A mitochondrial view of cell fate

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Editorial

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The progressive transition of cell fate identity towards more differentiated states is a defining feature of organismal development. Recent breakthrough studies on cellular reprogramming demonstrated that this unidirectional process can be manipulated and reverted. Therefore, cell fate identity is plastic and can be modulated and fine-tuned to allow the generation of specified cell types.

The mechanisms controlling this plasticity and cell fate specification are traditionally assumed to be almost entirely dependent on genetic/epigenetic regulation. However, this nuclear-centric view of cell fate identity might not be sufficiently exhaustive. Recently, mitochondria and energy metabolism have been shown to exert a critical role in governing stem cell reprogramming and differentiation. Metabolic intermediates may in fact function as epigenetic regulators. It is thus plausible that energetic requirement, redox homeostasis, and biosynthetic pathways, all of which are tightly linked to mitochondrial metabolism, may crosstalk with the nucleus to shape cellular identity.

In this special issue, entitled "*Mitochondria and metabolism remodeling in cellular reprogramming and differentiation*", we present seven review pieces by some of the key contributors of this nascent field summarizing the recent discoveries and upcoming challenges of the mitochondria/metabolic modulation in stem cell biology and in human disease states.

The first review by Folmes and Terzic [1] functions as a perfect introduction to the field. It provides a comprehensive and detailed overview of the implications of energy

metabolism and mitochondria for stemness, reprogramming, and differentiation, and how these would reflect into regenerative medicine practice.

The second manuscript by the group of Michael Teitell [2] focuses on the distinct features of stem cell mitochondria in the regulation of apoptosis. Deciphering these mechanisms would not only advance our understanding of the stem cell fate but may also help developing safer approaches for stem cell-based cellular replacement therapies.

The review by Ruohola-Baker and colleagues [3] describes the metabolic changes observed in naïve-to-primed embryonic stem cell development and in cardiomyocyte maturation. Importantly, the authors suggest that dissecting the metabolic switches taking place in physiological development may shed light on potential strategies for correcting them in pathological cases.

The piece written by Justin St. John [4] illustrates the relevance of mitochondrial genome, and its cross-talk with the chromosomal genome, during development and cellular reprogramming. In addition, it indicates how mitochondrial DNA may not only influence physiological differentiation but also the occurrence of human pathologies including cancer.

In the review written by my team [5], we address the impact of mitochondrial and metabolic modulation on neural differentiation. Human brain energy metabolism exhibits unique features and the difficulty in reproducing them with the current model systems may be at the bases of the lack of therapeutic strategies. It is thus our hope that a new era of human stem cell-based models may bring novel opportunities for untreatable brain diseases.

The article from the group of Ng Shyh-Chang [6] further explores the role of stem cell mitochondria during aging and age-associated diseases. The authors illustrate how stem cell factors and signaling pathways may converge on the mitochondria to modulate cellular and organismal longevity. Therefore, they conclude that targeting and repairing stem cell mitochondria might represent a strategy to counteract aging-related degenerative diseases in the future.

The current mitochondria-based therapeutic applications using mesenchymal stem cells are finally summarized in the manuscript by Yau-Huei Wei and colleagues [7]. The authors elucidate how the beneficial effect of mesenchymal stem cell transplantation may also be due to the transferring of stem cell mitochondria into the injured cells, thereby modulating cellular metabolism *in situ*. This may be relevant for improving the therapeutic outcomes of stem cell therapy in the future.

In conclusion, mitochondria and energy metabolism appear as key regulators of cell fate identity and plasticity. Every step towards the understanding of their underlying mechanisms may not only advance our appreciation of stemness, reprogramming, and differentiation, but may also bring novel important knowledge concerning human diseases and targeted therapeutic strategies. Exciting discoveries are in front of us.

Alessandro Prigione

"Mitochondria and Cell Fate Reprogramming"

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