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 intersections 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 intersections 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.](image-url)
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.

References

Chang HC, Solomon NM, Wassarman DA, Karim FD, Therrien M, Rubin GM, Wolff T (1995) phyllopod functions in the fate determination of a subset of photoreceptors in Drosophila. Cell 80: 463–472

Dickson BJ, Dominguez M, van der Straten A, Hafen E (1995) Control of Drosophila photoreceptor cell fates by phyllopod, a novel nuclear protein acting downstream of the Raf kinase. Cell 80: 453–462

Flores GV, Duan H, Yan H, Nagaraj R, Fu W, Zou Y, Noll M, Banerjee U (2000) Combinatorial signaling in the specification of unique cell fates. Cell 103: 75–85

Fuentesalba LC, Eivers E, Ikeda A, Hurtado C, Kuroda H, Pera EM, De Robertis EM (2007) Integrating patterning signals: Wnt/GSK3 regulates the duration of the BMP/Smad1 signal. Cell 131: 980–993

Halfon MS, Carmena A, Gisselbrecht C, Sackerson CM, Jimenez F, Baylies MK, Michelson AM (2000) Ras pathway specificity is determined by the integration of multiple signal-activated and tissue-restricted transcription factors. Cell 103: 63–74

Hasson P, Egoz N, Winkler C, Volohonsky G, Jia S, Dinur T, Volk T, Courey AJ, Paroush Z (2005) EGFR signaling attenuates Groucho-dependent repression to antagonize Notch transcriptional output. Nat Genet 37: 101–105

Nagaraj R, Banerjee U (2007) Combinatorial signaling in the specification of primary pigment cells in the Drosophila eye. Development 134: 825–831

Nagaraj R, Banerjee U (2009) Regulation of Notch and Wingless signaling by Phyllopod, a transcriptional target of the EGFR pathway. EMBO J 28: 337–346

Xu C, Kaufmann RC, Zhang J, Kladny S, Carthew RW (2000) Overlapping activators and repressors delimit transcriptional response to receptor tyrosine kinase signals in the Drosophila eye. Cell 103: 87–97