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MODELING OF THE INHERENCE OF FEEDBACK REGULATION AND STEM CELL BEHAVIOR IN GRANULOPOIESIS

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Long-standing controversies in hematopoiesis are the mechanisms of self-maintenance and differentiation commitment of the hematopoietic stem cells (HSC), and regulation of the peripheral control of hematopoiesis. In the present study, we have applied a three-dimensional cellular automaton (CA) model to granulopoiesis in order to identify the internally generative theoretical relationship between microscopic mechanisms and macroscopic behavior of hematopoietic processes. The number of mitotic event of the cells in a proliferating phase, the transit time of each of 15 differential stages from HSC to mature cells (designated as T1 to T15, and Tdup for HSC duplication time), and the neighborhood rules for HSC self-renewal were incorporated in this model system as analytical parameters. Homeostatic granulopoiesis was achieved when the following inequalities for the transit times were fulfilled: T1 > Tn (n = 2 to 15) and Tdup $\geq$ 1/2 T1. Importantly, stabilization of the cell production was induced in a negative feedback manner following external perturbation of the peripheral granulocyte numbers. The Tdup of individual HSC was dramatically fluctuated to produce the offspring responding to this perturbation. A single cell kinetic analysis demonstrated that symmetrical or asymmetrical cell division of the HSC was recruited in a transitional manner resulting in generation of the regulatory effect on the lineage-commitment processes. The inherence of feedback regulation would be a characteristic feature of the emergent dynamical property in the hematopoietic system. The CA modeling will provide the framework to analyze the behavior of HSC and to understand abnormal kinetics of the cells such as minimal residual disease in the treatment of leukemias.