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Tissue architecture, feedback regulation, and resilience to viral infection

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HIGHLIGHTS

- Tissue homeostasis is required for multi-cellular organisms.
- Tissue homeostasis is maintained by feedback regulation.
- Feedback regulation can be influenced by viral infections.
- We investigate the effect of viral infections on tissue homeostasis.
- Protection against tissue pathology is found to increase vulnerability to cancer.

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ABSTRACT

Tissue homeostasis is one of the central requirements for the existence of multicellular organisms, and is maintained by complex feedback regulatory processes. Homeostasis can be disturbed by diseases such as viruses and tumors. Here, we use mathematical models to investigate how tissue architecture influences the ability to maintain tissue homeostasis during viral infections. In particular, two different tissue designs are considered. In the first scenario, stem cells secrete negative feedback factors that influence the balance between stem cell self-renewal and differentiation. In the second scenario, those feedback factors are not produced by stem cells but by differentiated cells. The model shows a tradeoff. If feedback factors are produced by stem cells, then a viral infection will lead to a significant reduction in the number of differentiated cells leading to tissue pathology, but the number of stem cells is not affected at equilibrium. In contrast, if the feedback factors are produced by differentiated cells, a viral infection never reduces the number of tissue cells at equilibrium because the feedback mechanism compensates for virus-induced cells death. The number of stem cells, however, becomes elevated, which could increase the chance of these stem cells to accumulate mutations that can drive cancer. Interestingly, if the virus interferes with feedback factor production by cells, uncontrolled growth can occur in the presence of the virus even in the absence of genetic lesions in cells. Hence, the optimal design would be to produce feedback factors by both stem and differentiated cells in quantities that strike a balance between protecting against tissue destruction and stem cell elevation during infection.

1. Introduction

The functioning of multicellular organisms requires tight regulation of cellular behavior such that the number of tissue cells is maintained at constant levels. Human adult tissue is thought to be maintained by tissue stem cells that have self-renewal capacity. The tissue stem cells differentiate into transit amplifying cells that are capable of a limited number of divisions, and further differentiation results in terminally differentiated cells that cannot divide anymore (Crosnier et al., 2006). Terminally differentiated cells perform their function that is required for the tissue, and die after a certain period of time. Homeostasis is thought to be achieved by various negative feedback loops (Daluiski et al., 2001; Elgjo and Reichelt, 2004; Lander et al., 2009; McPherron et al., 1997; Tzeng et al., 2011; Wu et al., 2003; Yamasaki et al., 2003). An important process that is subject to regulation is the decision for stem cells to self-renew upon division (giving rise to two daughter stem cells), or to differentiate, thus giving rise to two daughter cells that are on the path to terminal differentiation. As the number of cells grows, feedback factors have been shown to block self-renewal and promote differentiation instead, which limits tissue size through the eventual

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death of terminally differentiated cells. Other feedback factors down-regulate the rate of cell division as the number of cells grows, thus also preventing excessive growth. Such feedback loops have been observed in a variety of tissues (Daluiski et al., 2001; Elgjo and Reichelt, 2004; Lander et al., 2009; McPherron et al., 1997; Tzeng et al., 2011; Wu et al., 2003; Yamasaki et al., 2003) and many feedback factors have been found to belong to the transforming growth factor β (TGF-β) super-family. For example, GDF11 is produced by neuronal cells in the mouse olfactory epithelium and provides feedback to inhibit the production of neurons. Lack of GDF11 leads to elevated production of neurons (Lander et al., 2009).

Tissue homeostasis can be disturbed by diseases. The development of tumors obviously leads to uncontrolled cell growth. Viral infection can lead to the depletion of tissue cells and compromised tissue function. There is also an interplay between viral infections and the development of tumors, with several viruses thought to contribute to tumor initiation (Butel, 2000; Zur Hausen, 2009). Because viral infections can destroy tissue cells, they thereby influence the feedback dynamics of the tissue, for example by reducing the level of feedback inhibition and thus inducing altered levels of cell proliferation and differentiation. In this paper we use mathematical models to study the consequences of viral infections for the dynamics of feedback regulation in otherwise healthy tissue. In particular, we ask how the design of regulatory circuits affects the protection against pathology. The models suggest the presence of an important tradeoff: if the regulatory mechanisms are designed to provide maximal protection against virus-induced tissue destruction, this can lead to increased levels of stem cell proliferation, which can promote the development of cancers. Interestingly, it is shown that in this case, viral interference with feedback factor production can lead to uncontrolled cellular proliferation even in the absence of induced genetic lesions in cells. In contrast, if tissue is designed to minimize the impact of the infection on stem cell proliferation, then virus-induced tissue destruction is maximized. Hence, evolution is likely to favor a tissue design that optimizes this tradeoff.

2. Results

2.1. The model

A model will be considered that includes two basic populations: (i) cells with self-renewal capacity, which includes both tissue stem cells and transit amplifying cells. For simplicity, this population will be collectively referred to as "stem cells", and is denoted by S. (ii) Terminally differentiated cells that cannot divide anymore, denoted by D. It is based on previous models (Lander et al., 2009; Lo et al., 2009; Rodriguez-Brenes et al., 2011) and given by the following set of ordinary differential equations that describe the time evolution of these cell populations.

$$\frac{dS}{dt} = r'Sp' - (1-p')r'S$$
$$\frac{dD}{dt} = 2(1-p')r'S - aD \qquad (1)$$

This represents a minimally parameterized model to describe tissue dynamics, which allows us to obtain analytical insights. Stem cells divide with a rate r'. With a probability p', division results in two daughter stem cells (self-renewal). With a probability 1-p', division results in two differentiated cells. Differentiated cells die with a rate a. The primes in the notation mean that these parameters can be influenced by negative feedback. Feedback factors can either be produced by stem cells or by differentiated cells. In the context of differentiation, this is expressed as $p' = p/(n_1S + n_2D + 1)$. Thus, the basic probability of self-renewal is given by p, and the parameters n_1 and n_2 describe the relative strength of feedback factors produced by stem and differentiated cells, respectively. Feedback on the rate of cell division is expressed by $r' = r/(m_1S + m_2D + 1)$. The parameter r describes the intrinsic rate of cell division, and the relative strength of feedback factors produced by stem and differentiated cells is given by m_1 and m_2, respectively.

Next, we introduce a viral infection into this model, assuming that the virus can only infect differentiated cells and not the stem cells. Denoting infected differentiated cells by I, this is formulated as follows according to standard virus dynamics equations.

$$\frac{dS}{dt} = r'Sp' - (1-p')r'S$$
$$\frac{dD}{dt} = 2(1-p')r'S - aD - bDI$$
$$\frac{dI}{dt} = bDI - a_dI \qquad (2)$$

The infection is modeled based on established virus dynamics formulations (Nowak and May, 2000; Perelson, 2002). Upon contact with uninfected differentiated cells, infection occurs with a rate b. Infected cells die with a rate a_d. Free virus particles are not explicitly taken into account but are assumed to be in a quasi-steady state. This is a well justified assumption in the field (Nowak and May, 2000) because the turnover of free virus is much faster than that of infected cells. In the presence of the virus infection, two types of differentiated cells exist (uninfected and infected), and both can potentially secrete feedback factors. Infected cells can maximally produce the same amount of feedback factors as uninfected cells, but may produce less due to viral impairment. Thus, the self-renewal feedback is now given by $p' = p/(n_1S + n_2D + fn_2I + 1)$, where $f \leq 1$. Similarly, the division feedback is given by $r' = r/(m_1S + m_2D + gm_2I + 1)$, where $g \leq 1$.

We will start by analyzing a scenario where there is only feedback on self-renewal/differentiation (p'). No feedback on the rate of cell division will be assumed to exist for now. Feedback on self-renewal is the most important feedback loop that enables the existence of a stable equilibrium in this system (Lander et al., 2009; Lo et al., 2009), and this simplification helps us obtain some key results. Subsequently, feedback on the rate of cell division is introduced and examined.

2.2. Feedback on self-renewal only

This section considers the scenario where there is feedback on self-renewal only, and the rate of cell division is simply given by the parameter r ($m_1 = m_2 = 0$). The following outcomes are observed. Persistence of the tissue requires that $p > 0.5$. In this case the system can converge to two different equilibria depending on the parameter values. If the infection is not established, the following equilibrium is observed:

$$S^{(0)} = \frac{a(2p-1)}{n_2 r + an_1}$$
$$D^{(0)} = \frac{r(2p-1)}{n_2 r + an_1}$$
$$I^{(0)} = 0$$

If the virus does establish an infection, the dynamics converge to the following steady state:

$$S^{(1)} = \frac{a_d[b(2p-1) - n_2(a_d - fa)]}{b(rfn_2 + a_d n_1)}$$
$$D^{(1)} = \frac{a_d}{b}$$
$$I^{(1)} = \frac{rb(2p-1) - a_d(rn_2 + an_1)}{b(rfn_2 + a_d n_1)}$$

Successful infection is established if the basic reproductive ratio of the virus (Anderson and May, 1991; Nowak and May, 2000) is greater than one, given by $R_0 = bD^{(0)}/a_d$.