Proyecto PID2022-137945OB-I00 financiado por MCIN/AEI/10.13039/501100011033/ y por FEDER Una manera de hacer Europa

Identificación del proyecto:

Modelos para el estudio de las células madre hematopoyeticas y leucémicas en estado de latencia (DormHSC)

Descripción del proyecto:

In the hematopoietic system, dormancy or deep quiescence is a well-documented physiological state for a subpopulation of hematopoietic stem cells (HSCs), while similar stem cell populations have been described for other tissues (eg. Neural, muscle, intestine, epithelial). Nevertheless some controversy exists on the distinction between dormant and quiescent state. Acquisition of a dormant or deep-quiescent state is an evolutionary strategy to maintain the integrity of important cells (such as stem cells) and ensure survival in different biological systems. Dormancy is regulated by a plethora of signals and downstream pathways (eg. Notch, Retinoic acid, mTOR) that are key to revert the dormancy state and to improve the regenerative capacity of adult tissues upon injury. In cancer and leukemia, dormancy has been well studied and it was long ago demonstrated that few cancer cells that persist after chemotherapy were able to come back years later. These resistant cells are dormant and have more recently been identified as cancer/leukemia stem cells and associated to therapy resistance.

Our recent data indicate that dormancy may operate from the first stages of hematopoietic stem cell development in physiological conditions (BioRxiv). This is a process that has not been studied before and it is relevant for HSC biology. Moreover, acquisition of a dormant phenotype may also be important for the generation of functional HSC in vitro, another important aspect that remains to be investigated. Our project will address the scientific topic of quiescence/dormancy control in normal HSC from their origin to adulthood, its impact in HSC generation in vitro, as well as in leukemia relapse after treatment. We aim to understand how dormancy is regulated in the physiological context of embryonic hematopoiesis and in the in vitro hematopoietic stem cell production and compare the process with that controlling the acquisition of the dormant and therapy resistant leukemic stem cell phenotype. We will define similarities and differences in both physiological and pathological context, which will be the base for the design of strategies to combat therapy resistant cancer populations.

By using four different experimental models: mouse embryos, embryoid bodies, gastruloids, and patient-derived xenografts (PDX) from relapsed human leukemic cells, we aim to understand the commonalities and differences of cell dormancy in the physiological and pathological context. We will use state-of-the-art technology to identify, analyze and reproduce the development of the dormant cells and to control reversion

of the dormant state.

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512.500,00€

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