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Review

Mitochondrial biology in cancer stem cells

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ABSTRACT

Cancer stem cells (CSCs) have been suggested to be responsible for tumor re-growth and relapse. Physiological and morphological knowledge of CSCs may be essential for the development of new therapeutic strategies targeting cancer development, progression, and recurrence. Current research is focused on a deeper understanding of CSCs metabolic profiles, taking into consideration their energy demands. Energy metabolism and mitochondrial function are important factors operating on stemness maintenance and cell fate specification. Due to the role of mitochondria as central hubs in the overall cell metabolism and death and survival pathways, research on their physiology in CSCs is of paramount importance to decipher mechanisms underlying their therapy-resistant phenotype. In this review, we focus on CSCs mitochondrial biology and mitochondria-related signaling pathways that contribute to CSCs survival and maintenance, thereby representing possible therapeutic targets.

1. Introduction

The existence of different tumor types and the concept of tumor heterogeneity were proposed decades ago, being now widely accepted [1]. Such heterogeneity is represented by differential tumor cell populations with distinct proliferative and differentiation capacities within the same tumor bulk. Pioneering studies from Hewitt et al. [2] together with a later work from Lapidot et al. [3] supported the idea of tumor heterogeneity, and suggested the hypothesis of cancer stem cells (CSCs) as tumor-initiating cells. Further studies by John Dick and colleagues [4] replicated and transferred these findings to different tumor types such as glioblastomas [5], breast [6] and colorectal tumors, among other neoplastic lesions [7], convincingly demonstrating the existence of CSCs.

Two models were proposed to explain tumor heterogeneity: the clonal evolution model (or stochastic model) based on the accumulation of mutations which leads to the loss of normal cell traits, and the CSCs model (or hierarchical model). In contrast with the stochastic model, the CSCs hypothesis suggests the existence of hierarchical and heterogeneous cell populations within a tumor. Given their ability to indefinitely proliferate, the stem-like counterparts of those cell populations would generate an entire tumor [8–10]. It is noteworthy that these two models are not exclusive, as showed in leukemic CSCs which undergo clonal evolution [8]. In fact, a publication from Tomasetti and Vogelstein [11] proposed that CSCs could be mostly originated from stochastic events occurring during DNA replication in normal adult stem cells. The authors claimed that cancer risk is strongly correlated with abnormal number of divisions in normal stem-cells. Random mutations during DNA replication would induce differential replication profiles which disrupt homeostatic balance of tissues, promoting tumor origin and development. Therefore, two hypotheses have been proposed regarding the origin of CSCs: one pointing out that a normal stem-progenitor suffering a hit mutation acquires tumorigenic potential and self-renewal abilities, and the second suggesting that CSCs can arise from cells that undergone epithelial-mesenchymal transition (EMT) in which epithelial cells transform and acquire the capacity to disseminate and migrate through different tissues, suffering latter additional dedifferentiation events [12,13].

Currently, CSCs are described as being a subset of tumor cells having unlimited self-renewal ability and the capacity to differentiate and generate cell diversity comprising a whole tumor. Specific CSCs phenotypes have been reported as clinically relevant to design strategies in order to prevent cancer initiation and relapse. This particular group of cells is highly tumorigenic, having high cell plasticity associated to the multiplicity of cell fate paths they can undertake, known as “dynamic stemness” [14–16]. It is possible to identify CSCs through the

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specific expression patterns of markers [17], which vary within different lineages. For instance, CD133 is normally associated with brain [18], prostate [19] and colorectal [20] tumors, while CD24 and CD44 are linked to breast [6] and pancreatic ones [20]. In the same direction, aldehyde dehydrogenase (ALDH) [21], the epithelial cell adhesion molecule (EpCAM, ESA, TROP1) [22] and microRNAs (miRNA) specific expression [23] are others examples of specific markers allowing for the identification of CSCs.

CSCs have the capacity to re-colonize either in the primary tumor bulk or in other distant sites from the primary tumor [24–26]. Among CSCs hallmarks, one can mention a slow cell-cycle kinetics [27], a high resistance to DNA damage and an increased capacity to repair such damage [28,29], together with a distorted telomerase function which was described to prompt cell immortality [30]. Moreover, CSCs also show an overexpression of multiple drug resistance transporters [31,32], and a higher resistance to mitochondria-mediated cell death mechanisms [33]. Their specific microenvironment, based in hypoxic conditions with low pH values, contributes to stemness maintenance, and leads to the acquisition of new phenotypes through natural resistant clone selection [34,35]. An important imprint on CSCs is their altered cell metabolism and related-signaling pathways which grants their resistant profiles, contributing to the failure of anticancer treatments.

Mitochondria are key organelles involved in several processes related to cell proliferation and survival. Mitochondrial functions in living cells include, between others, the regulation of calcium homeostasis, cell signaling and fatty acid oxidation. Overall, their most important function is the generation of ATP, which holds cell metabolism. Mitochondria have a central role in cell life and death decisions and recent research points out a strong interplay between mitochondrial function and pluripotency states [36,37]. Thus, a specific metabolic program involving mitochondrial remodeling appears to be intrinsically required to fullfil the demands of a pluripotency stage. It has been previously described that during stem cell differentiation, higher amounts of energy are needed, supporting a proper remodelling of the bioenergetic machinery in order to increase mitochondrial oxidation of substrates [38–40]. Given the central role of these organelles in cell life and death decisions, we will focus on mitochondrial physiology in CSCs biology.

2. Mitochondria in non-neoplastic stem cells

Stem cells are classified into three broad categories: embryonic stem cells (ESCs) arising from the inner mass of early blastocysts and sharing the ability to differentiate into cells from all three germ layers; somatic (or adult) stem cells (SSCs) that can be found in different adult tissues, and include cells such as mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs); and finally induced pluripotent cells (iPSCs) that are somatic cells (e.g. fibroblasts) artificially reprogrammed back into an embryonic-like state through overexpression of stemness transcription factors.

Although self-renewal and differentiation capacity diverge among the different types of stem cells, current evidence has demonstrated that the regulation of energy metabolism takes part in determining stem cells fate, especially by playing a critical role in stem cell maintenance and differentiation [41]. Thus, a large amount of data suggests a close connection between stemness and mitochondrial morphology and function. Mitochondrial ultrastructure presents clear alterations over the entire span of the cell differentiation process. Mitochondria from ESCs are more immature, rare and globular, presenting poorly developed cristae and a perinuclear localization [42,43]. The differentiation of ESCs results in more mature mitochondrial cristae in a more filamentous mitochondrial network. Beyond these morphological alterations, mitochondrial biogenesis, DNA content and energy metabolism are also changed over the differentiation process [43,44]. Mitochondrial DNA instability, including mutations and/or altered copy number, has been described to specifically affect stem cells viability, function and differentiation potential [45]. Interestingly, increased levels of mitochondrial DNA copy number and mitochondrial biogenesis were associated with cell differentiation [44,46], suggesting that decreased mitochondrial activity is favorable to a stemness phenotype.

The glycolytic pathway is preferred in ESCs that present low rates of mitochondrial respiration and high lactate production. Therefore, and similarly to cancer cells, ESCs exhibit the Warburg effect, in which glycolytic ATP production is preferred even in the presence of oxygen [47,48]. Although glycolysis is less proficient in terms of energy production, the generation of ATP is faster than by OXPHOS. Moreover, such preference for glycolytic-generated ATP is associated with lower reactive oxygen species (ROS) production [49] that accounts for stemness maintenance either on hypoxia or normoxia. Nevertheless, ESCs have the capacity to switch between anaerobic glycolysis and mitochondrial OXPHOS. This metabolic switch is frequently observed during ESCs differentiation, demonstrating an evident energetic plasticity in order to fulfill their specific energy requirements. In fact, differentiation of ESCs and iPSCs is associated with increased ATP levels and reduced lactate production [50]. Despite this, not all types of ESCs show this energetic plasticity [51]. One example was described in human ESCs (hESCs) which mostly meet their energy requirements via anaerobic glycolysis [51]. Zhou et al. [52] mentioned that although hESCs present a more complex and expanded mitochondrial network, the decreased expression of cytochrome c oxidase (COX) indicates a lower mitochondrial respiratory capacity.

Mitochondria also play a crucial role in the reprogramming of iPSCs. The conversion from somatic OXPHOS to stem-like glycolysis phenotype has been postulated to be required for reprogramming of cells into pluripotent stem cells. Hence, more than half of the proteins differentially expressed in iPSCs versus their differentiated counterparts show a mitochondrial location, underlining the conservation of certain mitochondria-related factors which seem to be particularly important for the maintenance of core pluripotency circuits [53].

Somatic stem cells, MSCs or HSCs, also present immature mitochondria, although with higher mitochondrial activity when compared to ESCs [54]. Their successful differentiation requires a further increase in mitochondrial biogenesis and activity, together with a decrease in the glycolytic flux [55–57].

It is undeniable that mitochondrial dynamics and biogenesis are involved in cell differentiation. Recent proof of concept is the studies from Parker et al. [58] and Khacho et al. [59]. Those authors demonstrated how changes in mitochondrial dynamics, namely through decreased mitochondrial fission [58] or favored fusion processes [59], lead to the maintenance of a stem cell-like pool.

All these data point out a bidirectional relationship between mitochondrial physiology and cell differentiation with important implications for regenerative medicine and cancer.

3. Mitochondrial physiology in cancer stem cells

Shifts on metabolic profiles have been recognized as driving forces for the initial stages of tumorigenesis [60]. It is known that different tumors show markers for CSCs, which are associated with tumor progression and tumor migratory capacity [21,61,62]. Considering tumor heterogeneity and CSCs as the hierarchical “bottom line” for cancer development and evasion [63], understanding CSCs metabolic features is of paramount importance to target their radio- and chemotherapeutic resistance profiles [64–66]. Metabolic aberrations in cancer related to mitochondrial dysfunction have been reported to be linked to the following hallmark pathways as i) proliferative potential, ii) impaired apoptosis, iii) increased anabolism and iv) decreased autophagy [67,68]. Such mitochondrial alterations connect drug resistance profiles with the blockade of cell death pathways. Regarding its metabolic profile, CSCs share some of the characteristics described in the previous section for ESCs. Actually, CSCs were reported by our group [43] and