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Mathematical study of feedback control roles and relevance in stress erythropoiesis

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ABSTRACT

This work is devoted to mathematical modelling of erythropoiesis. We propose a new multi-scale model, in which we bring together erythroid progenitor dynamics and intracellular regulatory network that determines erythroid cell fate. All erythroid progenitors are divided into several sub-populations according to their maturity. Two intracellular proteins, Erk and Fas, are supposed to be determinant for regulation of self-renewal, differentiation and apoptosis. We consider two growth factors, erythropoietin and glucocorticoids, and describe their dynamics. Several feedback controls are introduced in the model. We carry out computer simulations of anaemia and compare the obtained results with available experimental data on induced anaemia in mice. The main objective of this work is to evaluate the roles of the feedback controls in order to provide more insights into the regulation of erythropoiesis. Feedback by Epo on apoptosis is shown to be determinant in the early stages of the response to anaemia, whereas regulation through intracellular regulatory network, based on Erk and Fas, appears to operate on a long-term scale.

1. Introduction

All blood cells can be divided into three categories, red blood cells, white blood cells and platelets. Red blood cells (RBCs) are produced during a complex process called erythropoiesis, which is a part of haematopoiesis (production of blood). It involves haematopoietic stem cells, at the root of blood cell production, able to create all haematopoietic lineages (Weissman, 2000), first lymphoid and myeloid lineages, then, within the myeloid branch, different lineages and in particular erythroid lineage, the origin of red blood cells. Haematopoietic stem cells differentiate into immature erythroid cells, called erythroid progenitors, which are undifferentiated cells committed to erythroid lineage. Then, through maturation and differentiation stages, erythroid progenitors become reticulocytes, which are almost mature red blood cells. These latter end their maturation to become red blood cells and enter blood stream, where they transport oxygen to tissues.

Erythropoiesis consists in a series of cell divisions through which erythroid cells acquire differentiation markers. This process allows the production of sufficient amount of erythrocytes to transport oxygen to organs. Erythropoiesis can sometimes exhibit disorders, such as excessive proliferation of immature cells, as observed in acute leukaemias (Kowal-Vern et al., 2000; Mazzella et al., 2000). Such disorders can be caused by alteration of intracellular regulatory networks, which control cell fate (e.g. Madan et al., 2003), that is self-renewal (the ability to produce daughter cells of the same maturity), differentiation (the ability to produce more mature daughter cells) or apoptosis (programmed cell death). By maturity here we understand an accumulation of differentiation markers (like haemoglobin, for example). Hence, the regulation of erythropoiesis depends on a precise control of cell fate by means of intracellular proteins and growth factors.

One of the most studied growth factors, playing an important role in erythropoiesis regulation, is erythropoietin (Epo), a glucoprotein released by the kidney in response to hypoxia, that is a lack of oxygen in tissues. Glucocorticoids (GCs) are lipophilic hormones involved in the regulation of various physiological responses, and in particular in stress erythropoiesis. They are known to favour cell proliferation (Liapi and Chrousos, 1992). Growth factors operate by activating membrane receptors on cell surface to trigger intracellular protein activation.

Recently, Rubiolo et al. (2006) proposed a description of the regulatory network that controls erythroid progenitor fate: some

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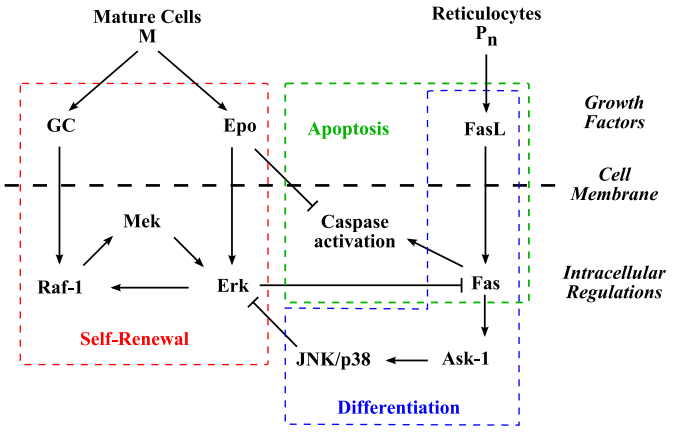

Fig. 1. Summary of intracellular protein interactions that determine erythroid progenitor fate, partially adapted from Rubiolo et al. (2006).

proteins are involved in a self-renewal loop, others in a differentiation/apoptosis loop, see Fig. 1. The first loop self-activates and inhibits the second one, whereas the second loop can inhibit the first one and, depending on Epo levels, induce either erythroid progenitor differentiation or apoptosis. Self-renewal loop relies on proteins of the MAPK family, the other loop is mainly controlled by Fas, a protein of the tumour-necrosis factor family.

Pioneering models of erythropoiesis regulation were proposed by Wichmann and Loeffler (1985), who modelled the dynamics of haematopoietic stem cells, erythroid progenitors and erythroid precursors (reticulocytes). They considered feedback controls from reticulocytes on progenitors and from progenitors on stem cells, they confronted their models with experimental data on stress erythropoiesis (bleeding, irradiation) and fitted model parameters. Later Wulff et al. (1989) and Wichmann et al. (1989) improved Wichmann and Loeffler's models. Bélair et al. (1995) proposed a model of erythropoiesis, partially based on previous works by Mackey (1978, 1979) and Mackey and Rudnicki (1994) on haematopoietic stem cell dynamics. In Bélair et al. (1995) the authors proposed an age-structured model describing erythroid cell dynamics, including an explicit control of differentiation by erythropoietin. This model was then improved by Mahaffy et al. (1998). Other works inspired by Bélair et al. (1995) proposed mathematical models of erythropoiesis (Ackleh et al., 2004, 2006; Banks et al., 2004). The erythropoietin-mediated inhibition of apoptosis has been considered in Adimy and Crauste (2007). The authors focused on the appearance of periodic haematological diseases, such as periodic chronic myeloid leukaemia (Fortin and Mackey, 1999). Recently we proposed an age-structured model of erythropoiesis taking into account feedback controls on progenitor self-renewal and apoptosis (Crauste et al., 2008). We confronted the model with experimental data on anaemia induced by phenylhydrazine injections and concluded the relevance of erythroid progenitor self-renewal for the response to stress.

Modelling of regulatory networks, involved in cell decision, has been the subject of recent analysis of lineage specification. Erythrocytes and platelets have one myeloid progenitor in common, known as megakaryocytic-erythroid progenitor (MEP). As a result of competition between two proteins, PU.1 and GATA-1, the MEP differentiates either into an erythroid progenitor or into a megakaryocytic progenitor. This choice has been studied by Roeder and Glauche (2006) and Huang et al. (2007). In both studies, models proposed by the authors demonstrated a bistable behaviour. This idea has been further developed in Chickarmane et al. (2009).

The main objective of this work is to develop a model of erythropoiesis which would allow evaluating the roles of different feedback controls in regulation of erythropoiesis in stress situations. We bring together interactions at the cell population level, growth factor actions and regulation of cell fate by intracellular proteins. From Rubiolo et al. (2006) we identify key proteins involved in the regulation of self-renewal, differentiation and apoptosis, and describe interactions between them. The resulting system is coupled with a model of erythroid cell dynamics. This latter, inspired by Demin et al. (2010), describes cell dynamics using self-renewal, differentiation and apoptosis rates of erythroid progenitors. The rates are determined by intracellular proteins, whereas growth factors and reticulocyte count control evolution of the intracellular proteins. Erythrocyte count, in turn, is responsible for growth factor production. The resulting model is confronted with experimental data on a severe anaemia, which allows determining the roles of the different feedback controls and their relative influences on regulation of stress erythropoiesis. We introduce the following feedback controls: in stress situations Epo inhibits apoptosis independently of intracellular regulatory network based on Erk and Fas (Gregory et al., 1999; Spivak et al., 1991), Epo and GCs promote Erk activation (Rubiolo et al., 2006; Sui et al., 1998), reticulocytes upregulate Fas (De Maria et al., 1999).

The work is organised as follows. In Section 2, we describe intracellular regulatory mechanisms, using available biological information. The resulting model is a nonlinear system of ordinary differential equations. This system describes the dynamics of two key proteins for cell fate regulation, Erk and Fas. We investigate the bistable behaviour of this system in order to explain the choice between cell self-renewal and differentiation or apoptosis. In Section 3 we present erythroid progenitor dynamics and dynamics of growth factors. We consider several sub-populations of erythroid cells according to their maturity. Two main growth factors involved in erythropoiesis regulation are considered: Epo and GCs. We obtain the complete model in Section 4. This multi-scale model is composed with $3(n+1)$ equations, where n is the number of erythroid progenitor sub-populations. Existence of steady states and their stability are briefly discussed in Section 4.2. In Section 6 we present simulations of anaemia and investigate the roles of different feedback functions for the regulation of erythropoiesis. The simulations are confronted with experimental data on anaemia, induced by injection of phenylhydrazine (Cherukuri et al., 2004). Roles of feedback controls by Epo on apoptosis rate, independently of the considered intracellular network, and by the intracellular regulatory network on cell fate are evaluated. Results show that both controls are important for the response, yet they do not operate at the same time and appear to have specific roles. We conclude with a discussion and present possible research directions indicated by this model.

2. Intracellular regulatory network

In a recent paper Rubiolo et al. (2006) investigated the differentiation process of erythroid progenitors. In particular, they identified key proteins involved in self-renewal and differentiation/apoptosis, see Fig. 1. Differentiation and apoptosis appear to be controlled by the same proteins. In fact, different proteins are involved both in cell differentiation and cell apoptosis, however, depending on external conditions, cells undergo either differentiation or apoptosis. For example, Epo has been shown to inhibit erythroid progenitor apoptosis (Koury and Bondurant, 1990). Hence, when Epo levels are low, erythroid