Recipe for inducing hematopoietic stem cells from ES cells

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Hematopoietic stem cell (HSC) is the most extensively studied stem cell, but yet its developmental pathway in mammals has not been fully explained. Because of this defect, the recipe for inducing hematopoietic cells from ES cells is not available. In this symposium, I will describe what we think would be the final scenario for development of HSC and a putative recipe for in vitro induction of HSC.

The scenario

Upon exfoliation of the mesoderm from the primitive streak, nascent mesoderm expresses both PDGFR□ and Flk1. Expression of a transcription factor (TF), Etv2/ER71 in this primitive mesoderm, induces extraembryonic mesoderm (EM), which is distinguished from other mesoderm by the surface phenotype. EM is $Flk1^{+}PDGFRa^{-}$ and give rise to EC and blood cell (BC). This population is completely lost in Etv2 KO. $Flk1^{+}$ EM is fated cell-autonomously to EC, as Etv2 induces an array of molecules that form a self-sustaining TF network required for EC fate. However, its fate is dominantly directed by expression of TFs relating to BC fate. In fact, EM spread over extraembryonic space and diversify into $Runx1^{-}Gata1^{-}$, $Runx1^{+}Gata1^{-}$ and $Runx1^{+}Gata1^{+}$ populations according to their localization. Labeling and tracking experiment demonstrates that $Runx1^{-}Gata^{-}$ population is fated exclusively to EC and contributes to the vascular system of YS and anterior and caudal-dorsal parts of embryo. $Runx1^{+}Gata1^{-}$ cells can differentiate both HSC and EC that contribute to the vascular system of caudal-ventral part of embryo and vitelline connections. All $Gata1^{+}$ population is fated to primitive erythrocytes. We also investigated the routes for each population to enter embryo. The primitive erythrocytes from $Gata1^{+}$ population requires circulation for their entry. $Runx1^{+}Gata1^{-}$ and $Runx1^{-}Gata1^{-}$ populations move directly to embryo by tissue movement before circulation starts. Only $Runx1^{+}Gata1^{-}$ population contributes to the hemogenic EC in the vitelline connection and AGM and differentiate to HSC. Runx1 expression at this stage is essential for priming this population to acquire the potential to HSC.

A Recipe

Transient overexpression of Etv2 help to enhance yield. Gata1 expression should be avoided. Runx1 expression should be bi-phasic.