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**In preprints:**

## **Get to know your neighbours: cell interface surveillance through a molecular zip code**

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One of the central questions of developmental biology has been how tissues define patterns with fixed boundaries, as exemplified by the classical French flag model from Lewis Wolpert. A second, related question is how do tissues maintain boundaries and prevent cells from deviating from the pattern? These mechanisms have important implications not only for the development of organisms but also for the emergence of cancer. Tissues should be able to recognize cells with aberrant expression programs and eliminate them and tumorigenesis prevails if surveillance mechanisms are not working efficiently. For decades, how tissues identify cells that deviate from the pattern has been a fascinating question. Many studies have focused on cell competition, a process in which defective cells are outcompeted by their more robust neighbours, but what happens when cells are “fit” and acquire an aberrant fate? Recent works propose that interface surveillance would be responsible for their elimination.

Interface surveillance was described in the *Drosophila* wing disc, an epithelial sac of cells that has well-defined anterior-posterior (A/P) and dorsal-ventral (D/V) axes by the end of larval development, which determines cell fate according to cell position. Inducing the formation of somatic clones with a different cell fate than the surrounding wild-type cells leads to the formation of an actomyosin ring, which forms a boundary surrounding the aberrant cells and causes their eventual extrusion from the epithelium (Bielmeier et al., 2016). In parallel, the JNK signalling pathway is activated on both sides of the actomyosin boundary to induce apoptosis and eliminate unwanted cells (Prasad et al., 2023). This mechanism explains how aberrant cells are eliminated, but how cells sense the presence of aberrant neighbours has, so far, remained unanswered.

In this preprint, Fischer and collaborators identify key signalling receptors that reproduce interface surveillance in the developing wing disc when differentially expressed (Fischer et al., 2023). The authors thus propose that surveillance mechanisms involve surface molecules that detect changes in neighbouring cells and that these molecules regulate the actomyosin cytoskeleton and activate the JNK signalling pathway. Under these assumptions, they screen for the distribution along the surface of the wing disc of receptors typically involved in axon guidance: Roundabout (Robo), Plexin, Frazzled (Neogenin in mammals), Ephrin and Leucine-rich repeat-domain receptors, all of which are increasingly gaining attention for their roles in epithelial biology. When investigating these molecules, the authors found very specific

expression patterns across the wing disc, with different receptors expressed in different parts of the disc. Altogether, these receptors form a complex spatial code that provides positional information beyond the disc's classical A/P and D/V axes, a sort of receptor coordinate system or 'zip code'.

When the receptor code is altered and patches of cells no longer match the pattern of their neighbours, the result is the formation of an actomyosin boundary surrounding the mismatched cells and bilateral activation of JNK signalling. A peculiarity of the code is that it is more sensitive to gross changes in expression. For instance, Robo3 is normally expressed at low levels in most regions of the wing disc, and over-expressing Robo3 results in a stronger surveillance response than silencing Robo3 expression. Similarly, Robo2 (which has a more complex expression pattern) elicits a stronger response when over-expressed in those regions where Robo2 is normally absent, compared to regions of high Robo2 expression. The preprint also shows that the expression of these surface molecules is controlled by the patterning systems of the wing disc, as would be expected from a spatial identity code.

Importantly, the authors show that over-expression of the oncogenic protein, Ras, also activates the interface surveillance response, as has been previously shown. However, the traditional explanation for this response would be to eliminate over-competing cells whereas, in this case, cells that activate the Ras pathway proliferate and suppress apoptosis. The authors show that Ras induces changes in the expression of the surface coordinate system, which is sufficient to activate the interface surveillance response. This suggests that surveillance response is a *bona fide* error-sensing pathway independent of cell competition surveillance. In accordance with this hypothesis, the authors show that expressing markers denoting 'winner' or 'loser' cells in cell competition does not affect the expression of the molecules of the surface coordinate system, supporting the existence of the two independent pathways.

This work opens a novel layer of regulation to study the mechanisms of quality control during tissue patterning and how developmental checkpoints are established to ensure proper morphogenesis. While the molecules that encompass the surface code belong to diverse protein families, they have all been implicated in axon guidance-type responses, such as actomyosin regulation, and some have been previously linked to JNK signalling activation.

Intriguingly, there is growing evidence in epithelia that the same molecules can also elicit morphogenetic processes, such as the formation of sharp tissue boundaries or cell rearrangements (Iijima et al., 2020; Paré et al., 2014). It, therefore, becomes essential to understand how cells respond to the activity of those molecules and switch between morphogenesis and developmental homeostasis. Exploration of data from single-cell analysis with spatial transcriptome data from different tissues should really help to determine whether fate maps can be translated in a similar code of such molecules and whether it defines a cellular basis for cell movements and/or cell death (Everetts et al., 2021; Karaikos et al., 2017).

## Footnotes

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