Survival of the fittest
Cell competition in the *Drosophila* wing

In multicellular organisms, cells are eliminated by programmed cell death if they fail to receive appropriate signals from their neighbors (Raff, 1992). The nature of the signals required for cell survival is currently one of the most interesting questions in biology. A recent report in *Nature* presents evidence that Decapentaplegic (Dpp), a secreted growth factor that forms a long-range extracellular protein gradient, acts as a survival factor in the *Drosophila* wing (Moreno *et al.*, 2002). If this role is conserved along with the protein, Dpp may be generally important in maximizing tissue fitness in multicellular organisms.

Thirty years ago, Ginés Morata and Pedro Ripoll used the *Drosophila* wing to study the cellular behavior of a group of dominant mutations that reduce the rate of cell division in a cell autonomous manner (Morata and Ripoll, 1975). *Minute* heterozygous flies are viable and of normal size but develop more slowly than do wild-type flies, due to defective ribosomal proteins. Furthermore, wild-type cells in a slow-dividing *Minute* heterozygous background cover large areas of the adult wing, and slow-dividing *Minute* heterozygous cells in a wild-type background are eliminated. The fact that *Minute* cells are eliminated only when they grow next to wild-type cells suggests that this phenomenon relies upon cell–cell interactions. Therefore, it was termed cell competition. A few years later, Ginés Morata and Pat Simpson performed an elegant experiment showing that the cell interactions on which this competition relies are short-range (Simpson and Morata, 1981). They again generated clones of wild-type cells in a slow-dividing *Minute* heterozygous background but analyzed the growth rates of both types of cells in greater detail. They found that wild-type cells in contact with *Minute* cells tend to divide more often than do those positioned in the center of the clone and that *Minute* cells not in contact with a wild-type clone are not eliminated.

Based on these experiments, cell competition was proposed to take place in the growing wing disc and to lead to the loss of slow-dividing *Minute* cells when confronted with wild-type cells. Thus, the process of cell competition may rely on the recognition of differences in division rates. However, given that *Minute* mutations are inefficient at protein translation, there may still be an alternative explanation: cell competition may also recognize differences in the translation of limiting cell survival proteins. Consistent with this, Morata and colleagues made a very interesting observation. *Minute* cells are preferentially eliminated in the center of the wing, near the

![Fig. 1.](image)

(A) Schematic illustration of the wing epithelium. Dpp (blue) is expressed in the center of the wing and forms a symmetric gradient. Dpp limits the expression of *brinker* (*brk*, red) to the lateral regions of the disc. (B) *Minute* cells (green) near the source of Dpp express *brk*, leading to JNK activation and apoptosis.
source of the growth factor Dpp. Burke and Basler (1996) have already shown that clones that lack the Dpp receptor Thick-veins (Tkv) and are positioned in the center of the wing disc behave in a similar manner. This is due to the upregulation of brinker (brk), a transcriptional repressor of Dpp target genes that is normally restricted to the lateral regions of the wing by Dpp signaling (Figure 1). When mutant for brk activity, these tkv clones survive (Campbell and Tomlinson, 1999). The Morata study shows that the behavior of Minute cells resembles that of clones lacking tkv activity: Minute cells in the center of the disc upregulate brk expression before being eliminated but survive when lacking brk activity. Thus, Minute and wild-type cells may be competing for limited amounts of the Dpp ligand. The authors propose the existence of a rate-limiting protein involved in capturing Dpp. Minute cells, which are expected to be less efficient at producing such a protein, might capture less Dpp than do wild-type cells. In such a scenario, Minute cells express brk, leading to activation of the JNK pathway and programmed cell death. Cell competition may be explained, therefore, in terms of competition for limited amounts of Dpp as a survival factor. Since Dpp is also required for wing growth, this may reflect a mechanism whereby weak cells are eliminated and Dpp signaling is maximized, thus ensuring the development of an adult wing of the ‘fittest’ size and shape. Cell competition visualized in fly wing cells may then represent a general ability of multicellular organisms to maximize tissue fitness.

References


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