

Correlation between stemness and mitochondria functionality

Giuseppina Nocca, Massimo Cordaro, Giuseppe E. Martorana

The application of stem cells to regenerative medicine is one of the most crucial field of research, the encouraging developments of which have been already employed in the clinics, although some lacunas in the understanding of stem cell functioning remain still unexplained.

In particular, the basic requirement for the use of stem cells in regenerative medicine is the steady maintenance of their properties during proliferation in prolonged cultures. Specific markers of the undifferentiated state are fundamental for checking cell phenotypes stability in the course of time and comparing cell lines among different laboratories. In fact, human stem cell lines, cultured for extended periods of time, show changes in karyotype stability, expression of cell surface markers, transcription factors and telomerase activity [1–3]. These modifications are an obstacle to scientists' capability to study and employ adult stem cells *ex vivo*. In the last years, several parameters were characterized to be directly correlated to the functions of stem cells and mitochondrial activity has been considered as particularly important for sustaining cell viability. Mitochondria, in fact, not only supply cells with the bulk of their ATP, but also refill cellular GTP, as well as control amino acid turnover and accomplish fatty

acids beta-oxidation [4]. Moreover, these subcellular organelles, together with the endoplasmic reticulum, serve also as a reservoir of cell calcium.

Some recent papers have analyzed mitochondrial activity and oxygen consumption rate alteration [5–10]. In the very last years, new interesting results were obtained and, in particular, some studies documented that each cell phase depend on a specific metabolic state [4, 11]. In fact, the metabolism of “pluripotent embryonic stem cells” (pESCs) is based on a steady high level of glycolysis while, during cell differentiation, glucose disposal through the glycolytic pathway decreases and mitochondrial oxidative phosphorylation increases [5, 12, 13]. Moreover, during stem cell differentiation, mitochondria modify their number, morphology and localization [10, 12–14].

Interestingly, when differentiated cells are transformed to “induced Pluripotent Stem Cells” (iPSCs), they switch their metabolism from oxidative phosphorylation back to glycolysis [15], whose inhibition blocks the de-differentiation process [15].

Some adult stem cells, such as Mesenchymal stem cells (MSCs) and long-term hematopoietic stem cells (LT-HSCs), require low level of oxygen to keep undifferentiated conditions. These cells live in niches, under hypoxic condition and they mainly use glycolysis to obtain ATP, thus limiting reactive oxygen species (ROS) production and subsequent damages to DNA and RNA [12, 13]. The relation between aerobic and anaerobic metabolism is much more varied and complex but, if a bit of simplification is allowed, all these results seem to indicate that cell pluripotency (stemness) is related to a really modest oxidative phosphorylation activity linked to the hypoxic conditions in which stem cells are kept living. Nevertheless, many metabolic aspects of stem cells (both adult and embryonic cells) are still not well understood and, for these reasons, is not always possible to obtain *in vitro* terminally differentiated cells from progenitor cells. The determination of these features might help us to establish whether the stem cells are in quiescent state and when they are fully capable of differentiating. This knowledge could permit the discovery of the linkages of metabolic profiles with different surface markers of stem

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cells (i.e., CD29, CD44, CD73, CD90, CD105 and CD166) and cell signaling pathways and useful for checking eventual deviations from the normal behavior of stem cells in cultures and sorting out defective cells for the prosecution of work.

Keywords: Mitochondrial function, Stem cells, Pluripotency

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Conflict of Interest

Authors declare no conflict of interest.

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