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Cell competition in development: information from flies and vertebrates

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Cell competition is a biological mechanism conserved from *Drosophila* to vertebrates wherein neighboring cells compare their relative fitness status resulting in the elimination of less fit cells by those with higher fitness. This is an active process that is essential for embryonic and organ development, tissue homeostasis, delay of ageing and in various disease models such as cancer. Recent research is beginning to unravel the various mechanisms of cell competition and the sensing of fitness status. Fitness fingerprints, death receptors, mechanical cell competition and a set of unknown genetic or signaling pathways are emerging as important pathways governing the mechanisms for cell to compare their relative fitness levels. In this review we are providing an account of recent advances which help summarize the mechanisms of operation and growing role of cell competition in regulation of oncogenesis in vertebrates.

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Introduction

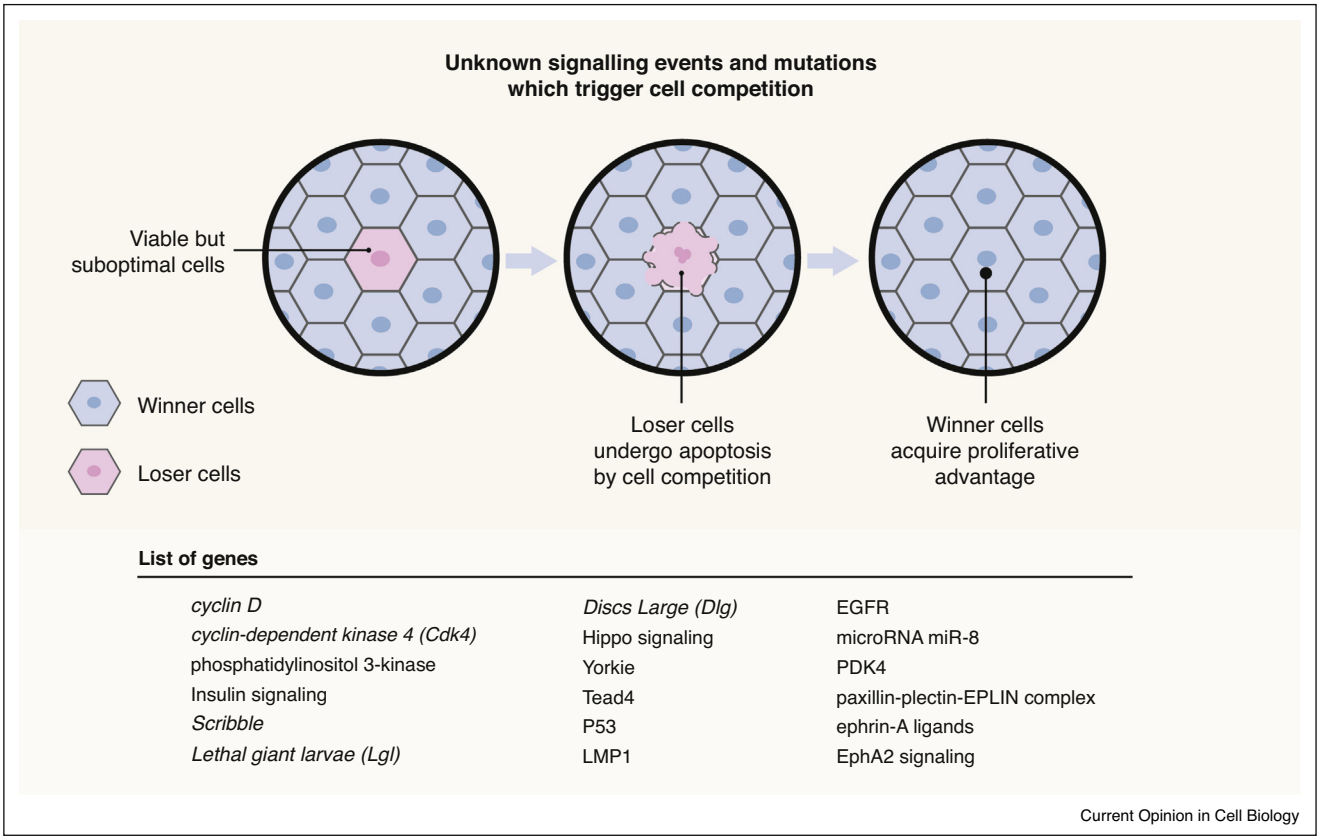
Any given cell along its life cycle will sustain a variety of stresses and insults that may render the cell viable, but suboptimal with reduced fitness. Thus, mechanisms which allow active elimination of such cells are essential to maintain tissue homeostasis and prevent the accumulation of suboptimal, less fit cells [1]. The important biological question here are what sensing and surveillance mechanisms are in place for cells with reduced fitness to be recognized and culled. Recent research has begun to investigate how cells of different fitness recognize each other and provide insight into the genetic and molecular signaling events governing cell competition.

In recent years, the field of cell competition has seen a surge of research aimed at understanding the mechanistic aspects. A variety of pathways have been discovered which participate in different cellular events found to contribute to competition. This raises the question of whether there are multiple mechanisms or pathways through which cell competition-induced recognition and apoptotic elimination of less fit cells occurs. In our opinion there are 3 major pathways for which research evidence is available; (1) comparison of cell fitness via fitness fingerprints, (2) competition triggered by mechanical forces, and (3) cell competition via death receptors. In addition, we have a number of pathways and genes which trigger cell competition, but their mechanisms remain unknown. All these mechanisms are discussed under section: unknown signaling events and mutations which trigger cell competition.

Comparison of cell fitness via fitness fingerprint

One proposed mechanism by which neighboring cells can exchange and compare fitness is through cell surface receptors, thus named fitness fingerprints. The suboptimal cells (Loser cells) display marks on the cellular surface that can be recognized by healthy cells (Winner cells) [2]. Cell competition mediated by fitness fingerprints is active in short ranges and promotes elimination of Loser cells by Winners either via direct contact or in nearby vicinity [2–9]. One of the most important fitness fingerprints discovered is the transmembrane protein, Flower (Figure 1) [2,10,11]. Flower is a conserved gene from *Drosophila* to humans and encodes two kinds of isoforms called Win (Ubi in *Drosophila*) and Lose. The expression of a specific isoform (splice variant) on the cell surface marks the cell to function as Winner or Loser [2,12]. These fitness fingerprints also act as recognition mechanisms downstream other cell competition triggers such as manipulation of *Myc*, *Minute*, *Scribble* and *Dpp*. Reduction in *Myc* expression, presence of heterogenous *Minute* mutation, *Scribble* deletion and reduction in *Dpp* signaling are all associated with concomitant expression of Flower Lose isoforms on the cell surface and thus, the acquisition of the Lose phenotype [13]. At the same time, Winner cells in these competition assays also express Flower Win isoforms on cell surface. Thus, expression of Flower Lose signals presence of an unfit cell to the immediate neighbors, as is observed in *Drosophila* wing disc [2], *Drosophila* neuronal cells [14], mouse tumor models [12]. Some insight about molecular mechanism regarding execution of Winner (gain of survival/proliferation ability) or Loser (apoptosis) phenotype downstream recognition by

Figure 1



A model is presented which shows how Winner and Loser cells can recognize and compare their relative fitness levels via fitness fingerprints. This mechanism of cell competition is rather comprehensive and explains the process from start to end, where recognition can be achieved by expression of Flower Win and Lose isoforms on cell membrane in Winner and Loser cells respectively. Downstream this recognition process, Loser cells expressing Flower Lose isoforms can activate certain cyto-protective genes such as SPARC which provides them with an opportunity to evade death. Another gene, AZOT is found to be unregulated in Loser cells downstream Flower and is responsible for activation of caspase and execution of apoptosis.

fitness fingerprints was recently discovered. A secreted protein, SPARC, was found to be expressed in Loser cells as a protective mechanism against apoptosis [15]. Interestingly SPARC protein in humans was also found to be overexpressed in boundaries of human cancers, at the tumor-stroma border [10]. A separate study found that the final decision of apoptosis in cells with reduced fitness was mediated by the calcium binding protein, Azot, via activation of the pro-apoptotic gene Hid [16]. Other well-known cell competition pathways have now been shown to function downstream of fitness fingerprint mechanisms. For example, apoptotic elimination of wild type cells when in contact with dMYC overexpressing cells in the *Drosophila* wing disc was found to function via Flower gene [17,18]. Similar to *Drosophila*, human cells expressing high *cMyc* levels outcompete cells with low *cMyc* [19••]. Given the expression pattern of *cMyc* in cancer, it was postulated that the *cMyc*-overexpressing cancer cells would have a higher fitness and outcompete stromal cells with low *cMyc* levels [10]. Supporting this hypothesis, a recent study showed the presence of *cMyc* overexpressing cells and caspase positive apoptotic cells at the tumor-stroma interface and within the tumor parenchyma [20••]. It will be interesting to observe whether Flower is involved in regulation of cMyc-induced cell competition in human cancers. In addition, differences in signaling intensity of several pathways such as bone morphogenetic protein (BMP)/Dpp, WNT/Wg, JAK-STAT have all been shown to induce cell competition via Flower gene. Low Dpp signaling in *Drosophila Minute* heterozygous cells imparts Loser phenotype via fitness fingerprint recognition mechanism during competition [18]. Mammalian pluripotent cells with low BMP signaling also function as Losers, and it is very likely that this mechanism also functions downstream conserved Flower fitness fingerprints pathway [21]. Normal cells with low JAK-STAT, WNT/Wg signaling or with Axin/APC mutations which block WNT/Wg signaling acquire Loser phenotype under regulation of the Flower pathway [22••,23,24]. Such studies have shown that multiple pathways act downstream of fitness mark-induced cell