Mathematical Modelling Of Human Megakaryopoiesis *Ex-Vivo*

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Abstract

Megakaryopoiesis is a complex process, which is commenced with the proliferation and the differentiation of hematopoietic stem cells (HSC) into megakaryocytes (Mk), followed by maturation and polyploidy of Mk and ended by platelet biogenesis. An *ex-vivo* two-stage protocol including HSC expansion and Mk lineage commitment of human umbilical cord blood cells (hUCB) were established [1]. In the first stage, hUCB $CD34^+$-enriched cells were expanded in co-culture with the bone marrow human mesenchymal stem cells (BM hMSC) in a cytokines cocktail pre-optimized for $CD34^+$ expansion. In the differentiation stage, a serum-free medium supplemented by a cytokines cocktail containing TPO and IL-3 were used. In order to describe the fate of HSC during the megakaryopoiesis, a mathematical model was established based on the kinetic of cell expansion and differentiation. This model reflects the kinetic of HSC $CD34^+$ cells, Mk ($CD41^+$ cells) and platelet ($CD42b^+$ cells) within the process. Using such a mathematical modelling, which computes the concentration of each subset during the time, can provide significant insight into the limiting steps involved in the protocol and how the interaction of different factors can affect the outcome of megakaryopoiesis process. A set of ordinary differentiation equation (ODE) were used, based on the mass balance, to analyze the proliferation and differentiation of HSC $CD34^+$ cells. These ODEs were solved and a general solution for each subset was fitted to the experimental result, using the least square method, to determine the unknown coefficient factors for expansion, differentiation and death of each subset. The establishment of such reliable kinetic model will be useful for development of an efficient bioreactor system devoted for production of specific hematopoietic product.

Keywords: Hematopoietic Stem Cell, Kinetic Modelling, Megakaryocyte, Megakaryopoiesis, Platelet, Umbilical Cord Blood.

References

[1] J. Hatami, P.Z. Andrade , D. Bacalhau, F. Cirurgião, F.C. Ferreira, et al, Proliferation extent of $CD34^+$ cells as a key parameter to maximize megakaryocytic differentiation of umbilical cord blood-derived hematopoietic stem/progenitor cells in a two-stage culture protocol. Biotechnology Reports 4: 50-55, 2014 .