Journal of Theoretical Biology 332 (2013) 161–170

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Can cell mortality determine division of labor in tissue organization?

Carlos Rodríguez-Caso *

Complex Systems Lab. Institute of Evolutionary Biology (CSIC-Universitat Pompeu Fabra), Dr. Aiguader 88, Barcelona, 08003, Spain

AUTHOR-HIGHLIGHTS

- I study by a mathematical model the role of division of labor in tissue optimality.
- The results show that cell turn-over imposes an inevitable reduction in function abilities.
- Reduction of function is smaller when division of labor is at work.
- Analytical results are in agreement with the experimental data available in literature.
- I explain why division of labor is a successful strategy at high cell-renewal.

ARTICLE INFO

Article history:
Received 31 October 2012
Received in revised form
25 January 2013
Accepted 1 May 2013
Available online 9 May 2013

Keywords:
Cell proliferation
Tissue architecture
Mathematical model
Tissue homeostasis
Division of labor

ABSTRACT

Tissue organization comes from the emergence of cell cooperation where cell homeostasis and function are performed as a trade-off of two excluding proliferative and differentiated cellular states. By introducing function in a population dynamics approach, I study the role of division of labor in tissue optimality when cell turn-over and limitation of space and resources are imposed as natural restrictions of a living tissue. The results indicate that although cell turn-over imposes a inevitable reduction in function abilities, the penalty is smaller when division of labor is at work, especially when a rapid cell-turnover and high cell density is a requirement for the tissue, as occurred in epithelia hierarchical tissues. Analytic results are in agreement with the experimental data available in literature. The study provides an explanation about why homogeneous tissues for which proliferative and functional tasks are performed by a same cell type are unlikely to be observed under high cell-renewal requirements.

Complex multicellular organisms are composed of several layers of organization, from cells to tissues and organs. The integration of cells into a higher level of organization constitutes one of the major achievements in the acquisition of multicellularity: the emergence of a self-maintained cell population able to perform a task for the entire organism (Michod et al., 2006; Michod, 2007). In this structure, cell elimination, either by apoptosis (Zhang and Xu, 2002; Renehan and Booth, 2001) or cell extrusion (Potten and Loeffler, 1990; Potten and Booth, 2002), constitutes an essential requirement for preventing non-functional cell accumulation. Then, function but also maintenance are two indispensable tasks for a tissue. However, replication and function are performed by two mutually excluding cells states: the proliferative and the differentiated one (Huang and Ingber, 2004). Inevitably, a trade-off between these two tasks is then needed for the acquisition of a functional tissue. Evidences of that can be found at different levels: In cell cultures, the arrest of the cell cycle commonly drives cells to differentiation (Harrison et al., 1985; Olson, 1992; Parker et al., 1995). *In vivo*, gut epithelium (Potten and Booth, 2002) offers a well-characterized example at genetic level in which enterocytes differentiate as they lose their capacity to proliferate.

Besides this opposition between function and replication in cells, another feature endows generality to the logic of tissue organization. Looking at the task allocation of functional and replicative roles, tissues seem to converge in two basic architectures. On one hand, we find hierarchical tissues in which replication and function are performed by two distinguishable cell proliferating and differentiated compartments. In these tissues, a proliferating bulk produces cells undergoing differentiation which end up into specialized and non-proliferating cells. These latter ones are the responsible for developing the tissue function. Tissues associated with an active cell turnover such as gut epithelium (Potten and Loeffler, 1990; Hall et al., 1994), skin (Potten and Booth, 2002), blood (Alberts et al., 2002) and mammary glands (Stingl et al., 2006) are examples of this architecture—see Table 1. On the other hand, we find the homogeneous tissues where cell renewal can be potentially committed by any cell of the tissue. In

* Tel.: +34 933160532.
E-mail address: carlos.rodriguez@upf.edu

0022-5193/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2013.05.001

Table 1
Comparative information of the kinetic values for distinct cell types taken form bibliography. A raw estimation of the δ value – the cell turnover parameter used in the HoM and HiM models – for different cell types is graphically interpolated as described in Fig. 6 from the available information of proliferating cell fraction and cell turnover of crypt cells in intestinal villi assuming full cell coverage of the tissue. See caption in Fig. 6 for δ calculation details.

Cell type	Tissue architecture	Lifespan (days)	% cell density	Refs.	δ estimation
Crypt cells	HiM-like	0.5	~100[a]	Potten and Loeffler (1990)	0.24
Epithelial cells (fundic and pyloric glands)	HiM-like	4	~100[a]	Kawai and Rokutan (1995)	0.03
Platelets	HiM-like	9	45[b]	Harker et al. (2000)	0.01
Erythrocytes	HiM-like	37–61	45[b]	Lurie and Danon (1992), Derelanko (1987)	$2–3\times10^{-3}$
Hepatocytes	HoM-like	200–300	80[c]	Grompe and Finegold (2001)	$6–4\times10^{-4}$
Endothelial cells	HoM-like	Months–years	~100[a]	Alberts et al. (2002)	$<4\times10^{-4}$ (>1 year)

[a] Full coverage of tissue surface cells without appreciable extracellular matrix.
[b] Percentage of the volume for total cells in blood (liquid tissue).
[c] Percentage of volume for liver cells in liver.

this case, dynamic changes between differentiated and replicating states are required. Under healthy conditions, hepatic tissues and endothelia are close to this type of organization (Alberts et al., 2002; Grompe and Finegold, 2001). Contrasting with the hierarchical ones, these tissues exhibit a less cell turnover—see Table 1.

In this work I explore the hypothesis of hierarchical and homogeneous organizations that may emerge as solutions of the trade-off between the function optimization and cell-renewal. According to this hypothesis, some questions can be formulated: Is there any optimal reason for these two alternative architectures? And if so, what is the weight of cell-renewal and function requirements in the choice of the type of architecture?

The following section presents a mathematical model that captures the trade-off between function and replication in a cell population with one restriction: individuals cannot perform at the same time both roles. Then, the role of division of labor is analyzed by the construction of hierarchical and homogeneous alternative architectures. Finally, analytical results from these general models are contrasted with data of kinetic values (i.e., growth and cell turn-over) of tissues obtained from literature.

1. Results

Assuming that tissues behave as a sort of cell communities, population dynamics (Case, 2000) provide us a suitable theoretical framework for our purposes. To start with, a working definition for a *minimal tissue* must be stated. The definition of a tissue provided in this work pursues as much as possible any loss of generality. Accordingly, a minimal tissue is defined as a self-maintained cell population that must perform a benefice (i.e. a function) for the entire organism.

1.1. General model for minimal tissue definition

Let us have a system formed by a population of cells n. In this simple model, not all the cells are in a proliferating state. Only a fraction of the population corresponds with the proliferating compartment, n_p, that replicates according to the rate M. In this particular system, the remaining cell bulk, n_d, does not participate in the replication but consumes the available resources as proliferating cells do. Therefore, the parameter M – which accounts for the inverse of the time required for cell division – only affects to n_p. Furthermore, we introduce a cell mortality defined by the parameter D. Such a parameter corresponds with the inverse of the cell life span and affects in the same manner to the whole cell bulk n. According to this description, a formalization of this particular system can be written as

$$\frac{dn}{dt} = Mn_p - Dn. \tag{1}$$

From this simple equation, we introduce the dependence of resources. We assume that n_p is not fixed and it depends on the population size by an effect of consumption of resources. A desirable behavior for our interests might account at least for two extreme situations. In one hand, a condition of unlimited nutrients should propitiate that all the population is able to proliferate, i.e., $n=n_p$. On the other hand, a condition of depletion of resources should capture the fact that no cell is able to perform its replication, formally $n_p=0$. A simple way to capture these extremes and other intermediate states is by defining $n_p=nf(n)$. For $f(n)$ we only can assure that it must be a decreasing function which acts as a fraction, ranging from zero to one. Although different forms of $f(n)$ may be taken, it is straightforward to see that a linear dependence of n in the form of $f(n)=1-bn$ leads to the well-known logistic growth, in this case coupled to an external mortality. Then, just defining $b=1/K$ and rewriting n_p in terms of $f(n)$ in Eq. (1) we obtain this more familiar expression, simple enough for our general considerations

$$\frac{dn}{dt} = M\left(1-\frac{n}{K}\right)n - Dn. \tag{2}$$

Here, K is the carrying capacity as appeared in the logistic equation (Case, 2000), i.e., the maximal number of cells allowed by a cell density dependence.

From Eqs. (1) and (2) we obtain that

$$n_p = \left(1-\frac{n}{K}\right)n. \tag{3}$$

Defining the non-proliferative compartment as $n_d=n-n_p$, we get that

$$n_d = \frac{n^2}{K}. \tag{4}$$

As we shall define later, n_d will correspond with the differentiated cell state responsible for function performance. For the moment, we will not introduce this role yet. However, although simplified and without introducing function, Eq. (2) fairly captures the general aspects for required cell homeostasis of a healthy tissue where no overgrowth or tissue regression occur (Alberts et al., 2002), as it happens in many of them in adulthood. Under these circumstances M, D and K are the representative parameters governing the model at the steady state condition.

Besides the availability of nutrients represented by the parameter K, tissues also live under spatial restrictions. In our model we introduce a space limit S – measured in number of cells – that indicates a physical upper bound for cell population size. Here, for the sake of simplicity, cell size variation is not considered in this