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Identificación del proyecto:

Recreación del nicho embrionario para la producción de células madre hematopoyéticas y sus derivados en gastruloides humanos

Descripción del proyecto:

Blood is the most widely used tissue at a therapeutic level for transfusions of red blood cells or platelets, after myeloablative treatments or for applications of immunotherapy or gene therapy. These procedures often depend on the generosity of voluntary donors, which entails infectious and alloimmunization risks. In addition, compatible donors for patients requiring hematopoietic stem cell transplantation are not always available, as it also happens with the globally scarce rare blood types. For these reasons, research to create renewable sources of hematopoietic stem cells (HSCs) with lymphoid, myeloid and erythroid potential, preferably bypassing the use of animals, has long been an intensive area of research.
Efforts to obtain renewable sources of transplantable HSCs have not been successful to date. Recent studies have generated transplantable hematopoietic cells by forced expression of transcription factors, thus providing a proof of concept for the idea. However, the physiological consequences of the long-term overexpression of transcription factors with exogenous gene modules and the lack of robustness of these protocols has hindered further development of these approaches.
HSCs arise at different times during mammalian development but the most relevant ones for clinical use, definitive adult HSCs, arise in a niche within the Aorta Gonadal Mesonephros (AGM) in the hemogenic endothelium. Much of our knowledge of this process is derived from studies on mouse which, over many years, has been a reference model for human biology. These studies have revealed that special endothelial cells with hemogenic potential undergo Endothelial to Hematopoietic Transition (EHT), identifiable by their expression of CD41, CD45 and c-Kit. It is unknow why only a very small number will acquire the stemness capacity to be HSCs at this stage, Despite the conservation of this process among vertebrates, it is increasingly obvious that there are significant differences between mouse and human adult HSCs which demand the study of their development in humans. However, this is hampered by our limited knowledge of the early stages of human development, in particular of early embryonic stages (the fourth and fifth weeks) which are crucial in laying down the HSC niches. Therefore, understanding the fundamental mechanisms that coordinate early events encompassing the process of gastrulation and the emergence of the AGM is essential for identifying the early stages of blood disease and, eventually, to obtain ex vivo sources of adult HSCs. This undertaking is challenged by the intrauterine development of mammalian embryos and ethical barriers associated with work on early stages of human development and, once this has been resolved, the difficulty of obtaining early embryos.

An ideal system for this purpose would use entirely human components to promote the formation of true therapeutic HSCs ex vivo without genetic modifications. In the last few years, a number or Pluripotent Stem Cell (PSC)-based systems have emerged that circumvent difficulties such as universal HLA-matched cells as the base for many hematopoietic products. However, these systems have also failed to produce HSCs with transplantable potential. A possible PSC based alternative lies in organoids, in particular the gastruloid model, developed by one of us, which shows much promise to study the early stages of mammalian. Mouse gastruloids have been recently observed to contain hemogenic progenitors and cells with HSC potential (unpublished). Here, we propose to build on this work, define characteristics of the HSC niche and, most significantly, extend these findings to human gastruloids to reveal the early stages of HSC development in humans, engineer their niches and obtain a renewable source of human HSCs as the base for an unlimited robust production of other blood products.

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