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Exploring strategies for cell rejuvenation and tissue regeneration: iPSC reprogramming as a unique opportunity to understand and cure aging

Many of the pathologies that could benefit from regenerative stem cell-based therapies are associated to aging. Emerging evidences indicates that adult stem cells exhibit functional shortcomings, including pronounced shifts in the types of mature effector cells produced as well as alterations in self-renewal capacity. Many intrinsic or extrinsic stress are able to accelerate the exhaustion of the proliferative capacity of stem cells or differentiated progenitors towards an ultimate senescence-like cell cycle arrest. Important and specific epigenetic modifications have been observed during this process, likely driving a specific gene expression –signature of cellular aging, and little is known about changes in large-scale genome organization during this aging process and or in different during senescence induced situations and its relationship with genetic instability. To further analyses this process and the relationship between replicative stress and chromatin reorganization, we followed the reorganization of chromatin dynamics features associated with senescence induction as well as the associated changes of the DNA replication program (Riviera-Mulia et al., 2017, Ogrunc et al., 2016, Prieur et al., 2016). To further understand, the interplay between genetics and epigenetics in tissue aging and to unravel molecular barriers, preventing cell rejuvenation of the age-related cellular physiology, we developed reprogramming strategies of somatic cells into induced pluripotent stem cells (iPSCs) to erase the hallmarks of cellular aging. Although this strategy provides a unique opportunity to derive patient-specific stem cells with potential application in autologous tissue replacement, limitation was revealed for elderly individuals, due to senescence described as a barrier to reprogramming that could drive genetic instability. To overcome this barrier and improve tissue regeneration, we developed an optimized reprogramming strategy that caused efficient reversing of cellular senescence and aging through reprogramming towards pluripotency. We demonstrated that iPSCs derived from senescent and centenarian fibroblasts have reset all the hallmarks of cellular aging, as telomere size, gene expression profiles, oxidative stress and mitochondrial metabolism, and are undistinguishable from hESC. Finally, we further demonstrate that re-differentiation, led to rejuvenated cells with a reset cellular physiology maintaining genetic stability, defining a new paradigm for human cell rejuvenation (Milhavet and Lemaitre 2014, Venables et al., 2013, Lapasset et al. 2011). Then we applied this knowledge to develop iPSC models for premature aging syndromes with high risk of genetic instability, to further explore the relationship between pathological and physiological aging. We will present and discuss data concerning opportunities and limits of using the iPSC technology for modelling pathologies involving replication stress, leading to senescence and ageing and genetic instability (Riviera-Mulia et al., 2017, Bouckenheimer et al., 2016, Lemey et al., 2016, Besnard et al., 2012, 2014).

Biography

Jean-Marc Lemaitre has completed his PhD in Molecular and Cellular Biology of Development and Senior Scientist since 2014. He was awarded in 2006 for an AVENIR INSERM Team program on aging and is currently Deputy Director at the Institute of Regenerative Medicine and Biotherapy (IRMB), the leader of INSERM research team and Director of a stem cell facility CHU (SAFE-iPSC). He was invited as speaker for 48 national and international conferences and seminars in France and abroad in the last 5 years.

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