Mechanistic Model Demonstrates Importance of Autocrine IL-8 Secretion by Neutrophils

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1 ABSTRACT

IL-8 (CXCL8) is a potent chemoattractant and pro-angiogenic factor that is involved in maintaining homeostasis and is implicated in a wide range of inflammatory disorders. IL-8 was initially understood to be produced by monocytes to induce neutrophil migration through binding surface receptors IL-8RA (CXCR1) and IL-8RB (CXCR2). Although neutrophil secretion of IL-8 has been reported as ranging from 0–10 molecules/cell/second [1,2], it is unclear how this may affect neutrophil activation. In this study, we create and parameterize a mechanistic model of IL-8 signaling using data from in vitro cell culture experiments. We use this model to estimate receptor internalization rates which had not been previously reported. Through sensitivity analyses and additional simulations, we find that neutrophil secretion regulates the level of IL-8RB available, especially in pM-range environments.

2 METHODS

We model IL-8 signaling on neutrophils using 9 coupled ordinary differential equations with 11 parameters (rate constants). The 9 equations were formulated to predict the level of the following proteins over time: free IL-8 in the supernatant, free and bound IL-8RA & B on neutrophil surfaces, and the internalized forms of these receptors. In this model, the amounts of these proteins are continuously affected by IL-8 binding to and unbinding from receptors, receptor internalization and synthesis, and IL-8 secretion by neutrophils.

We use this model to simulate three experiments from [2], a study characterizing IL-8 regulation of neutrophils. Using a non-linear least squares solver in MATLAB, we identify the optimal parameters that minimize the error between measurements from these experiments and the predictions of our model simulations.

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3 RESULTS AND DISCUSSION

Through optimization, we estimated the rate constants for the internalization of free and bound IL-8R ($0.7–5*10^{-4}$ s^{-1}) and the rate of IL-8 secretion by neutrophils (11.4 molecules/cell/s). While multiple optimal parameter sets were identified, the top 20% of solutions closely matched the experimental results and had parameter values within 2% of each other. Without neutrophil secretion of IL-8, the model was unable to fully capture the dynamics of IL-8RB recycling or the increases in IL-8 levels observed for neutrophils cultured without exogenous IL-8. Our model predicts that in high-IL-8 environments (~100 nM), the levels of surface IL-8 receptors are most sensitive to their internalization rates. However, in low-IL-8 environments, surface receptor levels are equally sensitive to neutrophil secretion. Additional simulations found that IL-8 secretion by neutrophils decreases the levels of IL-8RB available for binding in environments with less than 1 nM of IL-8.

The results here suggest that autocrine IL-8 secretion can lead to increased signaling through IL-8RB in key scenarios, such as in the blood of burn patients (27 pM IL-8) or respiratory distress patients (770 pM IL-8) [2]. Although studies have found IL-8 secretion by stimulated neutrophils to be about 50 times less than that of monocytes, neutrophils are at least 10 times more abundant than monocytes in peripheral blood [1], suggesting neutrophil secretion of IL-8 can indeed affect signaling in these low IL-8 environments.

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