Mechanisms underlying hemogenic induction in human fibroblasts

From 2015-02-18 to 2017-02-17, closed project

Objective

Hematopoietic Stem Cell (HSC) transplantation whether from bone marrow, mobilized peripheral blood or cord blood is the best example of regenerative cell therapy. HSCs have remarkable therapeutic applications in a broad range of diseases that affect the blood forming and immune system. Nevertheless, there remains a shortage of usable genetically-matched material for all needs. Growing HSCs in vitro from adult or fetal sources or generating them from embryonic stem cells has proven to be challenging despite 20 years of intensive research. An alternative approach would be to generate transplantable HSCs directly from patients own adult cells using programming technology. We have recently demonstrated the direct induction of mouse fibroblasts into hematopoietic progenitor cells using a combination of four transcription factors (TFs). This induction progress through an endothelial-like intermediate cell. We now have strong evidence that the same blood forming process can be induced in human skin-derived fibroblasts with a similar set of TFs. We first propose to characterize the human induction process using cell surface phenotypes, global gene expression analyses and functional assays. We further propose to dissect the molecular mechanisms of such induction by the identified group of TFs. Specifically, we will investigate the mechanisms that mediate this process by studying how these factors modify the epigenome and therefore directing and establishing a new cell identity. We propose to map TF binding, DNA methylation and histone modifications at a genome-wide level during the induction process. The dissection of such molecular mechanisms may ultimately allow for the use of programmed cells in the clinic. The successful generation of directly programmed HSCs will have a highly significant impact not only on patient specific therapeutics for immuno-hematopoietic diseases but also provide novel technologies to correct genetic disorders.

Related information

Report Summaries

Final Report Summary - INDUCING HEMOGENESIS (Mechanisms underlying hemogenic induction in human fibroblasts)
Coordinator

CENTRO DE NEUROCIENCIAS E BIOLOGIACELULAR ASSOCIACAO
UNIVERSIDADE DE COIMBRA, LARGO DE POMBAL
3004 517 COIMBRA
Portugal
EU contribution: EUR 202 630

Activity type: Higher or Secondary Education Establishments

Administrative contact: Lino Ferreira
Tel.: +351 231419040
Fax: +351 231419049
Contact the organisation

Subjects

Life Sciences

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