolic signatures of cancer cells and stem cells, Nat. Metab 1 (2019) 177–188, https://doi.org/10.1038/s42255-019-0032-0.
[68] J.M. Izquierdo, A.M. Luis, J.M. Cuezva, Postnatal mitochondrial differentiation in rat liver. Regulation by thyroid hormones of the β-subunit of the mitochondrial F1-ATPase complex, J. Biol. Chem. 265 (1990) 9090–9097, https://doi.org/10.1016/s0021-9258(19)38816-7.
[69] J.M. Izquierdo, J. Ricart, L.K. Ostronoff, G. Egea, J.M. Cuezva, Changing patterns of transcriptional and post-transcriptional control of β-F1-ATPase gene expression during mitochondrial biogenesis in liver, J. Biol. Chem. 270 (1995) 10342–10350, https://doi.org/10.1074/jbc.270.17.10342.
[70] C.T. Jones, T.P. Rolph, Metabolism during fetal life: a functional assessment of metabolic development, Physiol. Rev. 65 (1985) 357–430, https://doi.org/10.1152/physrev.1985.65.2.357.
[71] J.L. Joyal, T. Hagen, J.R. Aprille, Intramitochondrial protein synthesis is regulated by matrix adenine nucleotide content and requires calcium, Arch. Biochem. Biophys. 319 (1995) 322–330, https://doi.org/10.1006/abbi.1995.1300.
[72] R. Justo, M.P. Alcolea, B. Colom, A.N. Riera, M. Gianotti, F.J. García-Palmer, Morphofunctional changes in the mitochondrial subpopulations of conceptus tissues during the placentation process, Cell. Mol. Life Sci. 59 (2002) 2199–2209, https://doi.org/10.1007/s000180200019.
[73] R. Justo, J. Boada, M. Frontera, J. Oliver, J. Bermúdez, M. Gianotti, Gender dimorphism in rat liver mitochondrial oxidative metabolism and biogenesis, Am. J. Physiol. Cell Physiol. 289 (2005) C372–C378, https://doi.org/10.1152/ajpcell.00035.2005.
[74] S.D. Kharche, H.S. Birade, Parthenogenesis and activation of mammalian oocytes for *in vitro* embryo production: a review, Adv. Biosci. Biotechnol. 4 (2013) 170–182, https://doi.org/10.4236/abb.2013.42025.
[75] J. Kim, R.J. DeBerardinis, Mechanisms and implications of metabolic heterogeneity in cancer, Cell Metabol. 30 (2019) 434–446, https://doi.org/10.1016/j.cmet.2019.08.013.
[76] L.J. Kleinsmith, G.B. Pierce, Multipotentiality of single embryonal carcinoma cells, Cancer Res. 24 (1964) 1544–1551.
[77] A.S. Lee, C. Tang, M.S. Rao, I.L. Weissman, J.C. Wu, Tumorigenicity as a clinical hurdle for pluripotent stem cell therapies, Nat. Med. 19 (2013) 998–1004, https://doi.org/10.1038/nm.3267.
[78] J.G. Lees, D.K. Gardner, A.J. Harvey, Pluripotent stem cell metabolism and mitochondria: beyond ATP, Stem Cell. Int. 2017 (2017), https://doi.org/10.1155/2017/2874283.
[79] C.H. Lineweaver, P.C.W. Davies, Comparison of the atavistic model of cancer to somatic mutation theory: phylostratigraphic analyses support the atavistic model, in: The Physics of Cancer, World Scientific Publishing Co., 2020, 2020, pp. 243–261.
[80] G. Lippe, M.C. Sorgato, D.A. Harris, Kinetics of the release of the mitochondrial inhibitor protein. Correlation with synthesis and hydrolysis of ATP, Biochim. Biophys. Acta Bioenerg. 933 (1988) 1–11.
[81] S.M. Lloyd, J. Arnold, A. Sreekumar, Metabolomic profiling of hormone-dependent cancers: a bird's eye view, Trends Endocrinol. Metabol. 26 (2015) 477–485, https://doi.org/10.1016/j.tem.2015.07.001.

[82] M.-N. Lombard, J.-F. Houssais, F. Decloitre, B. Dutrillaux, Liver cells can spontaneously resume proliferation in long-term quiescent primary cultures, Cell Prolif 27 (1994) 177–189, https://doi.org/10.1111/j.1365-2184.1994.tb01415.x.
[83] T. Lonergan, B. Bavister, C. Brenner, Mitochondria in stem cells, Mitochondrion 7 (2007) 289–296.
[84] M. López De Heredia, J.M. Izquierdo, J.M. Cuezva, A conserved mechanism for controlling the translation of β-F1-ATPase mRNA between the fetal liver and cancer cells, J. Biol. Chem. 275 (2000) 7430–7437, https://doi.org/10.1074/jbc.275.10.7430.
[85] C. Lopez-Mediavilla, A. Orfao, M. Gonzalez, J.M. Medina, Identification by flow cytometry of two distinct rhodamine-123-stained mitochondrial populations in rat liver, FEBS Lett. 254 (1989) 115–120, https://doi.org/10.1016/0014-5793(89)81020-8.
[86] C. López-Mediavilla, A. Orfao, J. San Miguel, J.M. Medina, Developmental changes in rat liver mitochondrial populations analyzed by flow cytometry, Exp. Cell Res. 203 (1992) 134–140, https://doi.org/10.1016/0014-4827(92)90048-D.
[87] A.M. Luis, J.M. Izquierdo, L.K. Ostronoff, M. Salinas, J.F. Santaren, J.M. Cuezva, Translational regulation of mitochondrial differentiation in neonatal rat liver. Specific increase in the translational efficiency of the nuclear- encoded mitochondrial β-F1-ATPase mRNA, J. Biol. Chem. 268 (1993) 1868–1875, https://doi.org/10.1016/s0021-9258(18)53935-1.
[88] H.R. Luo, F. Loison, Constitutive neutrophil apoptosis: mechanisms and regulation, Am. J. Hematol. 83 (2008) 288–295, https://doi.org/10.1002/ajh.21078.
[89] O. Lytovchenko, E.R.S. Kunji, Expression and putative role of mitochondrial transport proteins in cancer, Biochim. Biophys. Acta Bioenerg. 1858 (2017) 641–654, https://doi.org/10.1016/j.bbabio.2017.03.006.
[90] A.H. Maehle, Ambiguous cells: the emergence of the stem cell concept in the nineteenth and twentieth centuries, Notes Record Roy. Soc. Lond. 65 (2011) 359–378, https://doi.org/10.1098/rsnr.2011.0023.
[91] N.A. Maianski, J. Geissler, S.M. Srinivasula, E.S. Alnemri, D. Roos, T.W. Kuijpers, Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis, Cell Death Differ. 11 (2004) 143–153, https://doi.org/10.1038/sj.cdd.4401320.
[92] N.A. Maianski, A.N. Maianski, T.W. Kuijpers, D. Roos, Apoptosis of neutrophils, Acta Haematol. 111 (2004) 56–66, https://doi.org/10.1159/000074486.
[93] M.A. Majerus, The relationship between the cancer cell and the oocyte, Med. Hypotheses 58 (2002) 544–551, https://doi.org/10.1054/mehy.2001.1532.
[94] E.N. Maldonado, D.N. DeHart, J. Patnaik, S.C. Klatt, M.B. Gooz, J.J. Lemasters, ATP/ADP turnover and import of glycolytic ATP into mitochondria in cancer cells is independent of the adenine nucleotide translocator, J. Biol. Chem. 291 (2016) 19642–19650, https://doi.org/10.1074/jbc.M116.734814.
[95] A. Mateos, A. Orfao, A. Almeida, M.I. Martin, C. Lopez-Mediavilla, J.M. Medina, J. Fermoso, Effect of ethanol consumption on adult rat liver mitochondrial populations analyzed by flow cytometry, Alcohol Clin. Exp. Res. 19 (1995) 1327–1330, https://doi.org/10.1111/j.1530-0277.1995.tb01620.x.
[96] S.P. Mathupala, Y.H. Ko, P.L. Pedersen, Hexokinase II: cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria, Oncogene 25 (2006) 4777–4786, https://doi.org/10.1038/sj.onc.1209603.
[97] P. May-Panloup, M. Boguenet, H. El Hachem, P.E. Bouet, P. Reynier, Embryo and its mitochondria, Antioxidants 10 (2021) 1–20, https://doi.org/10.3390/antiox10020139.
[98] S. McGuirk, Y. Audet-Delage, J. St-Pierre, Metabolic fitness and plasticity in cancer progression, Trends in Cancer 6 (2020) 49–61, https://doi.org/10.1016/j.trecan.2019.11.009.
[99] L. Minai, J. Martinovic, D. Chretien, F. Dumez, F. Razavi, A. Munnich, A. Rötig, Mitochondrial respiratory chain complex assembly and function during human fetal development, Mol. Genet. Metab. 94 (2008) 120–126, https://doi.org/10.1016/j.ymgme.2007.12.007.
[100] B. Mintz, K. Illmensee, Normal genetically mosaic mice produced from malignant teratocarcinoma cells, Proc. Natl. Acad. Sci. U.S.A. 72 (1975) 3585–3589, https://doi.org/10.1073/pnas.72.9.3585.
[101] R. Moreno-Sánchez, A. Marín-Hernández, E. Saavedra, J.P. Pardo, S.J. Ralph, S. Rodríguez-Enríquez, Who controls the ATP supply in cancer cells? Biochemistry lessons to understand cancer energy metabolism, Int. J. Biochem. Cell Biol. 50 (2014) 10–23, https://doi.org/10.1016/j.biocel.2014.01.025.
[102] R. Moschoi, V. Imbert, M. Nebout, J. Chiche, D. Mary, T. Prebet, E. Saland, R. Castellano, L. Pouyet, Y. Collette, N. Vey, C. Chabannon, C. Recher, J.E. Sarry, D. Alcor, J.F. Peyron, E. Griessinger, Protective mitochondrial transfer from bone marrow stromal cells to acute myeloid leukemic cells during chemotherapy, Blood 128 (2016) 253–264, https://doi.org/10.1182/blood-2015-07-655860.
[103] P.M. Motta, S.A. Nottola, S. Makabe, R. Heyn, R. Jansen, Mitochondrial morphology in human fetal and adult female germ cells, in: Human Reproduction 15, Oxford University Press, 2000, pp. 129–147.
[104] K. Nabi, A. Le, The intratumoral heterogeneity of cancer metabolism, in: Advances in Experimental Medicine and Biology, 1311, Springer, 2021, pp. 149–160.
[105] P.P. Naik, P.P. Praharaj, C.S. Bhol, D.P. Panigrahi, K.K. Mahapatra, S. Patra, S. Saha, S.K. Bhutia, Mitochondrial heterogeneity in stem cells, in: Advances in Experimental Medicine and Biology, 1123, Springer New York LLC, 2019, pp. 179–194.
[106] T. Nakazawa, K. Asami, H. Suzuki, O. Yukawa, Appearance of energy conservation system in rat liver mitochondria during development: the role of adenine nucleotide translocation, J. Biochem. 73 (1973) 397–406, https://doi.org/10.1093/oxfordjournals.jbchem.a130096.
[107] M.T. Nosek, J.R. Aprille, ATP- Mg Pi carrier activity in rat liver mitochondria, Arch. Biochem. Biophys. 296 (1992) 691–697, https://doi.org/10.1016/0003-9861(92)90628-A.
[108] P.C. Nowell, The clonal evolution of tumor cell populations, Science 194 (1976) 23–28, https://doi.org/10.1126/science.959840.
[109] H. Nury, C. Dahout-Gonzalez, V. Trézéguet, G.J.M. Lauquin, G. Brandolin, E. Pebay-Peyroula, Relations between structure and function of the mitochondrial ADP/ATP carrier, Annu. Rev. Biochem. 75 (2006) 713–741, https://doi.org/10.1146/annurev.biochem.75.103004.142747.
[110] A. Paffoni, T.A.L. Brevini, F. Gandolfi, G. Ragni, Parthenogenetic activation: biology and applications in the ART laboratory, Placenta Web. 29 (2008) 121–125.
[111] A. Paffoni, T.A.L. Brevini, E. Somigliana, L. Restelli, F. Gandolfi, G. Ragni, In vitro development of human oocytes after parthenogenetic activation or intracytoplasmic sperm injection, Fertil. Steril. 87 (2007) 77–82, https://doi.org/10.1016/j.fertnstert.2006.05.063.
[112] V.E. Papaioannou, M.W. Mcburney, R.L. Gardner, M.J. Evans, Fate of teratocarcinoma cells injected into early mouse embryos, Nature 258 (1975) 70–73, https://doi.org/10.1038/258070a0.
[113] J.H. Park, W.Y. Pyun, H.W. Park, Cancer metabolism: phenotype, signaling and therapeutic targets, NLM (Medline), Cells 9 (2020).
[114] P.L. Pedersen, Warburg, me and Hexokinase 2: multiple discoveries of key molecular events underlying one of cancers' most common phenotypes, the "Warburg Effect", i.e., elevated glycolysis in the presence of oxygen, J. Bioenerg. Biomembr. 39 (2007) 211–222, https://doi.org/10.1007/s10863-007-9094-x.
[115] G.B. Pierce, Chapter 8: teratocarcinoma: model for A developmental concept of cancer, Curr. Top. Dev. Biol. 2 (1967) 223–246, https://doi.org/10.1016/S0070-2153(08)60289-6.
[116] J.K. Pollak, The maturation of the inner membrane of foetal rat liver mitochondria, Biochem. J. 150 (1975) 477–488.
[117] J.K. Pollak, The interdependence of mitochondrial maturation and glycogen metabolism in perinatal rat liver, Biochem. Soc. Trans. 5 (1977) 341–348, https://doi.org/10.1042/bst0050341.
[118] J.K. Pollak, Mitochondrial heterogeneity in foetal and suckling rat liver: differential leucine incorporation into the proteins of two mitochondrial populations, Biochem. Biophys. Res. Commun. 69 (1976) 823–829, https://doi.org/10.1016/0006-291X(76)90949-9.
[119] J.K. Pollak, E.A. Munn, The isolation by isopycnic density-gradient centrifugation of two mitochondrial populations from livers of embryonic and fed and starved adult rats, Biochem. J. 117 (1970) 913–919, https://doi.org/10.1042/bj1170913.
[120] J.K. Pollak, M. Woog, Changes in the proportions of two mitochondrial populations during the development of embryonic chick liver, Biochem. J. 123 (1971) 347–353, https://doi.org/10.1042/bj1230347.
[121] J.K. Pollak, R. Sutton, The differentiation of animal mitochondria during development, Trends Biochem. Sci. 5 (1980) 23–27, https://doi.org/10.1016/S0968-0004(80)80073-9.
[122] V. Prpic, F.L. Bygrave, Maturation in liver mitochondria of Ruthenium red-sensitive calcium-ion-transport activity and the influence of glucagon administration in vivo and in utero, Biochem. J. 196 (1981) 207–216, https://doi.org/10.1042/bj1960207.
[123] A. Ratna, P. Mandrekar, Alcohol and cancer: mechanisms and therapies, Biomolecules 7 (2017), https://doi.org/10.3390/biom7030061.
[124] J.G. Satav, S.S. Katyare, P. Fatterpaker, A. Sreenivasan, Further characterization of rat liver mitochondrial fractions. Lipid composition and synthesis, and protein profiles, Biochem. J. 156 (1976) 215–223, https://doi.org/10.1042/bj1560215.
[125] B. Scherer, M. Klingenberg, Demonstration of the relation between the adenine nucleotide carrier and the structural changes of mitochondria as induced by adenosine 5′-diphosphate, Biochemistry 13 (1974) 161–170, https://doi.org/10.1021/bi00698a025.
[126] S.M. Schieke, M. Ma, L. Cao, J.P. McCoy, C. Liu, N.F. Hensel, A.J. Barrett, M. Boehm, T. Finkel, Mitochondrial metabolism modulates differentiation and teratoma formation capacity in mouse embryonic stem cells, J. Biol. Chem. 283 (2008) 28506–28512, https://doi.org/10.1074/jbc.M802763200.
[127] P. Schönfeld, S. Fritz, W. Halangk, R. Bohnensack, Increase in the adenine nucleotide translocase protein contributes to the perinatal maturation of respiration in rat liver mitochondria, BBA - Bioenerg 1144 (1993) 353–358, https://doi.org/10.1016/0005-2728(93)90120-5.
[128] S. Sell, On the stem cell origin of cancer, Am. J. Pathol. 176 (2010) 2584–2594, https://doi.org/10.2353/ajpath.2010.091064.
[129] T.N. Seyfried, C. Chinopoulos, Can the mitochondrial metabolic theory explain better the origin and management of cancer than can the somatic mutation theory? Metabolites 11 (2021) https://doi.org/10.3390/metabo11090572.
[130] T.H. Shepard, L.A. Muffley, L.T. Smith, Ultrastructural study of mitochondria and their cristae in embryonic rats and primate (N. nemistrina), Anat. Rec. 252 (1998) 383–392, https://doi.org/10.1002/(SICI)1097-0185(199811)252:3<383::AID-AR6>3.0.CO;2-Z.
[131] N. Shyh-Chang, G.Q. Daley, L.C. Cantley, Stem cell metabolism in tissue development and aging, Dev 140 (2013) 2535–2547, https://doi.org/10.1242/dev.091777.
[132] L. Škárka, K. Bardová, P. Brauner, P. Flachs, D. Jarkovská, J. Kopecký, B. Oštádal, Expression of mitochondrial uncoupling protein 3 and adenine nucleotide translocase 1 genes in developing rat heart: putative involvement in control of mitochondrial membrane potential, J. Mol. Cell. Cardiol. 35 (2003) 321–330, https://doi.org/10.1016/S0022-2828(03)00016-6.

[133] D. Solter, I. Damjanov, Teratocarcinomas rarely develop from embryos transplanted into athymic mice [16], Nature 278 (1979) 554–555, https://doi.org/10.1038/278554a0.
[134] C. Sonnenschein, A.M. Soto, Somatic mutation theory of carcinogenesis: why it should be dropped and replaced, Mol. Carcinog. 29 (2000) 205–211, https://doi.org/10.1002/1098-2744(200012)29:4<205::aid-mc1002>3.0.co;2-w.
[135] A.M. Soto, C. Sonnenschein, The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory, Bioessays 33 (2011) 332–340, https://doi.org/10.1002/bies.201100025.
[136] L.C. Stevens, The biology of teratomas, Adv. Morphog. 6 (1967) 1–31, https://doi.org/10.1016/b978-1-4831-9953-5.50005-6.
[137] L.C. Stevens, The development of transplantable teratocarcinomas from intratesticular grafts of pre- and postimplantation mouse embryos, Dev. Biol. 21 (1970) 364–382, https://doi.org/10.1016/0012-1606(70)90130-2.
[138] L.C. Stevens, D.S. Varnum, The development of teratomas from parthenogenetically activated ovarian mouse eggs, Dev. Biol. 37 (1974) 369–380, https://doi.org/10.1016/0012-1606(74)90155-9.
[139] N. Suzuki, S. Yamazaki, T. Yamaguchi, M. Okabe, H. Masaki, S. Takaki, M. Otsu, H. Nakauchi, Generation of engraftable hematopoietic stem cells from induced pluripotent stem cells by way of teratoma formation, Mol. Ther. 21 (2013) 1424–1431, https://doi.org/10.1038/mt.2013.71.
[140] B.B. Swelstad, C.L. Kerr, Current protocols in the generation of pluripotent stem cells: theoretical, methodological and clinical considerations, Stem Cell. Clon Adv. Appl. 3 (2010) 13–27, https://doi.org/10.2147/sccaa.s8051.
[141] A.S. Tan, J.W. Baty, L.F. Dong, A. Bezawork-Geleta, B. Endaya, J. Goodwin, M. Bajzikova, J. Kovarova, M. Peterka, B. Yan, E.A. Pesdar, M. Sobol, A. Filimonenko, S. Stuart, M. Vondrusova, K. Kluckova, K. Sachaphibulkij, J. Rohlena, P. Hozak, J. Truksa, D. Eccles, L.M. Haupt, L.R. Griffiths, J. Neuzil, M.V. Berridge, Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA, Cell Metabol. 21 (2015) 81–94, https://doi.org/10.1016/j.cmet.2014.12.003.
[142] H.L. Tang, H.M. Tang, K.H. Mak, S. Hu, S.S. Wang, K.M. Wong, C.S.T. Wong, H.Y. Wu, H.T. Law, K. Liu, C.C. Talbot, W.K. Lau, D.J. Montell, M.C. Fung, Cell survival, DNA damage, and oncogenic transformation after a transient and reversible apoptotic response, Mol. Biol. Cell 23 (2012) 2240–2252, https://doi.org/10.1091/mbc.E11-11-0926.
[143] T. Tataranni, C. Piccoli, Dichloroacetate (DCA) and cancer: an overview towards clinical applications, Oxid. Med. Cell. Longev. 2019 (2019), https://doi.org/10.1155/2019/8201079.
[144] A.P. Thankamony, K. Saxena, R. Murali, M.K. Jolly, R. Nair, Cancer stem cell plasticity – a deadly deal, Front. Mol. Biosci. 7 (2020), https://doi.org/10.3389/fmolb.2020.00079.
[145] L. Torresano, C. Nuevo-Tapioles, F. Santacatterina, J.M. Cuezva, Metabolic reprogramming and disease progression in cancer patients, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1866 (2020), https://doi.org/10.1016/j.bbadis.2020.165721.
[146] J. Traba, A. Del Arco, M.R. Duchen, G. Szabadkai, J. Satrústegui, SCaMC-1 promotes cancer cell survival by desensitizing mitochondrial permeability transition via ATP/ADP-mediated matrix Ca 2 buffering, Cell Death Differ. 19 (2012) 650–660, https://doi.org/10.1038/cdd.2011.139.
[147] V. Trézéguet, L. Pélosi, G.J.M. Lauquin, G. Brandolin, The mitochondrial ADP/ATP carrier: functional and structural studies in the route of elucidating pathophysiological aspects, J. Bioenerg. Biomembr. 40 (2008) 435–443, https://doi.org/10.1007/s10863-008-9178-2.
[148] E. Tsogtbaatar, C. Landin, K. Minter-Dykhouse, C.D.L. Folmes, Energy metabolism regulates stem cell pluripotency, Front. Cell Dev. Biol. 8 (2020), https://doi.org/10.3389/fcell.2020.00087.
[149] C. Valcarce, R.M. Navarrete, P. Encabo, E. Loeches, J. Satrústegui, J.M. Cuezva, Postnatal development of rat liver mitochondrial functions. The roles of protein synthesis and of adenine nucleotides, J. Biol. Chem. 263 (1988) 7767–7775, https://doi.org/10.1016/s0021-9258(18)68565-5.
[150] C. Valcarce, J. Vitorica, J. Satrustegui, J.M. Cuezva, Rapid postnatal developmental changes in the passive proton permeability of the inner membrane in rat liver mitochondria, J. Biochem. 108 (1990) 642–645.
[151] C. Valcarce, J.M. Cuezva, Interaction of adenine nucleotides with the adenine nucleotide translocase regulates the developmental changes in proton conductance of the inner mitochondrial membrane, FEBS Lett. 294 (1991) 225–228, https://doi.org/10.1016/0014-5793(91)81435-B.
[152] J. Van Blerkom, Mitochondria as regulatory forces in oocytes, preimplantation embryos and stem cells, Reprod. Biomed. Online 16 (2008) 553–569, https://doi.org/10.1016/S1472-6483(10)60463-4.
[153] J. Van Blerkom, Mitochondria in human oogenesis and preimplantation embryogenesis: engines of metabolism, ionic regulation and developmental competence, Reproduction 128 (2004) 269–280, https://doi.org/10.1530/rep.1.00240.
[154] J. Van Blerkom, Mitochondria in early mammalian development, Semin. Cell Dev. Biol. 20 (2009) 354–364, https://doi.org/10.1016/j.semcdb.2008.12.005.
[155] J. Van Blerkom, P. Davis, High-polarized (ΔΨmHIGH) mitochondria are spatially polarized in human oocytes and early embryos in stable subplasmalemmal domains: developmental significance and the concept of vanguard mitochondria, Reprod. Biomed. Online 13 (2006) 246–254, https://doi.org/10.1016/S1472-6483(10)60622-0.
[156] J. Van blerkom, P. Davis, Mitochondrial signaling and fertilization, Mol. Hum. Reprod. 13 (2007) 759–770, https://doi.org/10.1093/molehr/gam068.
[157] B.J. van Raam, W. Sluiter, E. de Wit, D. Roos, A.J. Verhoeven, T.W. Kuijpers, Mitochondrial membrane potential in human neutrophils is maintained by complex III activity in the absence of supercomplex organisation, PLoS One 3 (2008), https://doi.org/10.1371/journal.pone.0002013.
[158] M.G. Vander Heiden, R.J. DeBerardinis, Understanding the intersections between metabolism and cancer biology, Cell 168 (2017) 657–669, https://doi.org/10.1016/j.cell.2016.12.039.
[159] I. Vega-Naredo, R. Loureiro, K.A. Mesquita, I.A. Barbosa, L.C. Tavares, A.F. Branco, J.R. Erickson, J. Holy, E.L. Perkins, R.A. Carvalho, P.J. Oliveira, Mitochondrial metabolism directs stemness and differentiation in P19 embryonal carcinoma stem cells, Cell Death Differ. 21 (2014) 1560–1574, https://doi.org/10.1038/cdd.2014.66.
[160] A. Wanet, T. Arnould, M. Najimi, P. Renard, Connecting mitochondria, metabolism, and stem cell fate, Stem Cell. Dev. 24 (2015) 1957–1971, https://doi.org/10.1089/scd.2015.0117.
[161] O. Warburg, Injuring of respiration the origin of cancer cells, Science 123 (1956) 309–314, https://doi.org/10.1126/science.123.3191.309.
[162] O. Warburg, The Prime Cause and Prevention of Cancer, Triltsch, Würzburg, Germany, 1967, pp. 6–16.
[163] M. Wilding, G. Coppola, B. Dale, L. Di Matteo, Mitochondria and human preimplantation embryo development, Reproduction 137 (2009) 619–624, https://doi.org/10.1530/REP-08-0444.
[164] C.D. Wiley, J. Campisi, From ancient pathways to aging cells - connecting metabolism and cellular senescence 23, Cell Metab., 2016, pp. 1013–1021.
[165] I. Wilmut, A.E. Schnieke, J. McWhir, A.J. Kind, K.H.S. Campbell, Viable offspring derived from fetal and adult mammalian cells, Nature 385 (1997) 810–813, https://doi.org/10.1038/385810a0.
[166] D.C. Woods, Mitochondrial heterogeneity: evaluating mitochondrial subpopulation dynamics in stem cells, Stem Cell. Int. 2017 (2017), https://doi.org/10.1155/2017/7068567.
[167] X. Xu, S. Duan, F. Yi, A. Ocampo, G.H. Liu, J.C. Izpisua Belmonte, Mitochondrial regulation in pluripotent stem cells, Cell Metabol. 18 (2013) 325–332, https://doi.org/10.1016/j.cmet.2013.06.005.
[168] L. Yu, M. Lu, D. Jia, J. Ma, E. Ben-Jacob, H. Levine, B.A. Kaipparettu, J.N. Onuchic, Modeling the genetic regulation of cancer metabolism: interplay between glycolysis and oxidative phosphorylation, Cancer Res. 77 (2017) 1564–1574, https://doi.org/10.1158/0008-5472.CAN-16-2074.
[169] L.X. Zampieri, C. Silva-Almeida, J.D. Rondeau, P. Sonveaux, Mitochondrial transfer in cancer: a comprehensive review, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22063245.
[170] G. Zhang, B. Shang, P. Yang, Z. Cao, Y. Pan, Q. Zhou, Induced pluripotent stem cell consensus genes: implication for the risk of tumorigenesis and cancers in induced pluripotent stem cell therapy, Stem Cell. Dev. 21 (2012) 955–964, https://doi.org/10.1089/scd.2011.0649.
[171] J. Zhang, J. Zhao, P. Dahan, V. Lu, C. Zhang, H. Li, M.A. Teitell, Metabolism in pluripotent stem cells and early mammalian development, Cell Metabol. 27 (2018) 332–338, https://doi.org/10.1016/j.cmet.2018.01.008.
[172] W. Zhou, M. Choi, D. Margineantu, L. Margaretha, J. Hesson, C. Cavanaugh, C.A. Blau, M.S. Horwitz, D. Hockenbery, C. Ware, H. Ruohola-Baker, HIF1α induced switch from bivalent to exclusively glycolytic metabolism during ESC-to-EpiSC/hESC transition, EMBO J. 31 (2012) 2103–2116, https://doi.org/10.1038/emboj.2012.71.

LIST OF ABBREVIATIONS

ECGP: Egg Cell's Genetic Program
iPSC: induced Pluripotent Stem Cell
ESC: Embryonic Stem Cell
pESC: Parthenogenic Embryonic Stem Cell
PSC: Pluripotent Stem Cell
hESC: Human Embryonic Stem Cell
OXPHOS: Oxidative Phosphorylation
iMM: inner Mitochondrial Membrane
DCA: DiChloroAcetate
ADP: Adenosine 5'diPhosphate
ATP: Adenosine 5'Triphosphate
ANT: Adenine Nucleotide Translocase
ANT1, ANT2, ANT3: Adenine Nucleotide Translocase isoforms 1, 2, 3
SCaMC: ATP-Mg/Pi carrier protein
Pi: Phosphate
Mg: Magnesium
ATP-Mg2: divalent ATP-Mg
HPO2: divalent Phosphate
F1ATPase: The catalytic component of ATP synthase
IF1: The ATPase Inhibitory Factor 1