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To cite this article: Romain Levayer & Eduardo Moreno (2016) How to be in a good shape? The influence of clone morphology on cell competition, Communicative & Integrative Biology, 9:1, e1102806, DOI: [10.1080/19420889.2015.1102806](https://doi.org/10.1080/19420889.2015.1102806)

To link to this article: <http://dx.doi.org/10.1080/19420889.2015.1102806>



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Accepted author version posted online: 05 Jan 2016.



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## How to be in a good shape? The influence of clone morphology on cell competition

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### ABSTRACT

Cell competition is a conserved mechanism where slow proliferating cells (so called losers) are eliminated by faster proliferating neighbors (so called winners) through apoptosis.<sup>1</sup> It is an important process which prevents developmental malformations and maintains tissue fitness in aging adults.<sup>2</sup> Recently, we have shown that the probability of elimination of loser cells correlates with the surface of contact between losers and winners in Myc-induced competition.<sup>3</sup> Moreover, we have characterized an active mechanism that increases the surface of contact between losers and winners, hence accelerating the elimination of loser cells. This is the first indication that cell shape and mechanics can influence cell competition. Here, we will discuss the consequence of the relationship between shape and competition, as well as the relevance of this model for other modes of competition.

### ARTICLE HISTORY

Received 21 September 2015  
Accepted 28 September 2015

### KEYWORDS

apoptosis; cell-competition;  
cell sorting; *Drosophila*;  
morphogenesis; mechanics

Cell competition was defined as the disappearance of slow proliferating cells in the context of wildtype cells<sup>4</sup> by an active process of apoptosis.<sup>5</sup> It has later been shown to be based on a local communication between cells which involves the comparison of relative fitness<sup>6</sup> and induction of apoptosis in the less fit cells (so called “loser cells”) by the fitter cells (so called “winner cells”). Competition, and other related phenomena based on cell fitness comparisons using fitness fingerprints,<sup>2,7,8</sup> is necessary to avoid developmental errors and to maintain tissue fitness in the adult.<sup>2</sup> However, some mutations can also lead to an increase of fitness and produce “super-competitors,” which eliminate neighboring wild type (WT) cells and invade the tissue through the same competition mechanism.<sup>3,6,9,10</sup> As such, supercompetition was proposed to promote tumor expansion by promoting elimination and replacement of healthy cells by pre-tumoral cells.<sup>11</sup>

### The elimination of the loser cells: A fine tuned decision

Using the proto-oncogene Myc to induce competition, we performed for the first time long term live imaging of competition in the *Drosophila* pupal notum, a single layer epithelium.<sup>3</sup> We found that the probability of elimination of loser cells is set by 2 key

parameters. First, the probability of elimination correlates with the relative difference of concentration between losers and winners of the fitness marker *flower<sup>lose</sup>* (a transmembrane protein expressed in loser cells<sup>6</sup>). Secondly, loser cell elimination probability correlates with the proportion of apical perimeter shared with winner cells. More specifically, apoptosis is not significantly increased in loser cells sharing less than 40-50% of their contact with winners. Altogether, these results were suggesting that cells can compute the relative levels of *flower<sup>lose</sup>* with all their direct neighbors. The computation could be based on *cis* and *trans* interactions between Flower proteins or through other unknown molecules and receptors.

### Cell sorting and competition

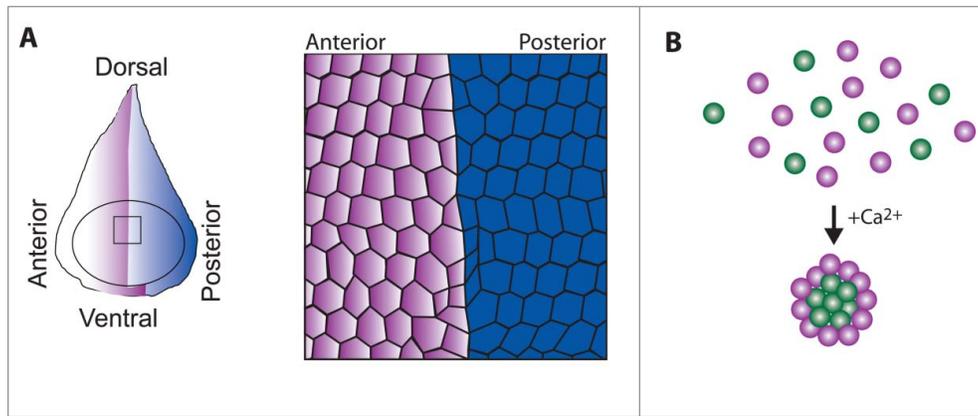
The concept of fitness encompasses several parameters, including cell anabolism, growth rate and the capacity to integrate in the epithelial layer.<sup>1</sup> As such, comparison of fitness only makes sense for similar cell type and should not occur between different lineages to avoid aberrant elimination of cells. Yet, we still do not know what makes fitness comparison ineffective between cell types. Lineage specificity could be based on the existence of cell type specific fitness markers. Yet, the only fitness marker so far characterized (the transmembrane protein Flower.<sup>6</sup>)

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**Figure 1.** Compartment boundaries and cell sorting. (A) Schematic of the antero-posterior compartment boundary in the *Drosophila* wing imaginal disc, which restricts the surface of contact between anterior cells (purple) and posterior cells (blue). (B) Embryonic cells from different lineages are mixed. Cell-cell adhesion reconstructs upon addition of calcium, leading to spontaneous sorting of the cell according to their lineage.

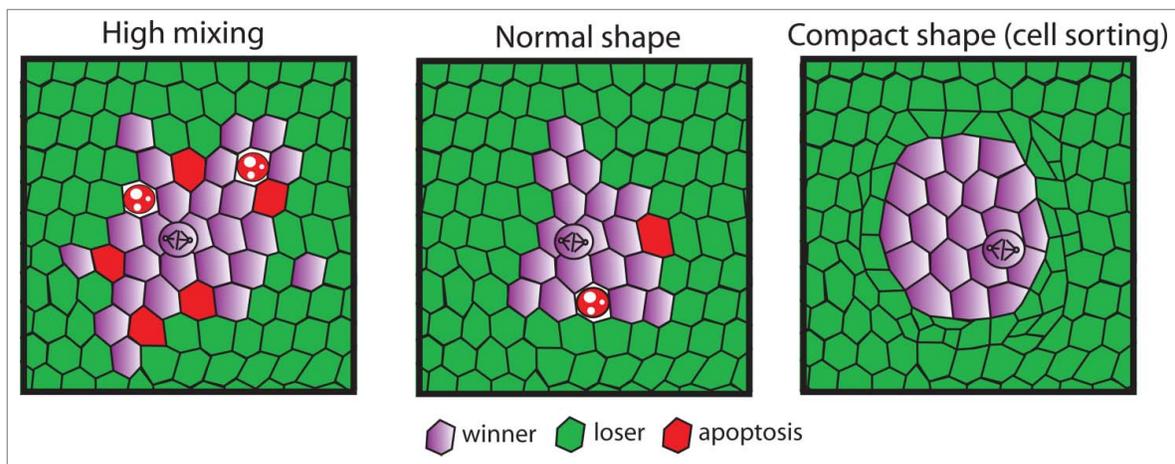
is not restricted to one cell lineage and is expressed in several cell types.<sup>6-8</sup>

Alternatively, lineage restriction could be driven by the topology of the contact between cells. We found that the form of the interface between winner and loser cells can modify the outcome of cell competition. For instance, the percentage of surface shared between cells across compartment boundaries (a frontier between different lineages) is on average close to 20% and therefore is sufficient to prevent cell competition (Fig. 1A). Cells from different embryonic lineages spontaneously sort (Fig. 1B) due to differential adhesion and/or tension,<sup>12</sup> which reduces the surface of contact between the 2 cell types. Therefore, the low surface of contact between different cell types could be sufficient to prevent inter-lineage competition.

Similarly, we found that larval starvation is sufficient to prevent high winner-loser mixing and block elimination of loser cells. This could prevent the elimination of suboptimal (but viable) cells in conditions where the organism cannot afford any waste. Altogether, the requirement of mixing for loser elimination provides a simple mechanism that could prevent inter-lineage competition and adjust competition to the environmental cues.

#### Generalization to other competition factors

Modulation of many pathways can induce competition, including the proto-oncogene *Myc*,<sup>9,10</sup> Minute mutations (encoding for ribosomes),<sup>4</sup> modulation of *Dpp*



**Figure 2.** The influence of clone shape on cell selection. Different scenarios of cell competition (winner cells in purple, loser cells in green) with high levels of winner-loser mixing, normal levels of mixing and cell sorting (low mixing of loser and winner cells) and the expected location of dying losers (red) based on the contact dependent death induction.

signaling,<sup>5</sup> modulation of the Hippo/Yki pathway,<sup>13</sup> modulation of Ras,<sup>14</sup> alteration of apico-basal polarity (Scribble,<sup>15</sup> Disc-large,<sup>16</sup> Lethal-giant-larvae,<sup>17</sup> Crumbs,<sup>18</sup> Mahjong,<sup>17</sup>) modulation of Wingless/Wnt<sup>19</sup> or JAK/STAT.<sup>20</sup> Many of these pathways eventually lead to a change in the cell fitness markers encoded by the protein Flower (*fwe*)<sup>6</sup> and its downstream target Azot.<sup>2</sup> We found that loser and winner cells actively mix through cell-cell intercalation,<sup>3</sup> which increases the probability to eliminate loser cells. However, the modulation of cell mechanics and clone shape during Myc competition is independent of *fwe*. Therefore, competition induced mixing may not be a general process. Accordingly, very different clone shapes have been reported for the different pathways involved in competition, including compact clones (involving cell sorting mechanism), clones with a WT shape, and clones with abnormal high levels of mixing (Fig. 2). How can we reconcile such diversity of shape with a contact dependent induction of death? First, despite the absence of active cell mixing, a significant proportion of loser cells will still share more than 40-50% of contact with winners and be eliminated. Secondly, the levels of induction of Flower and Azot can vary in different competition scenario and might be strong enough to induce elimination despite the low mixing. More specifically, their induction might be strong and fast enough to eliminate isolated cells before they divide and form large clones, similar to the fast elimination of cells overexpressing Brinker (an inhibitor of Dpp)<sup>5,6</sup> in the wing pouch. Finally, some elimination might be totally independent of Flower selection process. For instance, we did not observe induction of Flower in vicinity of clone overexpressing an active form of Ras.<sup>24</sup> An alternative mode of elimination could be based on mechanical stress. It was previously suggested that differential growth could generate mechanical stress in the tissue<sup>1,21</sup> (both within and outside the fast growing clone) which could participate in loser cell elimination. Loading of mechanical stress is only effective in epithelial tissue with low rate of junction remodelling (hence behaving more like a solid) which would otherwise release the stress. While this is very unlikely to apply to Myc and Minute dependent competition (where the rate of junction remodelling is abnormally high), this is compatible with other types of competition, including the Hippo/Yki and Ras dependent competition which form very compact clones.<sup>22,23</sup> A better assessment of cell shape inside and outside the clone in combination with live imaging of junction dynamics should provide key information regarding the local deformation of the tissue and the process of elimination of loser cells. In the near future, the knowledge accumulated in the field of morphogenesis will provide exciting and new prospective for

the understanding of cell competition, supercompetition and its contribution to tumor expansion.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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