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A model of neutrophil dynamics in response to inflammatory and cancer chemotherapy challenges

Thang Ho[a], Gilles Clermont[a,b,c], Robert S. Parker[a,c,*]

[a] Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA, United States
[b] Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, United States
[c] McGowan Institute for Regenerative Medicine, University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, PA, United States

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ABSTRACT

A mathematical model of neutrophil and granulocyte colony stimulating factor (G-CSF) dynamics is developed to capture the response of circulating neutrophil levels to inflammatory and anticancer drug challenges. Severe infection or trauma induces inflammation, leading to: (i) the recruitment of neutrophils to the site of infection; (ii) misdirected neutrophil recruitment to healthy tissue, which may cause tissue damage; and (iii) an increase in neutrophil production through the G-CSF signaling cascade. The model is calibrated using fast (endotoxin challenge) and slow (docetaxel chemotherapy) response data and used to examine neutrophil dynamics in response to different chemotherapy schedules and G-CSF mitigation of, or rescue from, neutropenia. The explicit incorporation of biology in this model provides a superior structure for use in designing and evaluating treatments aimed at modulating neutrophil dynamics in chemotherapy and responses to severe infection or trauma.

1. Introduction

Neutrophils comprise 55–70% of all leukocytes (Murphy, Travers, & Walport, 2011). As core components of the innate immune response, their main biological functions include chemotaxis to sites of inflammation, phagocytosis of microbial products or particles, and microbial killing. When an inflammatory stimulus such as infection develops in a body compartment, neutrophils are rapidly recruited from the circulation to this compartment following chemoattractant gradients. Blood neutrophil concentration is usually a measure of the severity of the physiological inflammatory response in the case of infection, yet very severe infection may consume the existing pool of neutrophils to a point where circulating levels are decreased, as may be observed in severe sepsis (Angus & Wax, 2001; Brown et al., 2006). A feedback effect of this neutrophil efflux from the circulating pool is an increase in neutrophil production in the bone marrow, mediated primarily via granulocyte-colony stimulating factor (G-CSF) (Presneill et al., 2000), and subsequent recruitment to inflamed tissue. G-CSF was trialed unsuccessfully as a neutrophil stimulating agent in patients with severe sepsis (Marshall, 2003). In the case of severe sepsis, the high neutrophil efflux is observed not only at the primary site of infection, but also in secondary, seemingly uninvolved tissues, such as the lung, causing bystander organ injury. This misdirected neutrophil recruitment may be an important factor in multiple organ failure, and ultimately death, as observed in animal models as well as in patients with severe inflammatory challenges (Kobayashi & DeLeo, 2009; Murphy et al., 2011; Serhan, Ward, & Gilroy, 2010).

Low neutrophil count is also a concern in chemotherapy, but occurs on a much slower time scale than in severe inflammatory challenges. Due to drug marrow toxicity (*e.g.*, from administration of paclitaxel, docetaxel, vinfluine, etc.), neutrophil precursors are eliminated from the bone marrow, leading to a drop in circulating neutrophil concentration, with a nadir approximately ten days following the administration of the cytotoxic agent (Friberg, Henningsson, Maas, Nguyen, & Karlsson, 2002; Lee & Ratajczak, 2009). This results in an increased propensity for infections, particularly when the absolute neutrophil count (ANC) dips below 500 cells per microliter of blood. G-CSF is often successful in mitigating the neutropenia observed with marrow-toxic chemotherapy (Morstyn et al., 1989; Nakano & Okutani, 2010).

While neutrophil dynamics have been actively studied in response to chemotherapy (de Bock et al., 2009; Friberg, Sandström, & Karlsson, 2010; Hansson et al., 2010; Wallin, Friberg, & Karlsson, 2009, 2010) few mathematical models describe the neutrophil dynamics in response to inflammation challenge (Chow et al., 2005; Song et al., 2012; Vodovotz, Clermont, Chow, & An, 2004).

* Corresponding author at: 1249 Benedum Hall, Pittsburgh, PA 15261, United States. Tel.: +1 412 624 7364; fax: +1 412 624 9639
E-mail address: rparker@pitt.edu (R.S. Parker).

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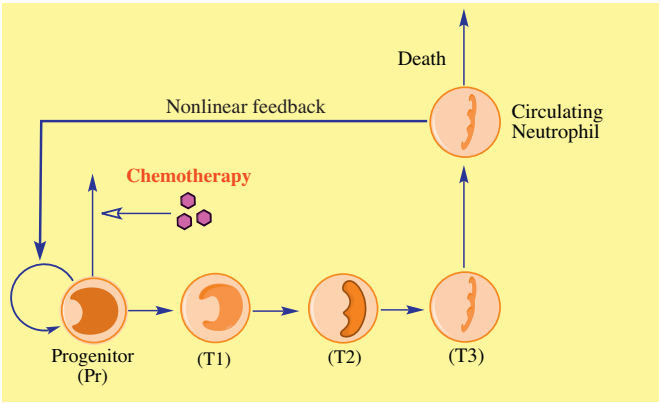

Fig. 1. Friberg et al. (2002) neutrophil model.

At present, there are no models unifying the dynamic response of neutrophil pools following challenges acting at different time scales. With inflammatory challenges, the neutrophil response is rather rapid (hours to 3–4 days) (Navarini et al., 2009; Summers et al., 2010), while for chemotherapy, the bone marrow depression does not begin until days 3–4 and then lasts up to several weeks (Bernard, Bélair, & Mackey, 2003; de Bock et al., 2009; Friberg et al., 2002). Using available information about the biological signaling cascade of neutrophil production and maturation and its feedback mechanism via the granulocyte-colony stimulating factor (G-CSF) signaling cascade, we introduce a biologically based mathematical model that captures neutrophil dynamics under a variety of challenges. The unified model is calibrated using existing data on lipopolysaccharide (LPS) as the inflammatory challenge and docetaxel as the drug-induced toxicity challenge. The model predicts the responses to a variety of chemotherapy schedules and G-CSF rescue strategies.

2. Modeling neutrophil dynamics

2.1. Cancer chemotherapy

Friberg et al. (2002) developed a phenomenological model to capture neutrophil dynamics following marrow-toxic chemotherapy. The model employs a neutrophil maturation chain leading to circulating neutrophils, and the nonlinear feedback mechanism driving proliferation depends on the ratio of plasma neutrophil concentration to its nominal value (see Fig. 1). The model does not represent G-CSF explicitly, though the authors note their feedback structure incorporates the effects of G-CSF among other activators (Friberg et al., 2002; Friberg & Karlsson, 2003; Karlsson et al., 2005). The toxic effect of anticancer drug(s) on the progenitor cells is described using an Emax model (Friberg & Karlsson, 2003), where progenitor cell elimination is a function of the drug concentration in the bone marrow ($(k_{37}D(t)/(k_{38}+D(t))Pr(t)$). The model captures neutrophil response data to several marrow-toxic chemotherapeutics (*e.g.*, paclitaxel, docetaxel, vinfluine) (Friberg et al., 2002). However, the dynamics of this model are too slow to capture neutrophil dynamics in response to an inflammatory challenge, thereby motivating the construction of a unifying model of neutrophil dynamics applicable to multiple challenges. The model developed herein retains the progenitor state, the maturation chain structure, and the circulating neutrophil pool (Pr, T1, T2, T3, and Nc, respectively, in Fig. 1). However, we expand the biology in the feedback regulation to explicitly incorporate the G-CSF signaling cascade. This increase in biological realism should facilitate the use of the model not only in the case of chemotherapy-induced neutropenia but also to capture the dynamics of other challenges such as immune response or sepsis.

2.2. Physiological structure and the neutrophil marginal pool

The human body is divided into compartments representing important tissues for drug dynamics or inflammation. Tissue compartments are connected anatomically via the blood circulation, and each tissue compartment is further subdivided into vascular and extravascular spaces. By explicitly incorporating physiology, local dynamics (*e.g.*, liver clearance, peritoneal inflammation) can be captured. Herein, drug dynamics are captured via a physiologically based pharmacokinetic model (Florian, 2008), while the inflammation responses are captured by a physiologically based flow model coupled to a detailed extravascular description of inflammation dynamics for pathogen/phagocyte/IL-1 interaction (Hogg, Clermont, & Parker, 2010). A neutrophil marginal pool has been included to capture rapid repletion dynamics for circulating neutrophil levels. The marginal pool is comparable is size to the circulating pool, and neutrophils from this pool are available for intermediate mobilization in response to external stimuli (Friberg & Karlsson, 2003; Orr et al., 2007; Orr, Taylor, Bannon, Geczy, & Kritharides, 2005; Rosinski, Yarmush, & Berthiaume, 2004). The marginal pool is modeled using an equilibrium process, with the equilibrium constant heavily dependent on the external stimuli. The dynamics of the marginal pools are described in Eq. (A.6)

2.3. Lipopolysaccharide (LPS) challenge

LPS, an inflammatory challenge, has been used in healthy volunteers to activate the neutrophil response (Suffredini et al., 1995). The LPS challenge is believed to trigger the inflammation cascade through the same mechanisms as those activated in sepsis. Three dynamic elements are added to the model to capture the effects of LPS on neutrophil response: (i) rapid mobilization of the neutrophil marginal pool; (ii) recruitment of immature neutrophils (T1, T2, T3) to the circulation; and (iii) LPS-induced clearance of neutrophil-LPS complexes (LPS bound to neutrophils). LPS effects are modeled as two compartments to capture the temporally disparate effects of the challenge. The first compartment (Eq. (1)) represents circulating LPS after I.V. injection, which drives neutrophil-LPS clearance and neutrophil mobilization from the marginal pool (Eq. (A.6)). The second LPS compartment (Eq. (2)) governs the slower inflammation dynamics that dictate neutrophil recruitment from bone marrow (Eqs. (A.2)–(A.4)). The clearance of LPS is integrated into the liver compartment of the physiological model, as follows:

$$\frac{dLPS}{dt} = -k_{39}LPS(t) \tag{1}$$

$$\frac{dI_1}{dt} = k_{39}LPS(t) - k_{40}I_1(t) \tag{2}$$

2.4. Biological feedback in neutrophil production

G-CSF has been identified as the key stimulating factor that triggers neutrophil production and maturation (Serhan et al., 2010; Stark et al., 2005). G-CSF production from stromal cells is the end product of an intricate signaling cascade (Fig. 2). Interleukin (IL)-23 production rate (Eq. (A.8)) is governed by neutrophil apoptosis, and this serves as the overall signaling cascade regulator. IL-23 activates T-cells to produce IL-17 (Eqs. (A.9)–(A.11)). Finally, IL-17 activates stromal cells to produce G-CSF (Eqs. (A.12) and (A.13)), which stimulates the production of progenitor cells and simultaneously accelerates neutrophil maturation (Stark et al., 2005). The G-CSF signaling cascade is captured by fourteen compartments, modeled using ordinary differential equations, as shown in Appendix A.