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, the fact that all these analyses were performed in the adult wing led to an alternative trivial explanation. Due to their deficiency in ribosomal proteins, *Minute* cells might be expected to differentiate more slowly than their wild-type counterparts, and, in the wing, undifferentiated cells might be eliminated during metamorphosis. Thus, the failure of *Minute* cells to survive in a wild-type background might be explained by a critical delay in the differentiation process. In their recent study, Morata and colleagues re-analyze the phenomenon of cell competition in the growing wing disc (Moreno *et al.*, 2002). First, they show that *Minute*

cells in a wild-type background are actually eliminated during the early, proliferative stages of wing development (prior to the onset of differentiation). The authors present evidence that this elimination is due to apoptosis: *Minute* cells are positive for TUNEL staining, and, when the viral apoptosis inhibitor p35 is expressed in wing cells, *Minute* cells are not eliminated. As expected, the size of these clones is still reduced. Because the JNK pathway mediates apoptosis in wing cells (Adachi-Yamada *et al.*, 1999), it was surmised to be involved in the elimination of *Minute* cells. Indeed, blocking the JNK pathway suppresses the death of these cells, resulting in the presence of *Minute* clones, albeit of small size.

For the last 30 years, it has been assumed that the process of cell competition is based only on differences in division rates. However, given that *Minute* mutations are inefficient at protein translation, there may still be an alternative explanation: cell competition may be also recognizing 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. (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 Thickveins (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

Adachi-Yamada, T., Fujimura-Kamada, K., Nishida, Y. and Matsumoto, K. (1999) Distortion of proximodistal information causes JNK-dependent apoptosis in *Drosophila* wing. *Nature*, **400**, 166–169.

Burke, R. and Basler, K. (1996) Dpp receptors are autonomously required for cell proliferation in the entire developing *Drosophila* wing. *Development*, **122**, 2261–2269.

Campbell, G. and Tomlinson, A. (1999) Transducing the Dpp morphogen gradient in the wing of *Drosophila*: regulation of Dpp targets by brinker. *Cell*, **96**, 553–562.

Morata, G. and Ripoll, P. (1975) Minutes: mutants of *Drosophila* autonomously affecting cell division rate. *Dev. Biol.*, **42**, 211–221.

Moreno, E., Basler, K. and Morata, G. (2002) Cell compete for Decapentaplegic survival factor to prevent apoptosis in *Drosophila* wing development. *Nature*, **416**, 755–759.

Raff, M.C. (1992) Social controls on cell survival and cell death. *Nature*, **356**, 397–400.

Simpson, P. and Morata, G. (1981) Differential mitotic rates and patterns of growth in compartments in the *Drosophila* wing. *Dev. Biol.*, **85**, 299–308.

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