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A Dynamic Differentiation Model of Granulocyte-Monocyte Progenitors

Bronson Weston
Virginia Polytechnic Institute and State University, bronsonw@vt.edu

Granulocyte-monocyte progenitor (GMP) cells play a vital role in the immune system as they mature into a variety of white blood cells, including neutrophils and macrophages. In the classical motif of GMP differentiation, GMP cells mature into one of two competing lineages, monocytes or granulocytes, depending on exposure to cytokines such as various types of colony stimulating factors (CSF). Granulocyte-CSF (G-CSF) induces granulopoiesis and macrophage-CSF (M-CSF) induces monopoiesis, while granulocyte/macrophage-CSF (GM-CSF) favors monocytic and granulocytic differentiation at low and high concentrations, respectively. Although these differentiation pathways are well documented, the mechanisms behind the diverse behavioral responses of GMP cells to CSFs are not well defined. Using dynamic systems theory, we explore the differentiation of GMP cells in response to varying dosages of G-CSF, M-CSF, and GM-CSF. Our model reproduces experimental observations of GM-CSF induced differentiation, and for the first time, we propose a mechanism for this intriguing behavior. Furthermore, we explore the differentiation of a fourth phenotype, monocytic myeloid-derived suppressor cells (M-MDSC), how they fit into the classical motif of GMP differentiation, and how progenitor cells can be primed for M-MDSC differentiation. Finally, we legitimize our model by comparing its results to numerous experiments and make intriguing predictions that should be explored by future experimental studies.