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Effect of stem cell turnover rates on protection against cancer and aging

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Abstract

Tissue stem cells are responsible for replenishing and maintaining a population of cells which make up a functioning organ. They divide by asymmetric cell division where one daughter remains a stem cell while the other daughter becomes a transit cell, which divides a defined number of times and differentiates. A fully differentiated cell has a finite life-span. A tissue can be maintained by various strategies. Stem cells can divide often and differentiated cells die often (fast turnover). Alternatively, stem cells can divide infrequently, and the differentiated cells are long lived (slow turnover). Genetic alterations and mutations can interfere with tissue homoeostasis. Mutations can induce senescence and apoptosis, and this can result in a reduction of the number of functioning tissue cells which could correlate with tissue aging. Alternatively, mutations can result in the carcinogenic transformation of cells and the formation of a tumour. Using mathematical models, I find that the cellular turnover rate affects the ability of genetic alterations to induce aging and the development of cancer. If mutations occur as a result of errors during cell division, the model suggests that a low cellular turnover rate protects both against aging and the development of cancer. On the other hand, if mutations occur independent from cell division (e.g. if DNA is hit by damaging agents), I find that a high cellular turnover rate protects against aging, while it promotes the development of cancer. Implications for optimal tissue design are discussed.

Keywords: Stem cells; Tissue architecture; Tissue design; Cancer; Aging; Mathematical models; Tradeoff; Evolution; Mathematical model

1. Introduction

Stem cells are characterized by their ability to differentiate into specialized cell types, which perform specific functions (Spradling et al., 2001; Verfaillie, 2005). There are thought to be two types of stem cells. Embryonic stem cells can in principle differentiate into any cell type of the body. On the other hand, adult or tissue stem cells are thought to only give rise to specific tissue cells. This paper concentrates only on tissue stem cells. In particular, I will investigate how the processes of stem cell division, differentiation, and death contribute to tissue aging and the development of cancer.

Tissue stem cells are thought to have the capacity to divide indefinitely. They maintain tissues and organs. Tissue maintenance is thought to occur through a process, which is called asymmetric cell division (Leedham et al., 2005; Roegiers and Jan, 2004). That is, upon division, one daughter of the stem cell is another stem cell. The second daughter is a cell which embarks on a pathway of proliferation and differentiation. As the cell divides, it becomes committed and performs its specific function. After a certain period of time, this committed cell will die and will be replaced by another cell, which has originated from further asymmetric stem cell divisions. A well-understood example is the colonic epithelium, where stem cells are thought to be located at the base of crypts and the differentiating cells move up the crypt to become epithelial cells which die after about a week (Potten, 1998). The process of asymmetric cell division ensures that the differentiated tissue cells can be produced while the number of stem cells remains constant.

It is unclear, how this process and the population size of stem cells in general is regulated. It is possible that stem cell dynamics are regulated to some extent by their micro-environment, also referred to as niche (Li and Xie, 2005; Spradling et al., 2001). Contact with specific cells, as well as

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cellular signalling, might ensure that one daughter cell remains a stem cell while the other daughter differentiates. Genetic mechanisms and signalling networks which drive asymmetric cell division are being discovered (Wodarz, 2005; Wodarz et al., 1999). It is also thought that stem cells can undergo symmetric cell division in specific circumstances (Kiger et al., 2000; Marshman et al., 2002; Potten, 1998). For example, if a stem cell divides to give rise to two stem cells, this can increase the population size of stem cells and compensate for stem cells, which have been lost due to cellular damage. Alternatively, a stem cell might divide to give rise to two differentiated cells. In this case, the population size of stem cells can be reduced if an imbalance has occurred. The mechanisms which regulate these processes are, however, not understood very well.

The kinetics of stem cells are important both in the context of aging and in the context of cancer (Bell and Van Zant, 2004; Krtolica, 2005; Martin et al., 1998; Potten et al., 2001; Weissman, 2005): (i) Aging can be defined on many levels. Here, we focus on the fraction of functioning tissue cells as a correlate of aging (Donehower, 2002; Potten et al., 2001; Tyner et al., 2002). The occurrence of apoptosis and senescence in stem cells and differentiated cells can lead to a reduction in the number of functioning tissue cells, and this can lead to the development of age related symptoms. Apoptosis and senescence can be brought about by mutations or alterations of the genome in general. (ii) Mutations can also lead to the initiation of cancers. Carcinogenic mutations allow an escape from normal tissue homoeostasis.

Thus, genetic mutations can result both in aging of the tissue and in the generation of tumour cells. How should the stem cell dynamics be designed in order to reduce the symptoms of aging and to minimize the occurrence of cancer? This is the subject of the paper. In particular, I will concentrate on the effect of cellular turnover. A given tissue size can be maintained in the context of different turnover rates. If turnover is fast, cells divide often and die fast. If turnover is slow, cells divide rarely and live longer. Using mathematical models, I investigate how different cellular turnover rates influence the ability of genetic alterations to induce symptoms of aging and to contribute to the development of cancer.

2. The model

This section introduces a mathematical model which describes the dynamics of stem cell division and differentiation (Fig. 1). This model builds on the information provided by previous modelling efforts in the context of tumorigenesis and tissue steady states (Cairns, 2002; Frank et al., 2003; Komarova and Wang, 2004; Michor et al., 2003; Tomlinson, 2000; Tomlinson et al., 1996; Wodarz, 2004; Wodarz and Komarova, 2005). This model will not be designed to have quantitative and predictive power. Rather, it will be used to explore trends and dependencies on a qualitative level, and can be used as tool to gain basic

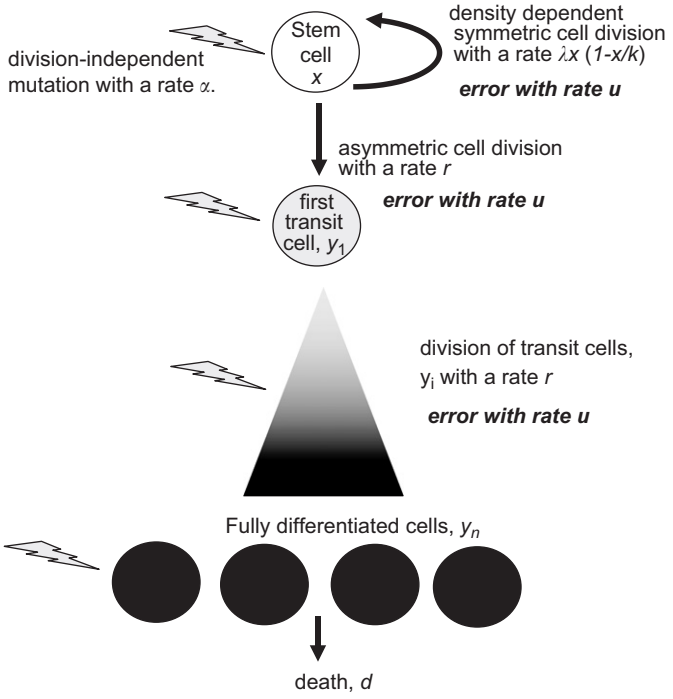

Fig. 1. Schematic representation of the assumptions which underlie the mathematical model. The model considers the population of stem cells, x, transit cells, y_i, and fully differentiated cells, y_n. Stem cells are assumed to divide asymmetrically, and the fully differentiated cells die with a given rate. During cell divisions, mutations can occur with a rate u, and all cell populations can obtain mutations independent from cell division with a rate α. This is denoted by the zig-zag symbol in the diagram.

insights into the kinetics of tissue maintenance and to obtain new hypothesis that can be addressed by experiment. Specific simplifications and limitations will be made explicit in the discussion. The model contains the following variables. The variable x denotes the population of tissue stem cells. That is, these cells are not differentiated at all. The variable y denotes cells which are on the differentiation pathway. This variable is broken down into a number of sub-variables. It is assumed that a number of n divisions are required to go from a stem cell to a fully differentiated cell. The first division event is the asymmetric division of a stem cell. While one daughter will be a stem cell, the other daughter will be a cell which has entered the first stage in the path of differentiation. Such cells are denoted by y_1. When these cells divide, they give rise to cell population y_2, and after n cell divisions, they are denoted by y_n. It is assumed that the cell population y_n is fully differentiated. Fully differentiated cells are assumed not to divide anymore, but die after a given period of time. A central component of the model is that cells can receive mutations. These can lead to cell death, senescence, or the transformation of cells. The model assumes that there are two ways in which mutations can occur. On the one hand, mutations may only occur upon cell division. This would happen if mistakes are made during DNA replication which are not corrected and persist. On the other hand, the occurrence of mutations may not require cell division (independent from