Journal of Theoretical Biology 404 (2016) 40–50

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Mathematical model for cell competition: Predator–prey interactions at the interface between two groups of cells in monolayer tissue

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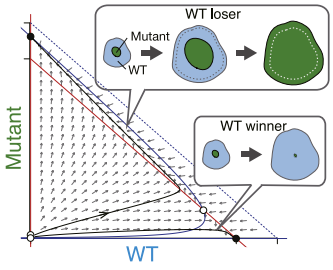
HIGHLIGHTS

- Mathematical models are constructed to investigate the phenomenon of 'cell competition' where one group of normal cells in epithelial tissues competes with another group of mutant cells through an interaction at their interface.
- The models can reproduce several typical experimental observations.
- An index of group fitness is proposed to predict the outcome of the competition between the two groups.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 15 December 2015
Received in revised form
1 May 2016
Accepted 21 May 2016
Available online 24 May 2016

Keywords:
Tumor suppression
Population model
Individual cell-based model
Group fitness
Drosophila

ABSTRACT

The phenomenon of 'cell competition' has been implicated in the normal development and maintenance of organs, such as in the regulation of organ size and suppression of neoplastic development. In cell competition, one group of cells competes with another group through an interaction at their interface. Which cell group "wins" is governed by a certain relative fitness within the cells. However, this idea of cellular fitness has not been clearly defined. We construct two types of mathematical models to describe this phenomenon of cell competition by considering the interaction at the interface as a predator–prey type interaction in a monolayer tissue such as epithelium. Both of these models can reproduce several typical experimental observations involving systems of mutant cells (losers) and normal cells (winners). By analyzing one of the model and defining an index for the degree of fitness in groups of cells, we show that the fate of each group mainly depends on the relative carrying capacities of certain resources and the strength of the predator–prey interaction at the interface. This contradicts the classical hypothesis in which the relative proliferation rate determines the winner.

1. Introduction

Interactions between cells play important roles in the normal development of organs and their functions. The phenomenon of 'cell competition', which is a certain kind of these interactions, has recently attracted the attention of a considerable number of researchers, because it is thought to assist a variety of biological events. Examples can be found in organ size control, the maintenance of multicellular organisms against pathological events such as tumor formations, and the selection of superior cells in stem cells (Moreno, 2008; Baker, 2011; de Beco et al., 2012; Vincent et al., 2013; Amoyel and Bach, 2014; Morata and Martín, 2007). The phenomenon of cell competition is defined as a competition between two groups of cells existing in the same tissue (in a single-layer tissue in most cases). An example of cell competition

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http://dx.doi.org/10.1016/j.jtbi.2016.05.031
0022-5193/

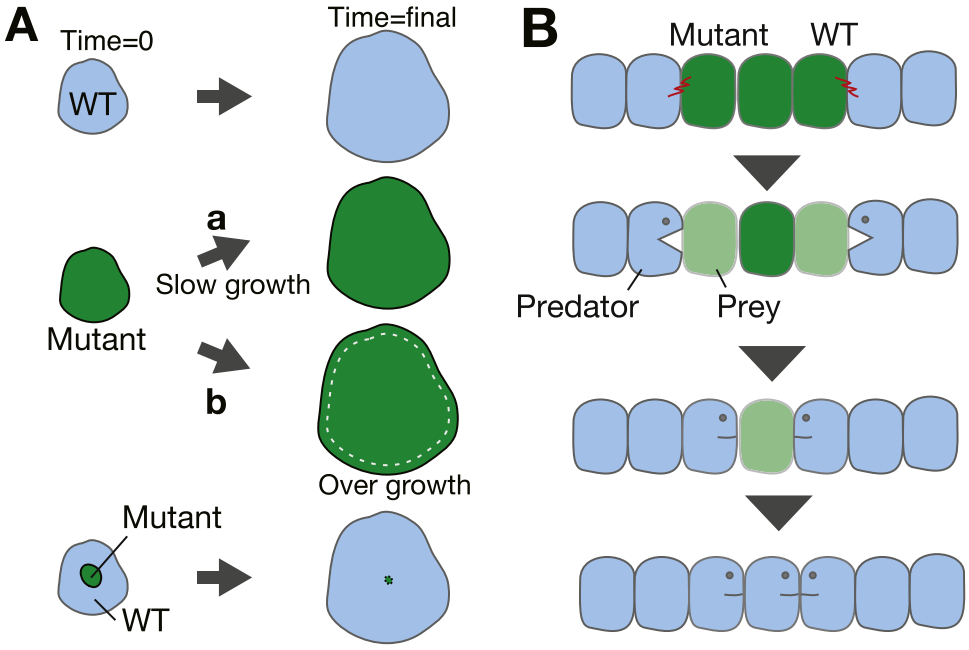

Fig. 1. Cell competition. (A) An example of cell competition between WT cells with higher fitness and mutant cells with lower fitness. Route **a** is for *Minute* mutant and **b** is for tumor-suppressor mutant. The dashed line shows the outline of a normal organ. (B) Side view of cell competition in a single-layer tissue (e.g., epithelium).

between wild-type (WT) cells with higher fitness and mutant cells with lower fitness is shown in Fig. 1A. Even a population consisting solely of mutant cells is viable, once the mutant cells are introduced into the WT-cell background, these cells are eliminated. Interestingly, the final size of the organ remains normal. The elimination process occurs by various means, e.g., cell death, phagocytosis, or extrusion, through a predator–prey-type interaction between WT cells and mutant cells at their interface (Fig. 1B). Then the group of cells with the higher fitness is termed the winner and the group of cells with the lower fitness is termed the loser.

The phenomenon of cell competition was first observed in a mosaic system of imaginal disc epithelium cells in fruit flies, *Drosophila* (Morata and Ripoll, 1975). A number of subsequent studies in both flies and mammals suggest that cell competition is universal: examples in mammalian systems appear in chimera systems of mice (Oliver et al., 2004), rat liver stem cells (Oertel et al., 2006), and systems of cultured cells (Hogan et al., 2009), as well as in intact *in vivo* mammalian organs (Clavería et al., 2013; Sancho et al., 2013; del Campo et al., 2014).

Extensive and quantitative studies have been reported in *Drosophila* systems. In their pioneering work, Morata and Ripoll studied a class of mutants named *Minute* (*M*), heterozygous mutants for genes encoding ribosomal proteins (Morata and Ripoll, 1975). *M*-flies are viable, but show slower growth than WT animals in their development (Fig. 1Aa). Intriguingly, *M*-mutant cells introduced into a WT-cell background cannot survive. At the same time, WT cells compensate for the space released by the death of mutant cells. It was shown that the phenomenon is induced by cell–cell interactions at the interface between the two cell groups. From this result, it was inferred that the fate of cells was related to their relative growth rates (Simpson, 1979; Simpson and Morata, 1981).

Later, however, it was reported that even cells with stronger growth competence can become losers in systems where clones of tumorigenic cells are introduced into normal epithelial tissues (Bilder, 2004). The genes responsible for this function are known as neoplastic tumor suppressors, e.g., apicobasal-polarity genes such as *scribble* (*scrib*) (Brumby and Richardson, 2003; Igaki et al., 2009; Ohsawa et al., 2011) and *lethal giant larvae* (*lgl*) (Menéndez et al., 2010), and endocytic genes such as *Rab5* (Ballesteros-Arias et al., 2014). In a tissue consisting of only mutant cells with a defective tumor-suppressing function, the tissue exhibits overgrowth to form the tumor (Fig. 1Ab), or additionally it proliferates faster. On the contrary, once surrounded by WT cells, the mutant cells are eliminated through cell competition to allow the organ to finally attain a normal size.

The above contradictory observations suggest that the fate of each cell group is not only governed by relative growth rates, but that additional complex factors are at play. Together, these could be termed "cellular fitness". However, this idea of cellular fitness has not been clearly defined (Amoyel and Bach, 2014). In this study, we construct mathematical models in Section 2 to explain the experimental observations including the contradictory phenomena in tumorigenic mutant systems against *M*-mutant systems. In Sections 3 and 4, we show that the model can reproduce several typical experimental observations in the cell competition system. By analyzing the model and defining a quantitative index for the degree of fitness, we show that the fate of each group of cells mainly depends on the relative carrying capacities of certain resources and the strength of the predator–prey interaction at the interface, rather than the relative proliferation rates (classical hypothesis).

2. Model

We follow two approaches in this paper: The main model is a population-based model and the second model is an individual cell-based model (Nishikawa and Takamatsu, 2016). The former has the advantage of using mathematical analysis to capture the general characteristics of the cell competition phenomena. The model, however, cannot directly include the spatial effect associated with the arrangement of two groups of cells. The latter model, which can directly simulate the behavior of individual cells, is introduced to verify the validity of the population-based model.