hematopoietic stem cell differentiation to predict the immune cell reconstitution in ex-vivo gene therapy

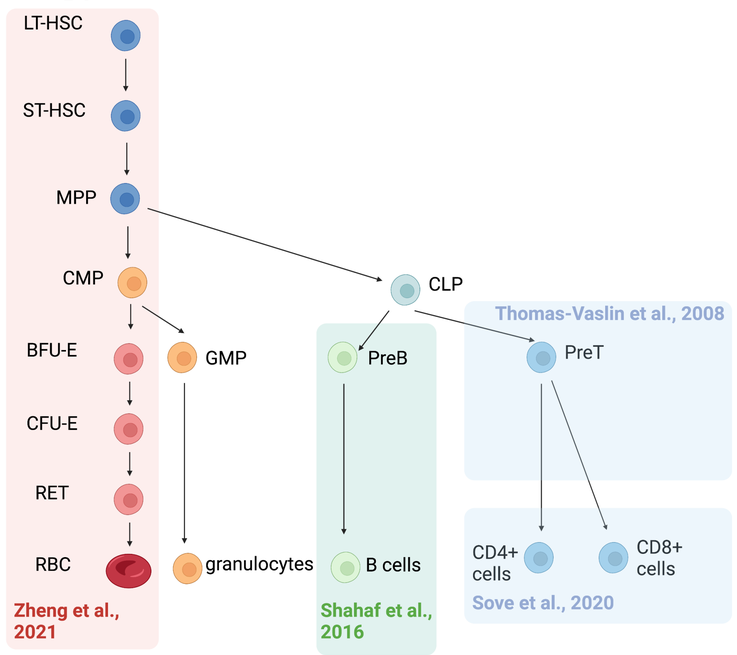
METRUM RESEARCH GROUP

Yuezhe Li[1], Eric Jordie[1], Tim Knab[1]

Abstract

The differentiation of mammalian hematopoietic stem cells (HSCs) is complex and multi-scale, providing an opportunity for mathematical modeling and simulation to aid in mechanistic understanding and ultimately inform drug development efforts. Historically, mathematical models have been developed that were focused on the development of a subset of cells, such as red blood cells (RBCs) [1], B cells [2], and T cells [3]. However, mathematical models that encompass the overall cellular system's complexity are rarely available.

Here, we develop an integrated quantitative systems pharmacology (QSP) model that characterizes multi-organ recapitulation of HSC differentiation by integrating literature models and adding novel features. The result is a more comprehensive representation of mammalian hematopoietic stem cell development. We demonstrate our integrated model can accurately capture the reconstitution of RBCs, B cells, and T cells following HSC transplant in mice. Moreover, the humanized model successfully predicted the reconstitution of granulocytes and lymphocytes in patients with adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) who underwent ex-vivo gene therapy.



Methods

We developed an integrated model that depicts the differentiation of hematopoietic stem cells (HSCs) into erythrocytes, lymphocytes, and granulocytes. The model was built incrementally by incorporating novel physiological-based features from literature while integrating published models [1-4].The resulting model represents multiple organs, including bone marrow, blood, thymus, and other lymphoid tissues. The model was developed using mice data before being scaled to human.

Results

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Conclusion

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