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Darwin's multicellularity: from neurotrophic theories and cell competition to fitness fingerprints

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Metazoans have evolved ways to engage only the most appropriate cells for long-term tissue development and homeostasis. In many cases, competitive interactions have been shown to guide such cell selection events. In *Drosophila*, a process termed cell competition eliminates slow proliferating cells from growing epithelia. Recent studies show that cell competition is conserved in mammals with crucial functions like the elimination of suboptimal stem cells from the early embryo and the replacement of old T-cell progenitors in the thymus to prevent tumor formation. Moreover, new data in *Drosophila* has revealed that fitness indicator proteins, required for cell competition, are also involved in the culling of retinal neurons suggesting that 'fitness fingerprints' may play a general role in cell selection.

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Darwinian cell competition in the body

Darwin's theory of natural selection has revolutionized our understanding of how organisms evolve. Often, the essence of his theory is formulated with 'the fittest survive', a term first coined by Herbert Spencer, to summarize the ideas of Darwin that better adapted organisms will live to have more offspring. In 1881, zoologist Wilhelm Roux argued that Darwinian competition and selection had not been considered for the development of tissues and organs. In his view, cells within our bodies were also likely to compete for space and limited resources. Such 'fights' among slightly varying 'parts of our bodies' would result in the 'selective breeding' of the most durable and the elimination of less durable parts (cells).

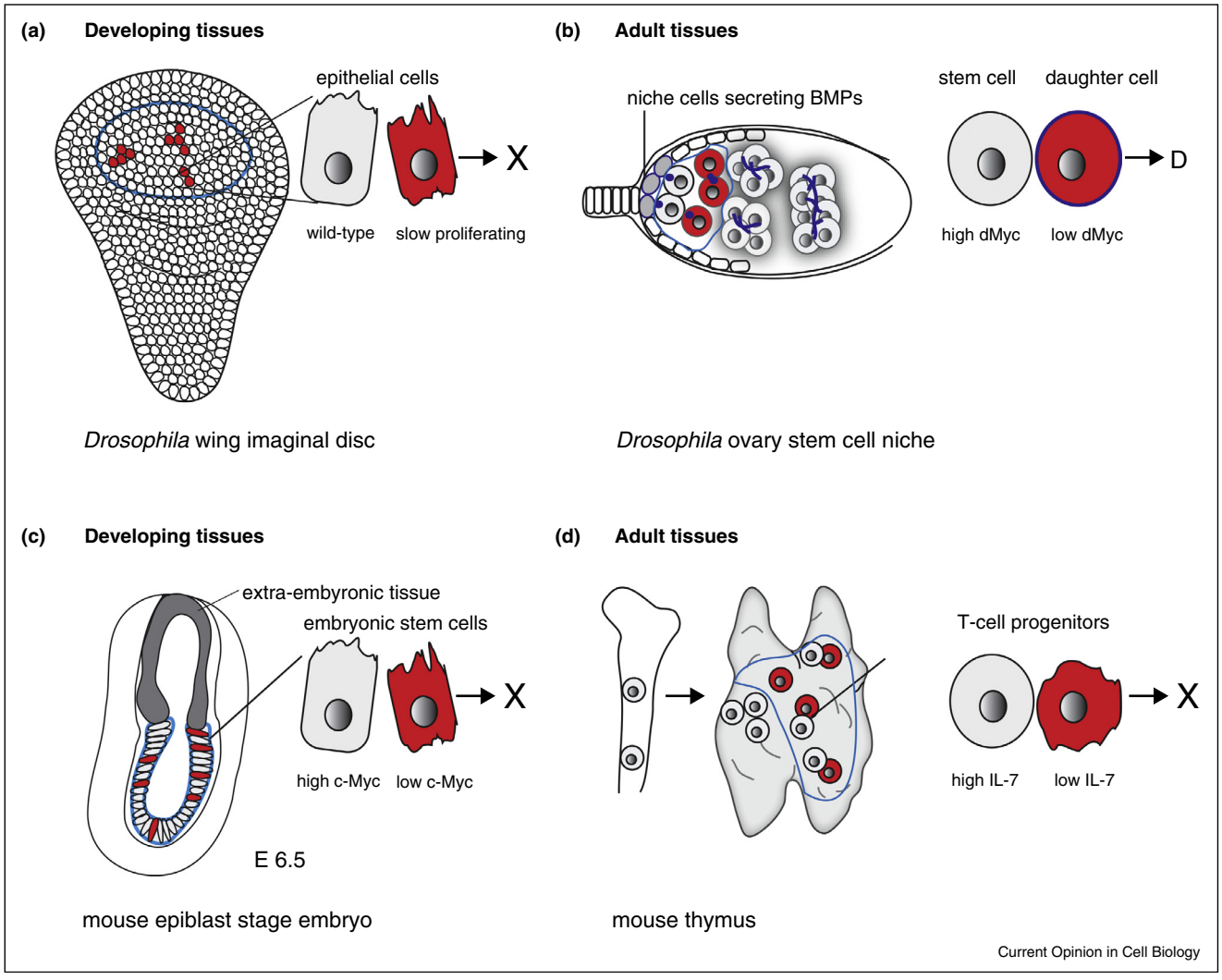
Along similar lines, Santiago Ramon y Cajal proposed a few years later that developing neurons may be engaged in a competitive struggle for space and nutrition, an idea which gained support in the framework of the neurotrophic theory and the discovery of nerve growth factor by Rita-Levi Montalcini and its isolation by Stanley Cohen in 1960 [1]. During nervous system development, large proportions of neurons die in almost every region of the nervous system. The normal death of these neurons occurs during a limited time window coinciding with target innervation [2]. Up to now, a large body of evidence has shown that neurons compete for limiting amounts of target-derived or paracrine factors, which support the survival of only a fraction of the initially generated neurons, thus potentially eliminating unfit or less suitable neurons from a larger population [3]. This provides a mechanism how the right number and probably also the right quality of neurons are chosen to innervate given target tissues. Many aspects of the neurotrophic theory have been molecularly proven, such as identification of further target and paracrine-derived survival factors and their corresponding receptors on developing neurons [4], but how exactly optimal neurons are identified is less clear.

In *Drosophila*, a process known as cell competition [5] eliminates cells with heterozygous mutations in ribosomal protein genes (*Minute* cells) through a mechanism that has been proposed to involve competition for extracellular factors and apoptosis [6]. Various genetic studies in *Drosophila* have established, that apart from *Minute* mutations (Figure 1a), also reduced growth factor signaling, lowered anabolic capacity or altered apico-basal polarity represent triggers for competitive interactions, which have been recently reviewed elsewhere [7–9].

In some situations, it has been shown that mutant cells can become 'supercompetitors' and behave as winners by outcompeting wild-type cells, which now turn into losers. For example, clones with elevated levels of *Drosophila myc* (*dmyc*), the homolog of the human *c-Myc* protooncogene, can convert into such supercompetitors. Supercompetitor cells expand in developing fly epithelia by inducing apoptosis in surrounding wild-type cells based on short range cell–cell interactions [10,11]. The 'enrichment' in supercompetitor (winner) clones is morphologically silent [10] because it is balanced by the concomitant loss of wild-type cells.

Although cell competition normally occurs in proliferating tissues, a recent study by Tamori and Deng has

Figure 1



Cell competition in *Drosophila* and mouse tissues.Cell competition occurs in *Drosophila* among epithelial cells of developing wing imaginal discs **(a)**. In adult flies, stem cells in the ovary germline niche compete with their daughters and among each other for niche-derived factors **(b)**. Cell competition in mice has been found to occur at the epiblast stage among pluripotent embryonic stem cells around embryonic day 6.5 (E6.5) **(c)**. In adult mice, competitive interactions take place among resident and fresh bone marrow-derived T-cell progenitors in the thymus. Blue lines mark areas of competition. The cross symbolizes apoptotic elimination, whereas D stands for niche exit and differentiation.

revealed that competitive interactions can also play a role in the postmitotic *Drosophila* follicular epithelium [12••,13]. The authors showed that follicular cells with heterozygous mutations in ribosomal protein genes (*Minutes*) or reduced levels of *mahjong* (*mahj*), a regulator of apico-basal polarity [14], are selectively lost by apoptosis from follicular epithelia, whereas no cell death was triggered in tissues made entirely of *Minute* or *mahj*−/− cells. In contrast, other factors known to trigger competition in mitotic epithelia (dMyc, activated growth factor signaling or apico-basal tumor suppressor genes) do not play a role in this type of competition. As a further difference, the eliminated cells due to competition are not replaced by cell proliferation. Instead, remaining winner cells increase in size by accelerating their endocycles in a process named compensatory cellular hypertrophy [12••].

To summarize, the outcome of both classical cell competition and supercompetition is a Darwinian-like selection, leading to long-term survival of certain cells over others.

The growing functions of cell competition

Until recently, work on cell competition was mainly carried out in *Drosophila* and relied heavily on the analysis of two experimentally induced populations (e.g. wild-type *vs.* mutant cells) in mosaic epithelia.

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