Cell Competition: The Embrace of Death

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DOI 10.1016/j.devcel.2007.06.002

Cell competition compares cells within a growing population and eliminates the weaker ones by apoptosis. In a recent issue of *Cell*, Li and Baker (2007) show in the *Drosophila* wing disc that cells fated to die induce in neighboring cells the activity of engulfment genes, whose function is essential to complete the apoptotic program.

Cell competition was discovered in the imaginal discs of *Drosophila* over 30 years ago (Morata and Ripoll, 1975). It describes a situation in which slow dividing, but otherwise viable, cells are eliminated from a population of more rapidly dividing cells. The slow dividing cells were heterozygous for a deletion of a *Minute* gene, a member of a gene family in the *Drosophila* genome that codes for the various ribosomal proteins (reviewed in Lambertsson, 1998). *Minute* mutations are homozygous lethal, and in heterozygous *(M/+)* condition cause a developmental delay, due to the slow division rate of the *M/+* cells in comparison with wild-type cells.

Subsequent work showed that cell competition is not limited to cells defective in ribosomal proteins. Cells with low activity of the insulin pathway (Bohni et al., 1999) or that are mutant for *dMyc* (the *Drosophila* homolog of the mammalian proto-oncogene *Myc*) also suffer cell competition (Johnston et al., 1999). The general idea is that it is a competitive process that compares cells within a population and eliminates the weaker ones. The elimination occurs by JNK-mediated apoptosis, apparently triggered by the inability of these cells to capture sufficient amounts of survival factors (Moreno et al., 2002).

There are also indications that cell competition is not restricted to *Drosophila.* Mouse cells heterozygous for a mutation defective in a riboprotein gene show decreased proliferation and are out-competed by wild-type cells (Oliver et al., 2004). Moreover, cell competition appears to play a role in rat liver reconstitution by transplanted stem cells (Oertel et al., 2006). Thus, it may represent a general phenomenon implicated in tissue homeostasis. There are other possible roles of cell competition during normal development and in tumor formation, but we will not discuss them here.

The critical aspect of cell competition is that it is a context-dependent process: *M/+* cells, as *dMyc* mutant cells used in other experiments, are viable, e.g., they can build normal adult flies. Yet these cells are eliminated if they are in the same compartment with others that divide faster. The context-dependent nature is illustrated dramatically by experiments altering the number of copies of *dMyc* (Moreno and Basler, 2004): wild-type cells, carrying two copies of the gene, are out-competed by artificially generated cells containing four copies.

It follows from this that there must be specific interactions between wild-type and *M/+* cells that do not occur within wild-type cells or within *M/+* cells which trigger cell competition.

This issue of the cellular interaction is the main theme of the paper in *Cell* (Li and Baker, 2007). They use various modifications of the classical Minute method to generate fast growing wild-type (+/+) cells in a slow growing *M/+* compartment, thus setting up the conditions for cell competition. Expectedly, apoptotic *M/+* (out-competed) cells appear very close to or at the borders of the fast growing clones, indicating that cell competition is triggered by short-range interactions. The presence of the general caspase inhibitor P35 prevents cell competition, as previously shown (Moreno et al., 2002).

Li and Baker (2007) examine the interactions between the +/+ and the *M/+* cells. For the sake of clarity we shall call the fast dividing +/+ cells "killer" and the slow dividing *M/+* cells, fated to die, "doomed". Differential labeling of the two types of cells allows visualization of some of the cellular events: the killer cells appear to engulf the doomed ones and eventually their corpses finish up inside the killer cells. This is a novel observation regarding cell competition and, though interesting, is not overly surprising as there are other examples of apoptotic cells phagocytosed by their neighbors. But interestingly, preventing death of *M/+* cells by adding P35 inhibits the engulfment process by killer cells, indicating that phagocytosis cannot operate on intact cells.

The real novelty comes from the functional analysis of several genes known to be active in the phagocytic and engulfment processes in *Drosophila* and other organisms. These genes include *draper* (*drpr*, related to the *C. elegans* engulfment receptor *ced1*), *wasp* (encoding an actin regulator required by *Drosophila* cells to phagocytose bacteria), *phosphatidyl serine receptor* (*psr*, involved in corpse engulfment in *C. elegans* and zebrafish), and the *Drosophila* homologs of the *C. elegans* cell engulfment genes *ced-5* and *ced-10.*

Li and Baker (2007) study the role of these genes in cell competition by generating clones of either killer or doomed cells which are at the same time mutant for any of the engulfment genes. The significant and surprising result is that mutant clones of killer cells show much reduced ability to induce apoptosis along their borders, indicating that activity of the engulfment genes is a requisite for cell competition. By contrast, the lack of these gene activities in doomed cells does

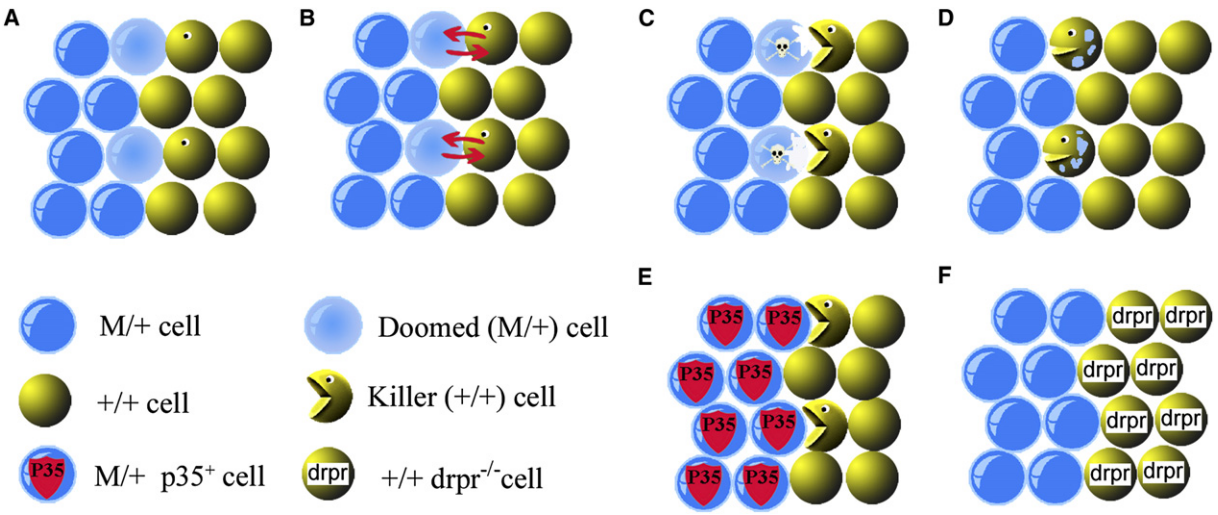

Figure 1. A Speculative Scheme of Events Leading to Cell Elimination by Competition

Fast dividing wild-type +/+ cells are labeled in yellow and the slow dividing *M*/+ cells in blue. In some cases, perhaps caused by their different levels of Dpp signaling, a pair of fast dividing and slow dividing cells initiate a series of interactions leading to the destruction of the slow ones. The first step (A) would be the establishment of the roles as doomed (light blue) and killer (eyed), (B) followed by reciprocal activations (C) of apoptotic and engulfment programs in doomed and killer cells respectively. (D) At the end the apoptotic corpses are phagocytosed by killer cells. (E) Blocking cell death with P35, or (F) perturbations in the engulfment program (illustrated by a mutation at *drpr,* one of the engulfment genes), inhibits cell competition.

not affect their ability to enter apoptosis. The authors also show that these genes are dispensable for normal growth and Dpp signaling; thus their role in cell competition is not linked to growth.

Therefore engulfment by killer cells is necessary for apoptosis and apoptosis of doomed cells is necessary for engulfment. All of these results indicate the following unexpected cascade of events during cell competition (illustrated in Figure 1): (1) establishment of doomed and killer roles in the interacting cells, possibly caused by their unequal levels of Dpp activity (Manjon et al., 2007; Moreno et al., 2002), (2) the doomed cells induce activity of engulfment genes in killer cells, (3) the killer cells induce apoptosis in the doomed ones by a mechanism that requires engulfment genes function, and (4) the killer cells engulf the doomed cells corpses.

The findings by Li and Baker (2007) provide new insights into the phenomenon of cell competition. They distinguish the contributions of both the killer and doomed cells and demonstrate that a whole set of new genes is involved in the process. This of course raises a number of new questions. Of particular interest are the molecular mechanisms implicated in the complex interactions between killer and doomed cells: the requirements for apoptosis and for engulfment activities, which are mutually necessary for cell competition. Other questions relate the significance of these observations in the mechanisms of apoptosis in *Drosophila* and other organisms.

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