Genetic regulation of metabolism during hematopoietic stem cell emergence

Brief description of project

During human embryonic development, the first emergence of hematopoietic stem cells (HSCs) occurs around week 5 of gestation in the aorta-gonad-mesonephros (AGM) region. At the cellular level, an endothelial cell with hemogenic capacity, termed hemogenic endothelial (HE) cell, gives rise to HSCs through a process called endothelial to hematopoietic transition (EHT). We are studying the EHT process *in vitro*, by differentiating human induced pluripotent stem cells (hiPSCs) to hematopoietic cells. In this context, we have found that a metabolic switch takes place during EHT and the transition from HE cells to hematopoietic cells is accompanied by increases in both glycolysis and oxidative phosphorylation. These two metabolic pathways were previously shown to be regulated by an interplay between the transcription factor FOXO1 and the metabolic regulator MYC in endothelial cells. The aim of this project is to investigate whether FOXO1 and MYC play a role in the metabolic switch that drives EHT.

Goals:

- Knockdown of FOXO1 and/or MYC in HE cells
- Assessment of the metabolic profiles of edited HE cells
- Evaluation of hematopoietic output from edited HE cells

Methods:

- iPS cell culture and hematopoietic differentiation
- Multi-color flow cytometry analysis/cell sorting
- Extracellular Flux Analysis (Seahorse)

Suggested reading:

Ditadi, A., Sturgeon, C.M., and Keller, G. (2017). A view of human haematopoietic development from the Petri dish. Nat. Rev. Mol. Cell Biol. 18, 56–67.

Wilhelm, K., Happel, K., Eelen, G., Schoors, S., Oellerich, M.F., Lim, R., Zimmermann, B., Aspalter, I.M., Franco, C.A., Boettger, T., et al. (2016). FOXO1 couples metabolic activity and growth state in the vascular endothelium. Nature 529, 216–220.

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