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Human hematopoietic stem cell differentiation follows a continuous Waddington-like landscape

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Multipotent hematopoietic stem cells are responsible for the lifelong production of all blood and immune cells. In the classical model of hematopoiesis, blood formation is believed to occur through stepwise progression of hematopoietic stem cells following a tree like hierarchy of oligo-, bi- and unipotent progenitors. However, this model is based on experimental approaches unable to describe how individual HSCs and their progeny enter lineage commitment during steady-state hematopoiesis. To establish a comprehensive model of human hematopoiesis, we have developed single-cell approaches that integrate single-cell RNA sequencing with flow cytometric and functional lineage potency data. This allows us to reconstruct developmental trajectories and to gain a detailed view on lineage commitment of individual HSCs into all major branches of human haematopoiesis. We found that individual HSCs do not pass through discrete intermediate progenitor cell stages. In contrast, HSC lineage commitment occurs in a gradual manner best described by a continuous Waddington landscape with initially flat but progressively deepening valleys. Our data determine a detailed model of developmental trajectories within this landscape and demonstrates that distinct gene expression modules operate in a combinatorial manner to control stemness, early lineage priming and the subsequent progression into all major branches of hematopoiesis. These results establish the concept of a developmental continuum, which can replace the differentiation tree as a comprehensive model of human steady-state hematopoiesis and provide a basis for the understanding of hematopoietic malignancies.

Biography

Simon Haas is Group Leader at the Heidelberg Institute for Stem Cell Technology and Experimental Medicine and the German Cancer Research Center. He is an expert in hematopoiesis with a special focus on stem cell biology. His research centers around the question how hematopoietic stem cells make complex lineage decisions to produce the variety of blood and immune cells.

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