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Commentary

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 (Kleinnijenhuis 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

☆ The ability for vertebrates to mount immunological memory has classically been regarded as the exclusive realm of the adaptive immune system. The innate immune system on the other hand has long been thought to lack the capacity to adapt after an encounter with a pathogen or vaccine. However, an increasing body of evidence challenges this distinction, defining the process of innate immune memory (also termed *trained immunity*) as a heightened responsiveness to a secondary infection owing to functional and epigenetic reprogramming of cells of the innate immune system (Netea et al., 2016). Many organisms that do not possess an adaptive immune system also exhibit enhanced innate resistance to reinfection (Milutinovic and Kurtz, 2016). Thus, the evolutionary conservation of innate immune memory across various phyla provides important opportunities to understand this biological process in humans. The novel findings presented in this issue of *EBioMedicine* by Torre et al. (Torre et al., 2017) describe the existence of similar mechanisms of trained immunity in planarians (phylum Platyhelminthes) and reveals novel insights regarding the epigenetic processes mediating gene expression changes essential for the trained phenotype.

☆☆ Blockade of planarian immune memory by pre-treatment with a pan-methylation inhibitor parallels similar findings in humans (Netea et al., 2016) and further underscores the importance of lysine methylation for trained immunity. This is supported by observations of *Smed-setd8-1*-dependent global increases in lysine methylation upon stimulation with *S. aureus*. However, without a direct measurement of chromatin methylation it is difficult to define how this methyl enrichment is distributed across different protein substrates and gene regulating functions. Enzymes that methylate histones also methylate lysines on various other proteins such as transcription factors, often influencing their stability and/or function (Keating et al., 2014). Indeed human SET8 regulates gene expression by methylation of lysines on both histones and transcription factors (Milite et al., 2016). Furthermore, methyltransferase enzymes can methylate each other. Therefore, the possibility that *Smed-setd8-1* methylates and thereby regulates other enzymes that in turn maintain lysine methylation should be considered in future studies.

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studies in the field of trained immunity have accordingly focused on differentiated innate immune cells such as monocytes, macrophages or natural killer cells. Importantly, these studies have revealed extensive reprogramming of the epigenome as the basis for innate immune memory (Novakovic et al., 2016). Epigenetic changes act at the level of chromatin: the dynamic complex of DNA and histone proteins that spatially determines the transcriptional competency of a gene by regulating its accessibility to the transcriptional machinery of the cell. Posttranslational chemical modification of chromatin components such as histone N-terminal tails distinguishes and instructs the assembly of open and closed chromatin structures, thereby influencing gene expression. The transfer of methyl groups (methylation) to lysine residues of specific histones by the SET domain of methyltransferase enzymes has emerged as an important factor enhancing the expression of antimicrobial genes by innate immune cells (Netea et al., 2016). Recent studies linking metabolic changes in trained cells with epigenetic reprogramming implicate particular classes of histone modifying enzymes as proponents of innate immune memory (Arts et al., 2016). However, the identities of the specific enzymes responsible for the myriad epigenetic changes remain elusive.

Torre and colleagues used a planarian experimental infection with *Staphylococcus aureus* as a model to study the properties of innate immune memory, with relevance for vertebrate immunity as well. In this model, infection of planarians with *S. aureus* changes innate immune responses in an adaptive manner, resulting in an improved rate of pathogen clearance upon subsequent reinfection. Indeed planarians are renowned for their capacity to fight infection and remarkable regenerative abilities. In the pursuit of a mechanistic link between these processes, Torre et al. identified two important novel mechanisms central to the induction of trained immunity (or *instructed immunity*, as defined by the authors). First, the authors demonstrate the importance of a specific population of pluripotent stem cells called neoblasts for innate immune memory. Second, through a series of experiments using RNA interference, the researchers revealed that genes important for innate immunity confer sustained resistance to *S. aureus* via a signaling cascade that is contingent on the *Smed-setd8-1* lysine methyltransferase.

These observations are significant for understanding responses during infection and vaccination in humans. One important aspect for which the study of Torre and colleagues is significant is for providing important clues on the physiological mechanisms mediating trained immunity in humans at the level of immune progenitor cells. The long-term protection conferred by vaccination with

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 KMT5A), 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).

Disclosure

The authors declare no conflicts of interest.

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