Invited Perspectives

Recent identification of an ERK signal gradient governing planarian regeneration

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ABSTRACT

Planarians have strong regenerative abilities derived from their adult pluripotent stem cell (neoblast) system. However, the molecular mechanisms involved in planarian regeneration have long remained a mystery. In particular, no anterior-specifying factor(s) could be found, although Wnt family proteins had been successfully identified as posterior-specifying factors during planarian regeneration (Gurley et al., 2008; Petersen and Reddien, 2008). A recent textbook of developmental biology therefore proposes a Wnt antagonist as a putative anterior factor (Gilbert, 2013). That is, planarian regeneration was supposed to be explained by a single decreasing gradient of the β-catenin signal from tail to head. However, recently we succeeded in demonstrating that in fact the extracellular-signal regulated kinases (ERK) form a decreasing gradient from head to tail to direct the reorganization of planarian body regionality after amputation (Umesono et al., 2013).

The beginning of our quest to find such an anterior-specifying factor started from our comprehensive screening of Dugesia japonica for anterior-blastema-specific genes. However, we could not identify any such genes. Instead, our screening revealed genes that showed extensive activation in both the anterior and posterior blastema within 12–24 h after amputation (Tasaki et al., 2011a). One of them was the mkp (MAP kinase phosphatase) gene. It is known that its expression is activated by active MAP kinase to form a feedback loop, suggesting that MAP kinase may be activated during a very early stage of regeneration, just before the formation of either an anterior and/or a posterior blastema. We next succeeded in demonstrating that signaling by ERK, one of the MAP kinases, is required not only for blastema formation but also for the transition of neoblasts from the stem cell state to the differentiating state (Tasaki et al., 2011a,b).

Next we focused on possible additional function(s) of MAP kinase, since the ERK signal was suppressed in the posterior blastema, but enhanced in the anterior blastema, from 48 h to 72 h after amputation (Fig. 1). We therefore investigated how the ERK signal is suppressed at the posterior end, and found that the β-catenin signal has the ability to suppress the ERK signal at the posterior end. β-catenin-RNAi planarians maintained the ERK activity in their posterior blastema, resulting in ectopic head formation from the posterior blastema (Gurley et al., 2008; Petersen and Reddien, 2008; Hayashi et al., 2011). Interestingly, β-catenin-RNAi planarians also showed up-regulation of the ERK signal in the anterior blastema, suggesting that β-catenin has the ability to suppress the ERK signal in general (Umesono et al., 2013). That is, the β-catenin signal may contribute to forming the decreasing ERK signal gradient from head to tail by forming a decreasing gradient in the opposite direction. This point is the most important finding of our research. Based on these findings, we proposed a default model as follows: the neoblasts can enter into the differentiating state after activation of the ERK signal and then start to differentiate into brain neurons as a default fate, but the β-catenin signal modulates their fate by suppressing the ERK signal (Umesono et al., 2013). This is one reason why no anterior gradient molecule(s) could be identified for a long time, although many researchers tried to do so.

The next question we addressed was how β-catenin is activated only in the posterior part of the body. Incidentally, we had already obtained the answer to this question (Yazawa et al., 2009). That is, we detected constitutive and ubiquitous expression throughout the body of the Hedgehog (Hh) receptor gene, patched (ptc), which is known to suppress wnt gene expression. Thus, wnt expression is normally suppressed in all regions of the planarian body through a ptc-mediated signal. When Hh binds to ptc, this suppression is reversed and the expression of wnt is activated. Interestingly, we found that the hh gene is transcribed in the central nervous system in planarians. Thus, if Hh-containing vesicles are normally transported from the (−) to the (+) ends of tubulin along the microtubules.

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in the axons, Hh might be released at the posterior end of the axons when the body is transected, and then Hh would bind to ptc to activate wnt expression at the posterior end of the fragments after amputation. We speculate that this is the mechanism of the asymmetric activation of wnt genes in the posterior blastema.

As a next step, we are interested in the extent to which a similar system is used in other animals. When we inhibit planarian ERK signaling by inhibitor treatment or RNAi, the neoblasts cannot differentiate into any type of cells, even though they maintain their proliferative ability. Consequently, inhibitor–treated planarians cannot form a blastema, and thus lose regenerative ability (Tasaki et al., 2011a). Interestingly, this property can also be observed in mouse embryonic stem (ES) cells. That is, mouse ES cells treated with ERK inhibitors cannot differentiate into any type of cell and can be maintained in a pluripotent state when simultaneously treated with a GSK3 inhibitor (the so-called “2i condition”) (Ying et al., 2008). Now it has become popular to culture ES cells under the “2i condition” in order to prepare a homogeneous population of pluripotent-state cells. Therefore, it is possible to speculate that ERK signaling might have an important, conserved role in exiting from the pluripotent state of cells in various animals (Nakanoh et al., 2013). ERK inhibitor–treated hydra also show regeneration arrest (Manuel et al., 2006). However, the reason for this regeneration defect is not so clear. Hydra has three distinct stem cell lineages, but we do not know whether all three lineages are affected by ERK inhibition. Further research on the function of ERK signaling in hydra regeneration will be necessary in order to clarify the generality of the role of ERK signaling in multicellular organisms.

References


