Planarians SET New Paths for Innate Immune Memory

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The importance of trained immunity for vertebrate host defense is evidenced by broad non-specific protection conferred by certain vaccines (Kleijnjenhuis et al., 2012), while it may play a maladaptive role in chronic inflammatory diseases such as atherosclerosis (Bekkering et al., 2014). The training effect manifests as a significantly heightened sensitivity to a secondary encounter with a pathogen or microbial product, characterized by enhanced secretion of pro-inflammatory mediators specifically by cells of the innate immune system. Most

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Bacillus Calmette–Guérin (BCG) far exceeds the lifespan of innate immune cells in the circulation (Kleinnijenhuis et al., 2012). The capacity to induce innate immune memory in pluripotent neoblasts in planarians advocates the possibility that innate immune cell precursors in vertebrates can also mount epigenetic and functional reprogramming and thus mediate innate immune memory. Indeed, myeloid cell progenitors have been demonstrated to mediate long-term TLR2-induced tolerance (Yanez et al., 2013), and a similar role may be expected for trained immunity.

An important observation is also that Smed-setd8–1 in planarians is homologous to human SET8 (also known as KMT3A), indicating potential for a similar regulatory function in vertebrates. Studies exploring epigenetic changes associated with innate immune memory have focused predominantly on post-translational modifications of H3 histones. Torre et al. now provide the impetus to expand this search to the tails of H4 histones, which are methylated only at lysine 20. Methylation of H4 histones has previously been associated with transcriptional memory in diabetic rodents (Zhong and Kowluru, 2011), although the precise regulatory function of this modification remains controversial (Milite et al. 2016). Importantly the addition of a single methyl group to H4 histones is associated with transcriptional activation (Barski et al., 2007), and SET8 is the only enzyme known to write this modification (Milite et al., 2016).

To conclude, the elegant study by Torre et al. describes a system of acquired resistance in planarians that shares several important features with trained immunity in vertebrates. Infection with S. aureus initiates a program of heightened defense against the same pathogen. It remains to be seen how closely this system mirrors the broad non-specific memory of trained immunity. Nevertheless, the central role of neoblasts and Smed-setd8–1 informs about potential new research paths in the search for epigenetic regulators of innate immune memory in vertebrates. Identification of these key factors will greatly accelerate the realization of novel therapeutic approaches to the treatment of infectious and auto-inflammatory diseases, as well as the improvement of vaccination programs (Netea et al., 2016).

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**References**


**Disclosure**

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