https://doi.org/10.1038/s41590-023-01595-x

Innate immune memory, trained immunity and nomenclature clarification

Trained innate immunity (TRIM) is a newly emerging field of study that is of focal importance in immunology. Defined as an enhanced immune responsiveness of innate immune cells to a future challenge owing to memory of a prior encounter, TRIM existed as a latent, yet ignored, concept even before it was coined as such and systematized as a new field[1,2]. Epidemiological studies indicating antigen-agnostic protective effects of certain vaccines unrelated to their target disease, experimental animal studies showing lymphocyte-independent enhanced resistance to secondary infection, and evidence of memory-based broad protection against reinfection in invertebrates and plants (reviewed in refs. 1,3) were largely overlooked in the face of the concept that immunological memory was the exclusive prerogative of adaptive immunity. Given the importance of immune memory for host defense and survival, it is now thought that trained innate immunity evolved first, as an epigenetically based memory devoid of specificity, before antigen-specific immunological memory developed in jawed vertebrates, leading later to the acquisition of recombination-activating genes and hence the ability to generate a diverse repertoire of antigen-specific receptors[4].

Precise immunological nomenclature has always been a formidable challenge, given the complexity and plasticity of the immune response[5], and this is particularly true for a newly emerged area of immunological research. Despite earlier efforts to clarify key terms in the field[2], it may still be unclear whether TRIM is different from persistent innate immune activation or even from innate immune memory. The latter is so intimately related to TRIM that the two terms are often used interchangeably, especially given that TRIM represents a functional consequence of de facto innate immune memory. Although this is acceptable, for precision where this is warranted, we think that both terms are necessary in the immunological literature.

Whereas the term 'innate immune memory' describes the epigenetically imprinted and recallable memory of inflammation, 'trained innate immunity' refers to the prepared and improved innate immune response that occurs, as a result of the imprinted memory, upon restimulation (Fig. 1). The 'training' of a cell (akin to the training of an athlete) does not represent a permanent or fixed state of preparedness, as the underlying epigenetic adaptations are eventually reversible. This is in stark contrast to adaptive immune memory, which is based on permanent genetic changes in clonally expanded populations of memory lymphocytes. Using again the analogy with athletic training, trained athletes, like trained cells, cannot maintain their prepared state of enhanced performance forever without further training. In other words, innate immune memory is the founding biological principle upon which lies the induction of TRIM.

With respect to distinguishing TRIM from 'prolonged cellular activation', we maintain that these terms refer to completely different processes. By definition, TRIM is a state of enhanced immune preparedness during which immune activation (that which induced TRIM in the first place) has returned to the basal level and hence does not persist in the absence of an infection or a secondary stimulus. This is not simply an abstract definition but

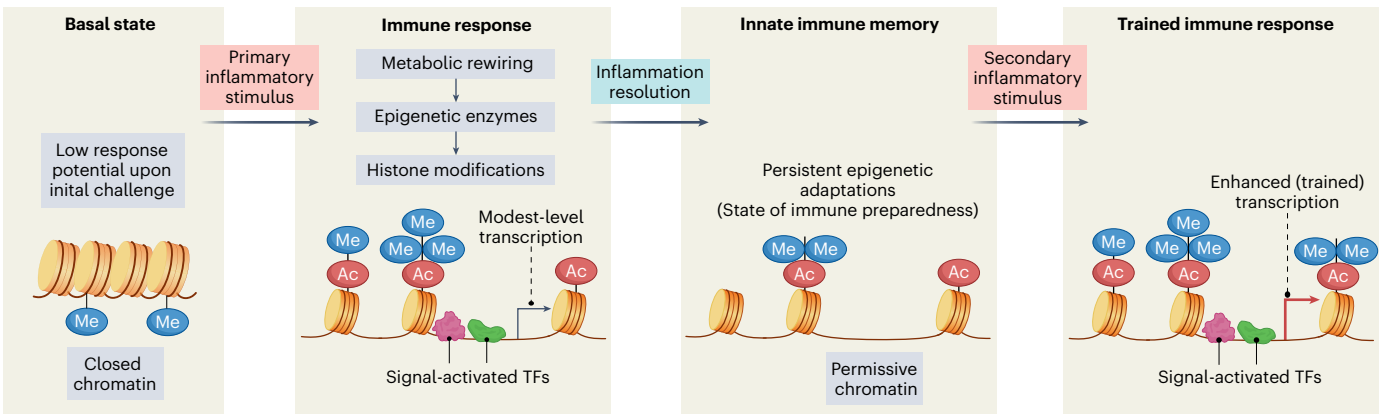

Fig. 1 | Induction of innate immune memory that leads to trained immune response after restimulation. Exposure to inflammatory stimuli (such as microbial molecules, including β-glucans, or cytokines, such as interleukin-1β) can induce innate immune memory (in bone-marrow-derived hematopoietic stem and progenitor cells or in mature innate immune cells). A naive, unstimulated cell (far left) displays highly condensed chromatin. However, its stimulation leads to the deposition of chromatin marks (such as histone acetylation (Ac) or methylation (Me)) that promote chromatin unfolding and facilitate gene transcription (middle left). These epigenetic changes may persist or may be only partially removed even after the resolution of inflammation (that is, after cessation of the stimulus) (middle right) and may thus generate durable and recallable innate immune memory. This state of immune preparedness – which is based on accessible (permissive) but transcriptionally inactive chromatin – enables faster recruitment of transcription factors (TFs) and enhanced transcription of target genes after secondary challenge with the same or different stimuli (far right).

is supported by experimental data. When the inducing stimulus subsides, the system is essentially indistinguishable from the basal state in terms of transcriptional and functional phenotype[6–8]. The differentiating principle is that the epigenetic adaptations are maintained in the immune preparedness ('trained') state (Fig. 1). Trained hematopoietic stem and progenitor cells retain persistent changes in the accessibility of specific factors that drive myeloid lineage development and inflammation and thereby augment the responsiveness of the respective immune genes to secondary stimulation[6]. A study has shown that transplantation of bone marrow from 'trained' animals (in which inflammation and enhanced myelopoiesis have returned to baseline) transfers the trained phenotype to naive recipients, which are therefore endowed with increased immune responsiveness to future challenges[7]. In the same study, the epigenetically imprinted myeloid bias in hematopoietic stem and progenitor cells was transplantable to naive recipient mice and resulted in a decreased proportion of lymphocytes and increased proportion of myeloid cells with enhanced inflammatory responsiveness[7].

The TRIM field is no longer in its infancy, but it is still evolving, with the need to address key questions. For instance, the epigenetic mechanisms underlying the TRIM phenotype — especially when transmitted transgenerationally — remain incompletely understood. Moreover, the exact role of further mechanisms (such as metabolic rewiring) in inducing TRIM should be pursued, as should the quest to develop TRIM-based modulation therapies (aiming to enhance resistance to infections and tumors while mitigating inflammatory and autoimmune diseases). In this endeavor, a nomenclature with precise and differentiative terms would be a valuable communication tool conducive to further progress.

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Published online: 24 August 2023

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Competing interests

M.G.N. is a scientific founder of Lemba, TTxD and Biotrip. The other authors declare no competing interests.