Regulatory networks of hematopoietic stem cells and their micro-environment

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Abstract

Hematopoietic stem cells (HSC) are thought to be regulated by extracellular cues from the *niche*, which triggers downstream signal transduction cascades within the HSC. Current studies have, so far, not resulted in comprehensive understanding of the signaling networks dictating HSC fate. In the present study, theoretical systems-biology and experimental hematology

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approaches are combined to determine the role of the niche in orchestrating HSC epigenetic machinery and the cell cycle. Thus, time-course gene expression analysis both of co-cultured Lin- Sca-1+ Kit+ (LSK) and HSC-supportive UG26-1B6 stromal cells was performed. Microarray results were independently confirmed by RT-qPCR, demonstrating 80% agreement for the selected candidate genes. Search space reduction using clustering analysis shows that the most intense molecular cross-talk between LSK and stromal cells occurs during the first 24h of co-culture. Gene function enrichment analysis revealed molecular patterns characteristic of cell adhesion and migration, as well as MAPK-regulated proliferation. Also, epigenetic regulators mediating gene silencing are down-modulation. Interestingly, similar analysis of stromal cells revealed both up- and down-regulated genes also associated with cell adhesion, migration, proliferation as well as vasculature development. In both LSK cells and stromal cells, among the most significantly up-regulated genes, were signaling intermediated belonging to the TGFβ signaling pathway. By integrating gene expression data with various sources of prior knowledge (e.g., protein interaction databases and semantic text mining) an in silico hypothesis was generated predicting the putative role of TGFβ signaling in HSC mobilization by regulating the G0/G1 phase transition of the cell cycle and the epigenetic modifications accompanying it. Current work is focused on the experimental validation and refinement of the model.