ALTERATIONS OF GENOME-WIDE DNA METHYLATION DURING NEURAL DIFFERENTIATION OF ADIPOSE DERIVED STEM CELLS: IMPLICATIONS IN REGENERATIVE MEDICINE

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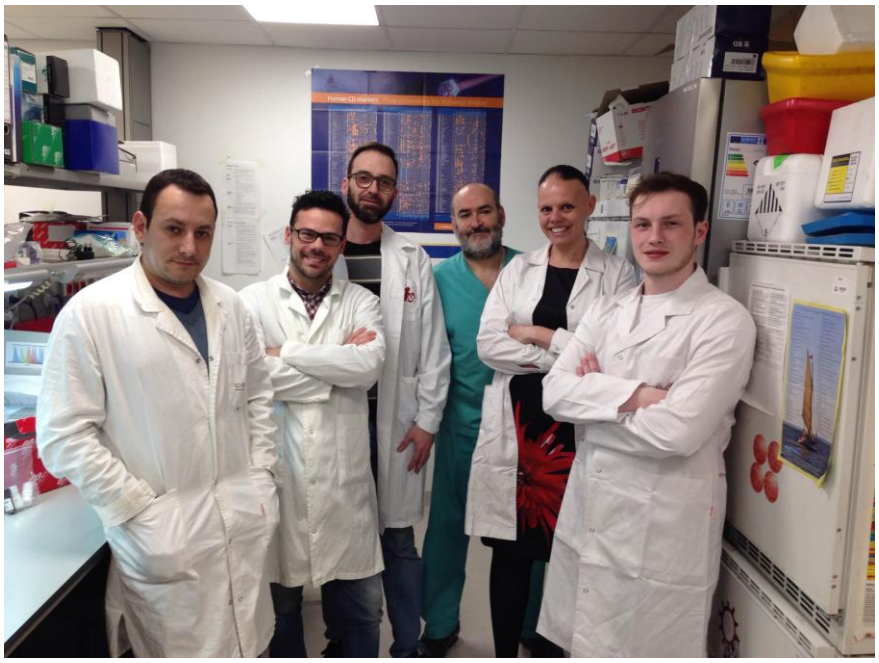


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Adipose tissue is a source of adult multipotent stem cells. The lack of ethical problems for their extraction, the reduced risk of immunogenicity in the receiver and their easily purification from liposuctions are the main advantages of their use for clinical purposes. Due to these features, there are described several methods for the transdifferentiation of adipose-derived stem cells along neural lineages using in vitro approaches.

Although human adult stem cells represent a promising tool for new clinical concepts in supporting cellular therapy in spinal cord and brain injuries, many questions remain to be explored to in order to certify an appropriate quality assurance and control of these cells. Due to the importance of assuring cell identity after reprogramming, the project aims to compare the epigenetic profiles of neural cells from in vitro reprogramming of adipose-derived stem cells and in vitro neurons from normal primary tissues. Are in vitro cells faithfully copying the patterns of primary neurons? Another important question: is there a risk of tumorigenesis due to adipose-derived stem cells transplantation?

In order to achieve these goals fat samples from liposuctions were selected and stem cell lines were generated. Microarray-based methylation studies and gene expression at genome-wide level were performed using the most advanced technology. Profiles of adipose stem cells, neural cells derived from stem cells, normal primary neurons and neuroblastoma cell lines were compared.

We conclude that the methylome of neurons derived in vitro from adipose stem cells does not faithfully reproduce the epigenome of primary neurons (those found naturally in an individual). It is interesting to note that these epigenetic differences are not due to the new acquisition of cancer hallmarks. Taking into consideration our results we conclude that the altered patterns of CpG methylation and gene expression observed in tumors from the nervous system are not common to the differential epigenome observed between in vivo neurons and in vitro neural lineages obtained for regenerative medicine. In addition, the project has identified changes in the regulation of specific genes that can be used to improve the quality of the neural lineages generated from multipotent stem cells.

Knowledge of the epigenetic patterns of adipose-derived stem cells and their neural derivatives allowed us to gain further insight in understanding neurogenesis. This

knowledge could help the improvement and design of novel guides for assuring stability in stem-cell-based therapies. Furthermore, the pathways through which deficient function of specific genes lead to an increased cancer risk could allow us to gain further insight in the tumorogenesis risk of stem cell therapy.

As a conclusion, caution should be exerted prior to employing adipose-derived stem cells or their derivatives in a clinical setting in Regenerative Medicine by applying appropriate test to ensure integrity not only of the genome (absence of genetic mutations) but also the epigenome. Therefore, CpG methylation patterns of specific genes could be considered as quality and security biomarkers in stem-cell-based therapy.