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Phyllopod at the intersection of developmental signalling pathways

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One of the striking findings in developmental genetics over the past two decades is the realization that a very small number of conserved signalling pathways directs most, if not all, aspects of development of multicellular organisms, by transmitting extracellular signals to the cell nucleus, to modify gene expression programs. How can such a small number of distinct pathways regulate an amazingly diverse array of developmental switches? The secret seems to lie in the capacity of the pathways to interact with each other and generate a varied array of outputs. Exemplifying this is a study by Nagaraj and Banerjee in this issue of *The EMBO Journal*, describing a novel function of the EGFR signalling target Phyllopod in the regulation of Notch and Wingless signalling in the *Drosophila* eye.

Generation of complexity during development relies on sequential decisions cells make, to refine the coarse initial asymmetries and create an ever-increasing complexity. The capacity of one pathway to trigger or repress the next one provides the basis for refinement of patterns. These interactions may take shape as simple on/off switches, or as a more complicated circuitry using, for example, a 'feed forward' logic that assures that the next programme will be turned on only upon sustained activation. This principle was showed for the induction of primary pigment cell fate by the combined activity of EGFR and Notch pathways (Nagaraj and Banerjee, 2007).

Another strategy to combine the outputs from different pathways, which seems to be the most prevalent one, is to carry out the integration at the promoter level of each target gene. This strategy provides an enormous flexibility, as it allows to incorporate distinct design principles into each promoter, such that the pathways can be antagonistic or synergistic in the context of different promoters. In addition, the integration of tissue-specific elements into the target-gene promoters provides the tissue context and cell 'history', such that the same pathway(s) can trigger distinct genes in different tissues (Flores *et al*, 2000; Halfon *et al*, 2000; Xu *et al*, 2000). As these intersections take place at the final output step, they do not involve cross modulation of the 'hardware' of each pathway, which executes transduction of the signal from the extracellular milieu to the nucleus.

There are also global interactions between pathways, such that activation of one pathway facilitates or attenuates the response of a battery of target genes of another pathway, in a coordinated manner. These interactions necessitate an effect of one pathway on an integral signalling component of the other, leading to a global effect on all target genes. Only few instances for this type of modulation have been reported. For example, RTK signalling, leading to MAPK phosphorylation of Groucho, attenuates the activity of Groucho as a transcriptional repressor, and affects its global activity in the context of the Notch pathway (Hasson *et al*, 2005). Similarly, MAPK and Wnt-regulated GSK3 phosphorylation of Smad proteins was reported to attenuate the overall response of cells to BMP ligands (Fuentealba *et al*, 2007). The article by Nagaraj and Banerjee provides another example for the global effect of EGFR signalling on both Notch and Wingless (Wg) pathways (Nagaraj and Banerjee, 2009).

This article identifies a specific negative regulatory mechanism for the Notch and Wg pathways, which functions at the level of endocytic vesicles. The adaptor protein Phyllopod (Phyl) allows a balanced level of activated components of Notch and Wg pathways to be made available. The phenotypic consequences of the loss of Phyl function in the developing eye include the loss of R1, R6 and R7 photoreceptor cells, over-specification of the non-neuronal cone and pigment cells and a loss in the specification of bristle complex (Chang *et al*, 1995; Dickson *et al*, 1995). The article shows that Phyl reduces the levels of Delta, Notch and Wg within endocytic vesicles and facilitates their targeting for degradation (Figure 1).

As trafficking through endocytic vesicles is normally required for maturation of these proteins, the block at the early endosome stage in the absence of Phyl leads to increased Notch and Wg signalling. Phyl function is required to remove signalling components from the endocytic vesicles after a round of signalling, but not directly from the plasma membrane before signalling, thus regulating the residence time of the components of Notch and Wg signalling pathways

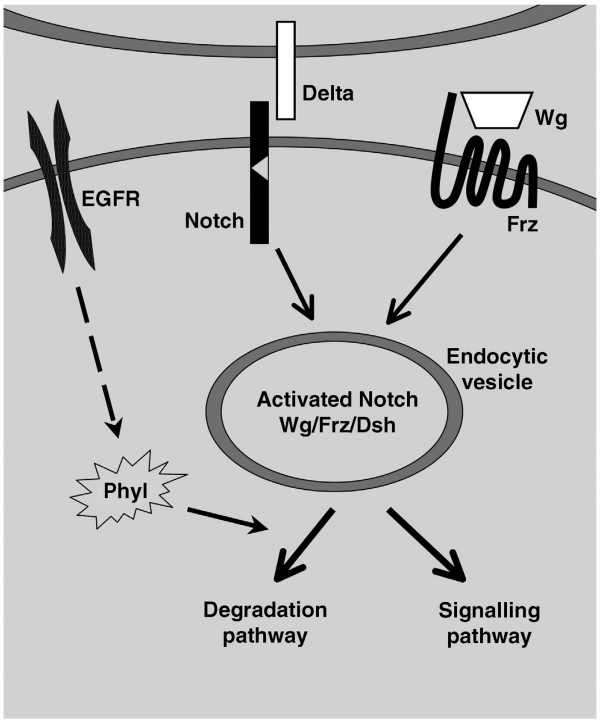

Figure 1 Schematic representation of the function of Phyl in regulating Notch and Wingless signal transduction (adapted from Nagaraj and Banerjee, 2009). See text for details.

in early endocytic vesicles. As *phyl* is a transcriptional target of EGFR signalling in the eye, these observations suggest a negative cross talk between RTK and Notch/Wg pathways. Post-transcriptional downregulation of Notch and Wg signalling by Phyl allows fine-tuning of the signal and creates a delicate balance between active signalling of Notch/Wg pathways and their degradation by the lysosomal pathway.

Hard-wired interconnections between signalling pathways, such as those described in the article by Nagaraj and Banerjee, may potentially compromise combinatorial complexity and regulatory flexibility. In this case, however, the connection is initiated by EGFR-induced transcription of *phyl* and can therefore be restricted to specific tissue settings requiring this particular global interaction between the EGFR and Notch/Wg pathways.

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