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Review

Mitochondrial bioenergetic function and metabolic plasticity in stem cell differentiation and cellular reprogramming ☆

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ABSTRACT

Background: The self-renewal ability and pluripotent differentiation potential of stem cells hold great promise for regenerative medicine. Many studies focus on the lineage-specific differentiation and expansion of stem cells, but little is known about the regulation of glycolysis and mitochondrial biogenesis and function during these processes. Recent studies have demonstrated a strong correlation between cellular metabolism and the pluripotency and differentiation potential of stem cells, which indicates the importance of bioenergetic function in the regulation of stem cell physiology.
Scope of review: We summarize recent findings in the control of stem cell competence through the regulation of bioenergetic function in embryonic, hematopoietic, mesenchymal, and induced pluripotent stem cells, and discuss the up-to-date understanding of the molecular mechanisms involved in these biological processes.
Major conclusions: It is believed that the metabolic signatures are highly correlated with the stemness status (high glycolytic flux) and differentiation potential (mitochondrial function) of stem cells. Besides, mitochondrial rejuvenation has been observed to participate in the reprogramming process.
General significance: Understanding the metabolic regulation of stem cells will have great value in the characterization and isolation of stem cells with better differentiation potential. It also provides novel strategies of metabolic manipulation to increase the efficiency of cellular reprogramming. This article is part of a Special Issue entitled Biochemistry of Mitochondria, Life and Intervention 2010.

1. Introduction

1.1. Energy metabolism, an emerging issue in stem cell biology

Mitochondria, the powerhouse generating ATP and the warehouse where several vital biosynthetic pathways take place in mammalian cells, adjust their number and function in different types of cells in response to different energy demands. These changes are effected by mitochondrial biogenesis, which must be accomplished through the coordinated expression of proteins encoded by nuclear DNA as well as by mitochondrial DNA (mtDNA) [1]. The biogenesis and functions of mitochondria are important in the homeostasis of cell physiology, but little is known about their roles in the maintenance and differentiation of stem cells. Stem cells are characterized by two essential functions: the self-renewal ability and multiple differentiation potential, which enable them to give rise to progenies in different tissues throughout the lifespan of an organism, and make them extremely valuable in the application of cell therapy and tissue engineering [2]. The competence of stem cells is regulated by intrinsic signals such as transcriptional and epigenetic regulation of an array of stemness genes as well as extrinsic factors such as the microenvironment and oxygen availability in niches [3]. Recently, researchers reported that stem cells have specific metabolic signatures distinct from somatic cells, and that metabolic pathways as well as mitochondrial function are also involved in the regulation of stem cell physiology [4–6]. However, the biological significance and molecular mechanisms underlying the metabolic regulation of stem cell properties remain largely elusive. In this review, we discuss recent advances in the investigation of mitochondrial roles in stem cell biology, which are summarized in Fig. 1.

Abbreviations: bFGF, basic fibroblast growth factor; Pol γ, DNA polymerase γ; ESC, embryonic stem cell; HIF, hypoxia-inducible factor; HSC, hematopoietic stem cell; iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; mtTFA, mitochondrial transcription factor A; NOX, NAD(P)H oxidase; NSC, neural stem cell; PHD, prolyl hydroxylase; ROS, reactive oxygen species; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau protein; $\Delta\Psi_m$, mitochondrial membrane potential

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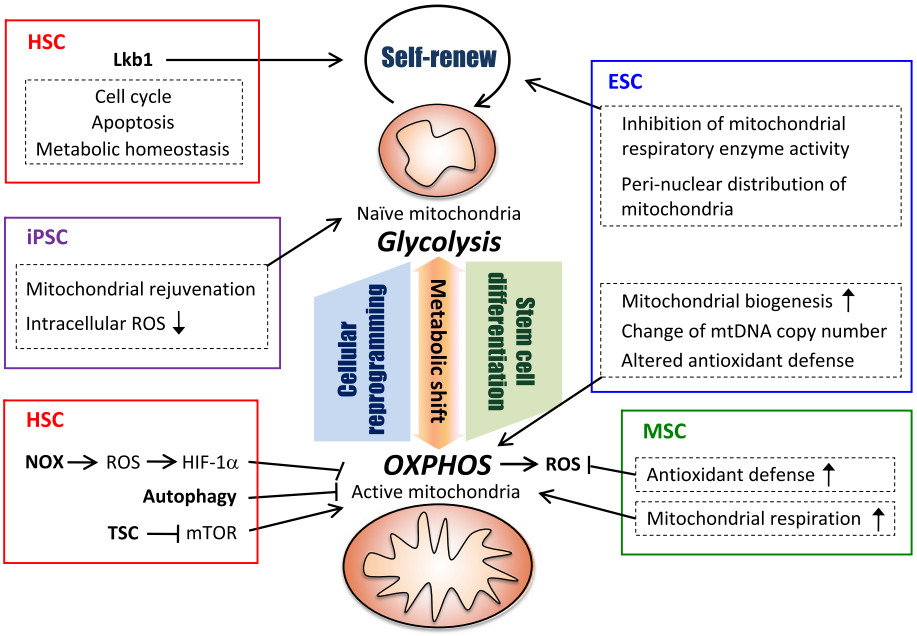

Fig. 1. The metabolic regulation of self-renewal and differentiation of stem cells. This schematic figure summarizes the metabolic regulation and mitochondrial changes in the maintenance of self-renewal capability and induction of differentiation of three types of stem cells. The upper-left panel shows that Lkb1 can regulate HSC self-renewal through altering metabolic homeostasis, and the lower-left panel shows that NOX–ROS signaling can stabilize HIF-1α; autophagy pathway is active in HSC to prevent mitochondrial activation; TSC inhibits mTOR-mediated mitochondrial biogenesis, and these three mechanisms contribute to the maintenance of self-renewal capability of HSCs. The middle-left panel shows that cellular reprogramming induces rejuvenation of mitochondria and decrease of intracellular ROS of iPSCs. The upper-right panel shows that the respiratory enzyme complex activity and distribution of mitochondria are associated with ESC pluripotency. On the other hand, mitochondrial activation is essential for the differentiation of ESCs. The lower-right panel shows that the metabolic shift from glycolysis to mitochondrial respiration is critical for the differentiation of MSCs. ESC, embryonic stem cells; HIF-1α, hypoxia inducible factor-1α; HSC, hematopoietic stem cells; iPSC, induced pluripotent stem cells; MSC, mesenchymal stem cells; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NOX, NAD(P)H oxidase; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

2. Embryonic stem cells

Embryonic stem cells (ESCs) are derived from the inner cell mass of blastocysts, and they have the pluripotent differentiation ability to give rise to cells of all three germ layers [7], which makes them an invaluable source for cell therapy in clinical application. There are plenty of studies focusing on the regulation of pluripotency and differentiation of ESCs, and some recent reports have provided evidence that cellular metabolism plays an important role in these processes. Cho and coworkers [8] examined the bioenergetic function and redox status of hESCs during spontaneous differentiation. They observed a profound activation of mitochondrial biogenesis such as increase in the mitochondrial mass, mtDNA copy number and intracellular ATP content as well as maturation of mitochondrial ultrastructure in conjunction with a dynamic change in the expression of antioxidant enzymes. This finding demonstrates a dramatic difference in the metabolic phenotype between ESCs and their differentiated progenies. Saretzki et al. [9] also observed an increase of mitochondrial mass during spontaneous differentiation of hESCs along with an increase of intracellular and intra-mitochondrial ROS and DNA damage, presumably due to the down-regulation of antioxidant enzymes, which indicates that ESCs tend to protect themselves from excess oxidative stress caused by oxidative metabolism. Another study using confocal microscopy also revealed that the proportion of mitochondria with high mitochondrial membrane potential ($\Delta\Psi_m$) was very low in hESCs as compared with their differentiated cardiomyocytes [10], indicating a low mitochondrial function in ESCs. Afterwards, Kondoh et al. [11] showed that the proliferative capacity of mESCs is strongly correlated with the glycolytic flux and inversely related to mitochondrial oxygen consumption, which indicates that low oxidative metabolism is characteristic of ESCs. Moreover, Varum et al. [12] showed that inhibition of mitochondrial respiratory enzyme Complex III by the treatment of hESCs with either 20 nM antimycin A or 20 nM myxothiazol could recapitulate the effect of basic fibroblast growth factor (bFGF) on the maintenance of pluripotency of hESCs in the absence of bFGF. They demonstrated that antimycin A acted partially through the FGF receptor pathway and that mitochondrial ROS was involved in this regulation. Their findings strongly suggest that repression of mitochondrial function is essential for the maintenance of the pluripotency of ESCs and manipulation of metabolic pathways may be a promising strategy in the regulation of stem cell physiology. However, the opposite observation was also reported to suggest that mitochondrial metabolism is not repressed and oxidative phosphorylation is important for the energy supply of ESCs. Birket and coworkers [13] showed that hESCs rely more on aerobic metabolism (77% of ATP from oxidative phosphorylation) than do hESCs-derived neural stem cells (NSCs), which is consistent with the higher expression levels of mitochondrial genes in hESCs as compared with a panel of differentiated cell types. The authors speculated that the high ATP turnover of hESCs is associated with a higher rate of secretion of macromolecules. However, they could not exclude the possibility that NSCs might exist in a transitional cell status that had a metabolic energy demand lower than that of ESCs, and that the mitochondrial bioenergetic function of mature neurons was higher than that of ESCs.

In addition to the regulation of pluripotency, mitochondrial function is also a determinant of the differentiation capability of ESCs. Schieke et al. [14] showed that mESCs with low $\Delta\Psi_m$ and low mitochondrial oxygen consumption rate were more easily to be induced to undergo mesodermal differentiation and resistant to teratoma formation, while those with high $\Delta\Psi_m$ behaved the opposite way. They identified mTOR (mammalian target of rapamycin) as an integral factor coupling the regulation of mitochondrial metabolism to the cell fate of ESCs. Spitkovsky et al. [15] found that mitochondrial biogenesis was enhanced during *in vitro* cardiogenic differentiation of mESCs and mitochondrial respiratory enzyme Complex III activity was essential for the initiation of myocardial differentiation. Similarly, Chung and coworkers [16,17] reported that the metabolic shift from glycolysis to mitochondrial respiration was required for the differentiation of mESCs into functional cardiomyocytes. Crespo and coworkers [18] showed that the mitochondrial ROS produced from