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

Liwu Li
Virginia Polytechnic Institute and State University

John Tyson
Virginia Polytechnic Institute and State University

The Diverse Effects of GM-CSF on Granulocyte-Monocyte Progenitor Cell Differentiation: Mechanisms of Action

Bronson R. Weston[1], Liwu Li[2], and John J. Tyson[2]

[1]Genetics, Bioinformatics, and Computational Biology, Virginia Polytechnic Institute and State University

[2] Department of Biological Sciences, Virginia Polytechnic Institute and State University

Differentiation of granulocyte-monocyte progenitor (GMP) cells results in a variety of white blood cells, such as neutrophils and macrophages, which execute diverse tasks of the innate immune system. Due to the specific demands of the body, this process is heavily regulated via cytokines, such as granulocyte/macrophage colony stimulating factor (GM-CSF). While many cytokines strongly favor one lineage over another, GM-CSF has an intriguing, dose-dependent, effect on differentiation, as it favors monopoiesis and granulopoiesis at low and high concentrations, respectively. Although this behavior is well documented, the mechanisms behind the diverse behavioral responses of GMP cells to GM-CSF are not well understood. Here, we propose a network of interactions between the GM-CSF receptor and transcription factors that control GMP differentiation. We convert the interactions into a set of differential equations, and explore the properties of this mathematical model using dynamical systems theory. Our model successfully reproduces the concentration-dependent behavior of GM-CSF induced differentiation, and we propose a three-component mechanism driving this behavior. Furthermore, our model predicts GM-CSF induced differentiation of a particularly interesting phenotype, the monocytic myeloid-derived suppressor cell (M-MDSC). These cells are well known for their ability to promote tumor angiogenesis and metastasis. We demonstrate that the same mechanisms that leads to the concentration-dependent response of GMP cells to GM-CSF, makes GM-CSF a capable inducer of the M-MDSC phenotype.