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Stem cell regulation: Implications when differentiated cells regulate symmetric stem cell division

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HIGHLIGHTS

- Differentiated cells (DCs) might regulate symmetric stem cell (SC) division.
- This implies that changes in the dynamics of DCs can affect the fitness of SCs.
- Tyrosine kinase inhibitors (TKIs) are used to treat chronic myeloid leukaemia (CML).
- TKIs increase the death rate of DCs, but have most likely no direct effect on SCs.
- TKIs might have an indirect effect on SCs if DCs regulate symmetric SC division.

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ABSTRACT

We use a mathematical model to show that if symmetric stem cell division is regulated by differentiated cells, then changes in the population dynamics of the differentiated cells can lead to changes in the population dynamics of the stem cells. More precisely, the relative fitness of the stem cells can be affected by modifying the death rate of the differentiated cells. This result is interesting because stem cells are less sensitive than differentiated cells to environmental factors, such as medical therapy. Our result implies that stem cells can be manipulated indirectly by medical treatments that target the differentiated cells.

1. Introduction

Most tissues of the body go through continuous cell turnover du to apoptosis. This cell turnover can also give tissues the ability to self-repair after injury. In general, tissues are maintained by a small group of slowly replicating cells with the capacity to both self-renew and generate differentiated progeny required by a given tissue (Morrison et al., 1997; Reya et al., 2001). Cells that have these two capabilities are called *stem cells*. Differentiated cells perform their function and eventually die – they go through a number of divisions, obtaining various stages of differentiation, until the fully differentiated cells stop dividing (Donohue et al., 1958; Cronkite and Fliedner, 1964; Ogawa, 1993). Although it seems reasonable to propose that all tissues arise from tissue-specific stem cells, rigorous identification and isolation of these stem cells have only been accomplished in a few instances. For example, *haematopoietic stem cells* have been isolated and shown to be responsible for the generation and regeneration of the blood-forming system and the immune system, called the *haematopoietic system* (Baum et al., 1992; Morrison and Weissman, 1994). The haematopoietic stem cells are located within the bone marrow and segregated among different bones throughout the body. Like several other models (Loeffler and Wichmann, 1980; Agur et al., 2002; Østby et al., 2003; Østby and Winther, 2004; Coiljn and Mackey, 2005; Adimy et al., 2006; Dingli and Michor, 2006; Dingli et al., 2007a,b; Wodarz, 2008; Marciniak-Czochra et al., 2009; Stiehl and Marciniak-Czochra, 2012; Lenaerts et al., 2010; Manesso et al., 2013), the model presented in this paper is inspired by the haematopoietic system. However, it applies to all other tissues that have similar architecture.

An important aspect, related to self-renewal and generation of differentiated cells, is the fate of the two daughter cells when a stem cell divides (Dingli et al., 2007b; Morrison and Kimble, 2006; Yamashita et al., 2003). *Symmetric division* is defined as generation

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of daughter cells destined to acquire the same fate. In this paper, symmetric stem cell division is defined as *symmetric self-renewal* if both daughter cells are stem cells and *symmetric differentiation* if both daughter cells are differentiated. In the former case the number of stem cells increases by one, whereas in the latter case the number of stem cells decreases by one. Stem cells can rely completely on symmetric division. On the other hand, if one daughter cell has stem cell identity and the other daughter cell starts to differentiate, it is called an *asymmetric stem cell division*. This type of division is particularly attractive because the stem cells manage to both self-renew and produce differentiated cells with a single division (Yamashita et al., 2003). However, a disadvantage of asymmetric stem cell division is that it leaves stem cells unable to expand in number. Serial haematopoietic transplantation supports the existence of all three types of divisions (McKenzie et al., 2006).

1.1. Stem cell niche

Since the number of stem cells is much smaller than the number of differentiated cells, the stem cells must be protected and tightly regulated. As discussed by Gentry and Jackson (2013), the *stem cell niche*, which is the restricted region in an organ that supports stem cell behaviour, may be crucial in both aspects (Fuchs et al., 2004; Nikolova et al., 2006; Yin and Li, 2006; Simons and Cleavers, 2011). The niche is composed of both localised signalling cells and an extracellular matrix that control stem cell fate. However, relatively little is known about the exact behaviour of most types of stem cells, and one of the reasons for this is that it is not possible to reconstruct niches scientifically, which makes it difficult to maintain stem cells *in vitro*, because signals from the niche affects stem cell survival, self-renewal, and differentiation.

Germline stem cells are unique stem cells in that they are solely dedicated to reproduction and transmission of genetic information from generation to generation. Through the use of genetic techniques in *Drosophila germline stem cells*, exciting progress has been made in understanding molecular mechanisms underlying interactions between stem cells and stem cell niches (Morrison and Kimble, 2006; Yamashita et al., 2003; Wong et al., 2005). The knowledge gained from studying *Drosophila* germline stem cells has provided an intellectual framework for defining the stem cell niche and molecular regulatory mechanisms for other adult stem cells, such as the haematopoietic stem cells.

The number of cells in a given tissue is approximately constant under normal conditions. It is generally believed that the number of stem cells is approximately constant under normal conditions, and that they differentiate and self-renew at relatively constant rates to replace mature cells and to keep the stem cell number at a certain normal level (Loeffler et al., 1988; Shortman and Naik, 2009). One strategy which stem cells can accomplish these two tasks is asymmetric stem cell division. A classical example of asymmetric division is provided by *Drosophila* germline stem cells. The outcome of a *Drosophila* germline stem cell division depends on the spindle orientation relative to the Hub cells in the stem cell niche, and results from the unequal distribution of intracellular regulators and extracellular (Hub-derived) signals between daughter cells during mitosis (Morrison and Kimble, 2006; Yamashita et al., 2003; Wong et al., 2005). The result is that when a *Drosophila* germline stem cell divides, one daughter remains in the stem cell niche and retains stem cell identity, and one daughter is left outside the stem cell niche and begins to differentiate. Research on *Drosophila* germline stem cells has provided a clear-cut example of how the stem cell niche promotes stem cell maintenance. Similarly, the haematopoietic microenvironment in the bone marrow also plays an important role in the regulation of haematopoietic stem cell organisation (Lemischka, 1997; Bertolini et al., 1997; Aiuti et al., 1998; Thiemann et al., 1998). Self-renewal depends on local growth conditions, namely, on the direct contact between stem cells and stroma cells (Wineman et al., 1996; Verfaillie, 1998; Koller et al., 1999). However, there are no *in vivo* experiments that reveal exactly how proliferation of haematopoietic stem cells is regulated. Thus, it is not clear whether these cells divide asymmetrically or symmetrically under normal conditions. Serial haematopoietic transplantation indicates that both types of divisions occur under steady state (McKenzie et al., 2006). As discussed later in Section 1.3, theoretical work by Shahriyari and Komarova (2013) and McHale and Lander (2014) illustrate that the symmetric stem cell division can protect against cancer, and this indicates that stem cells divide symmetrically.

Although the number of haematopoietic stem cells remains nearly constant under normal conditions, they can expand rapidly in response to injury to the bone marrow, such as stem cell transplantation (McKenzie et al., 2006). This means that asymmetric stem cell division cannot be the complete story, because it leaves stem cells unable to expand in number. Since the number of stem cells increases with one after symmetric self-renewal, it is likely that the rate of such divisions depends on the number of stem cells, since the haematopoietic stem cells can regenerate after tissue damage. Indeed, *Drosophila* germline stem cells, which normally divide asymmetrically, can be induced to self-renew symmetrically to regenerate an additional stem cell after an experimental manipulation in which one stem cell is removed from the stem cell niche (Morrison and Kimble, 2006; Yamashita et al., 2003; Wong et al., 2005).

1.2. Extracellular regulation

Extracellular signalling molecules regulate the dynamics of cell proliferation and differentiation. However, the precise nature of these processes are in general not known (Layton et al., 1989; Aglietta et al., 1989; Metcalf, 2008; Fried, 2009). An example of extracellular signalling molecules is the *haematopoietic cytokines* that control the production of haematopoietic cells. Each of these cytokines has multiple actions mediated by receptors that can initiate various responses – survival, proliferation, differentiation, maturation, and functional activation. Individual haematopoietic cytokines can either regulate one specific lineage or multiple lineages (Metcalf, 2008). Moreover, for some haematopoietic cell types, such as stem cells or megakaryocyte progenitors, the simultaneous action of multiple cytokines is required for proliferative responses. Unlike other extracellular signalling molecules, like hormones, that have a limited, or single, organ source, the haematopoietic cytokines have many tissue sources, e.g. kidney, liver, lung, muscle and membrane-displayed factors on local stromal cells (Aglietta et al., 1989; Metcalf, 2008). This is one of the reasons why it is difficult to establish the precise source of a haematopoietic cytokine in any particular situation and to predict its ultimate fate. Results from theoretical work regarding the haematopoietic system (Wodarz, 2008) and crypt cells (Potten and Loeffler, 1990) indicate that changes in stem cell number and their cyclic activity are associated with changes in the demand of the mature cell stages. Marciniak-Czochra et al. (2009) designed a six-compartment model to test different hypotheses concerning regulation of self-renewal and differentiation by a feedback signalling factor. Since the precise nature of how extracellular signalling molecules such as cytokines control proliferation and differentiation is still unknown, Marciniak-Czochra et al. assume that the signal intensity is

$$s = \frac{1}{1 + kC_6}, \tag{1}$$