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Cell competition and its implications for development and cancer

Yoichiro Tamori, Wu-Min Deng*

Department of Biological Science, Florida State University, Tallahassee, FL 32306-4370, USA

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Abstract

Cell competition is a struggle for existence between cells in heterogeneous tissues of multicellular organisms. Loser cells, which die during cell competition, are normally viable when grown only with other loser cells, but when mixed with winner cells, they are at a growth disadvantage and undergo apoptosis. Intriguingly, several recent studies have revealed that cells bearing mutant tumor-suppressor genes, which show overgrowth and tumorigenesis in a homotypic situation, are frequently eliminated, through cell competition, from tissues in which they are surrounded by wild-type cells. Here, we focus on the regulation of cellular competitiveness and the mechanism of cell competition as inferred from two different categories of mutant cells: (1) slower-growing cells and (2) structurally defective cells. We also discuss the possible role of cell competition as an intrinsic homeostasis system through which normal cells sense and remove aberrant cells, such as precancerous cells, to maintain the integrity and normal development of tissues and organs.

Keywords: Cell competition; Canalization; Competition-dependent cell death; *Drosophila* models; Cellular proliferation; Cellular growth; Tumor-suppressor genes

1. Introduction

The concept of competition for survival between cells has long been intensively studied by microbiologists—the microbial antagonism induced by bacteriocin of *Escherichia coli* and *Pseudomonas aeruginosa* and the viral killer toxin of yeast and paramecium are representative examples (reviewed by Riley and Wertz, 2002; Schmitt and Breinig, 2006)—but biologists studying multicellular systems had barely considered the concept of competition between cells of the same species in a tissue until Morata and Ripoll (1975) discovered the phenomenon of cell competition in *Drosophila*. They used the developing wing imaginal disc of *Drosophila* to study the behavior of cells bearing a group of dominant mutations (known as the "*Minute*" mutations) that reduced the rate of cell division in a cell-autonomous manner (Morata and Ripoll, 1975). *Minute* heterozygous (*M*/+) flies develop more slowly than wild-type flies because of a defect in their ribosomal proteins but are viable and show normal body size. Morata and Ripoll (1975) generated mitotic clones of wild-type cells in a slower-growing *M*/+ field and found that the wild-type clones occupied most areas of the adult wing, and at the same time, *M*/+ cells were eliminated from the mosaic field. A few years later, Simpson and Morata (1981) showed that this phenomenon depends on a short-range cell−cell interaction. These investigators again generated wild-type clones in an *M*/+ background and studied the growth rates of both clones in greater detail. They found that wild-type cells adjacent to *M*/+ cells tended to divide more often than those positioned in the center of the clone and that *M*/+ cells not in contact with wild-type cells were not eliminated. Because this regulation of balance between proliferation of faster-growing wild-type cells and elimination of *M*/+ cells depended on cell−cell interaction, they named the phenomenon "cell competition."

Interestingly, several recent studies have revealed that cells bearing mutant tumor-suppressor genes, which show overgrowth and tumorigenesis in a homotypic situation, are frequently eliminated, through cell competition, from

Abbreviations: nTSGs, neoplastic tumor-suppressor genes; SGCs, slower-growing cells; SDCs, structurally defective cells; JNK, c-Jun N-terminal kinase; *M*/+, *Minute* heterozygous; dMyc, *Drosophila* Myc; SWH, Salvador/Warts/Hippo; *mahj*, *mahjong*; *lgl*, *lethal giant larvae*; MDCK, Madin−Darby canine kidney.

* Corresponding author. Tel: +1 850 645 1501, fax: +1 850 645 8447.
E-mail address: wumin@bio.fsu.edu (W.-M. Deng).

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epithelial tissues in which they are surrounded by wild-type cells. This suggests that cell competition is an intrinsic tumor-suppression mechanism that assures elimination of precancerous cells and epithelial integration. Cell competition might also be involved, at the cellular level, in canalization, a concept introduced by Waddington (1942) to describe the reduced sensitivity of a phenotype to genetic and environmental perturbations and defined by Wilkins (1986) as the stabilization of developmental pathways by multiple genetic factors within the genome: a form of genetic buffering. A number of studies have suggested that an intrinsic canalization system during development robustly assures the consistent size and shape of organs (Larsen, 2005), and recent studies have shown that cell competition accomplishes just this regulation at the cellular level (de la Cova et al., 2004). Because, in the process of cell competition, elimination of suboptimal loser cells is accompanied by compensatory proliferation of optimal winner cells with the result that final size and shape of organs are finely normalized, adult organ size becomes more variable when cell competition is blocked in developing tissues. The mechanism underlying the phenomenon therefore not only assures sensing and elimination of potentially deleterious (e.g., precancerous) cells during development but is also tightly connected to the organ-size control system.

Tumors are caused by uncontrolled proliferation of transformed mutant cells with activated oncoproteins and/or inactivated tumor-suppressor proteins, and malignant neoplasias arise from tumor cells that have lost the ability to assemble and create tissues of normal form and function (Weinberg, 2007). In other words, cancer can be viewed as a disease that arises when mutant cells fail to obey the intrinsic tissue-integrity and organ-size control system. Because the process of cell competition is deeply involved in maintenance of tissue integrity and regulation of organ size, especially when a mutant cell is spawned in a wild-type tissue, tumorigenesis occurs once the mutant cells break the rules of these systems. Here, we survey different types of genes whose mutant cells have been shown to induce cell competition in *Drosophila* and categorize those mutants into two distinct groups based on their phenotypes in an epithelial tissue. Mutants in the first category (slower-growing cells, SGCs) show slower growth than wild-type cells, and those in the second category (structurally defective cells, SDCs) show structural defects such as epithelial apicobasal polarity defects. Overview and comparison of the processes of cell competition induced by these two groups will help to reveal the mechanisms of cell competition and its relevance to cancer.

2. Hallmarks of cell competition

Since the introduction of accessible genetic-mosaic analysis tools in *Drosophila*, such as FLP−FRT mitotic recombination (Xu and Rubin, 1993) and Flip-out-Gal4-UAS (Ito et al., 1997), phenotypic analysis of a vast array of genes has been performed in later stages of development (late larva and adult). Substantial numbers of these mutant cells experimentally generated in developing wild-type tissues by means of mitotic recombination techniques have shown defects in their proliferation or survival. The first hallmark of cell competition is survival defect of loser cells. In cell competition, outcompeted loser cells undergo apoptosis and are eventually eliminated from tissues. Most of this apoptosis is observed at the boundary between two clones, winner cells and loser cells, because cell competition is based on direct cell−cell interaction between two different types of clones (Fig. 1A−D). Perhaps more accurate, then, is to say that the first hallmark is not just apoptosis of loser cells but "competition-dependent apoptosis"; loser cells adjacent to winner cells at their clone boundary undergo apoptosis. The second hallmark is that loser cells remain viable in a homotypic field where they come into contact only with the same loser cells. Examination of a group of loser cells mixed with winner cells in a mosaic tissue therefore shows that loser cells in the center of a loser clone do not show apoptosis, whereas those at the periphery do (Fig. 1D).

In the initial stage of cell competition, two different types of cells compare their competitive abilities to determine winners and losers. Most previous reports have shown that slowly proliferating cells undergo apoptosis when they are surrounded by rapidly proliferating cells, but activation of cyclin D/Cdk4 or the insulin/insulin-like growth-factor receptor pathway, which accelerates cell division or cellular growth, respectively, does not cause cell competition (de la Cova et al., 2004), suggesting that a difference in cell growth rate alone does not always trigger cell competition. Although all factors conferring competitive ability on cells are not yet known, we know that the competitive ability of *Minute* heterozygous (*M*/+) cells is lower than that of the wild-type cells. When *Drosophila* geneticists confront a phenotype of mutant cells showing a disadvantage in their proliferation or impairment in their survival in a mosaic tissue with wild-type cells, the "*Minute* technique" is commonly used to recover the mutant cells in mosaic tissues. *Minute* causes a marked developmental delay in heterozygotes. Wild-type clones in *M*/+ genotypes have a growth advantage over their *M*/+ neighbors and are often very large. Garcia-Bellido et al. (1973) exploited this phenomenon as a general method for the production of large somatic clones normally showing defects in their proliferation or survival in a wild-type background (Ashburner et al., 2005). Many such mutant cells that are outcompeted by wild-type cells have been shown to survive when they confront *M*/+ cells instead of wild-type cells, in this *Minute* technique. This result could arise from an alleviation of the competitive pressure, but technically this technique reduces proliferation speed of competitors, suggesting that the recovery of mutant clone size could be just a result of a proliferation race. Cell competition is not just a proliferation race but is survival of the fittest based on a cell−cell interaction. Therefore, when the *Minute* technique rescues such cells from elimination and the competition-dependent cell death observed at a boundary with wild-type clones, we can say that the mutant cells fulfill the third hallmark of cell competition (Fig. 1E).