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RESEARCH HIGHLIGHT

Trained through generations

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Cellular & Molecular Immunology (2022) 19:653–654; https://doi.org/10.1038/s41423-022-00846-5

The first scientists to coin the term "trained immunity" were Mihai G. Netea, Jessica Quintin, and Jos W.M. van der Meer in a 'Perspective' article in 2011 [2]. With the publication of vast amounts of experimental data and follow-up reviews, the concept that the innate immune system can develop a memory function in parallel to the well-recognized adaptive memory, mediated by B and T lymphocytes, is largely accepted. The cells that are responsible for trained immunity are mainly myeloid cells (monocytes, macrophages) and innate lymphoid cells (ILCs), such as natural killer (NK) cells and helper ILCs [3]. Studies of trained immunity frequently focus on infections, revealing increased protection against the same or a different pathogen after the first encounter with a microbe.

Among the infectious agents investigated in this context, Bacillus Calmette Guerin (BCG), an attenuated *Mycobacterium bovis* strain used in many countries as a protection against tuberculosis caused by *Mycobacterium tuberculosis*, is predominant. This vaccination can indeed induce some cross-protection against other bacteria (nontuberculous mycobacteria, various agents of lower respiratory tract infections), fungi (*Candida albicans*), and viruses (among them the influenza A virus and possibly to some extent the agent of COVID-19, SARS-CoV-2) [4].

Regarding the mechanisms underlying trained immunity, epigenetic and transcriptional changes as well as metabolic reprogramming are considered the main factors and have been abundantly documented [4, 5].

Not only infections but also psychological stress, such as early life adversity (ELA), may impact innate immune cells. Thus, when a human cohort of young adults who were institutionalized after birth and subsequently adopted were compared with controls raised by their natural parents in Luxembourg, significant phenotypic (accelerated maturation) and functional (reduced degranulation capacity) alterations in NK cells from the former were observed [6]. Likewise, when rat pups were separated from their mother during the early postnatal phase for 180 min daily and exposed to restraint stress in adulthood, their NK cells became phenotypically more mature than their control, non-ELA-exposed counterparts, and they were found to be functionally severely deficient in cytotoxic activity against the YAC-1 tumor cell line [6].

All the examples of trained immunity mentioned above take place within a single organism and can better protect this organism against pathogens or other forms of stress encountered at a later stage.

In contrast, Katzmarski et al. [1] investigated the trained immunity phenomenon across generations in vertebrates, namely, in C57BL/6 mice. The authors first sublethally infected male mice with *C. albicans* and bred them one month later with healthy females. The control group consisted of noninfected (PBS-treated) males and similarly naïve females. As systemic nonlethal candidiasis is known to lead to resistance to subsequent bacterial infection (through epigenetic mechanisms) [7], it was tempting to check whether this would hold true in the offspring of these mice, called the F1 exposed generation. Exposed and control F1 animals were then systemically infected with the Gram-negative bacterium *Escherichia coli*. Very interestingly, the exposed group quickly showed a lower bacterial burden in different target organs, accompanied by stronger immune cell infiltration and increased cytokine production (intergenerational protection; Fig. 1).

To go a step further and analyze whether the transmission of the resistance would be transgenerational, that is, affect the F2 offspring of F1 mice themselves not exposed to fungal or bacterial infections, the authors mated F1 exposed and F1 control males with control females and repeated the same for the F2 exposed and F2 control generations (giving rise to F3 offspring). Whereas the reduced burden of *E. coli* was still observed in F2 exposed mice, the effect had disappeared in F3 offspring (Fig. 1). For Katzmarski et al., these data underline the concept of "a nongenetic transgenerational transmission of trained immunity from F1 to F2 mice" [1].

Furthermore, they confirmed their results in a second experimental model generated in a different animal facility, where F0 mice were intraperitoneally injected with zymosan from *Saccharomyces cerevisiae*, and then the F1 exposed or F1 control offspring were challenged with the Gram-positive pathogen *Listeria monocytogenes*. Again, the F1 exposed mice resisted the infection much better (better survival, lower pathogen burden, reduced weight loss) [1].

More mechanistically, as trained immunity has previously been related to changes in the bone marrow myeloid compartment [7], it was established that in the transgenerational model of resistance to infection, this niche was modified toward less 'patrolling' monocytes and a higher activation level of common monocyte progenitors [1]. Genomic regions located close to those involved in myeloid cell development and activation were more accessible in the F1 exposed group than in the F1 control group. Gene set enrichment analysis revealed a bias toward the differentiation and activation of the monocyte lineage [1].

Interestingly, another study, also published in *Nature Immunology* [8] and with a very similar overall experimental approach as in Katzmarski et al., concluded that there is no intergenerational transmission of immunity to *M. tuberculosis*, *C. albicans* and influenza virus after the priming of the immune system with BCG, *Candida albicans* and the pathogen-associated molecular pattern β-glucan.

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Received: 15 February 2022 Accepted: 19 February 2022
Published online: 11 March 2022

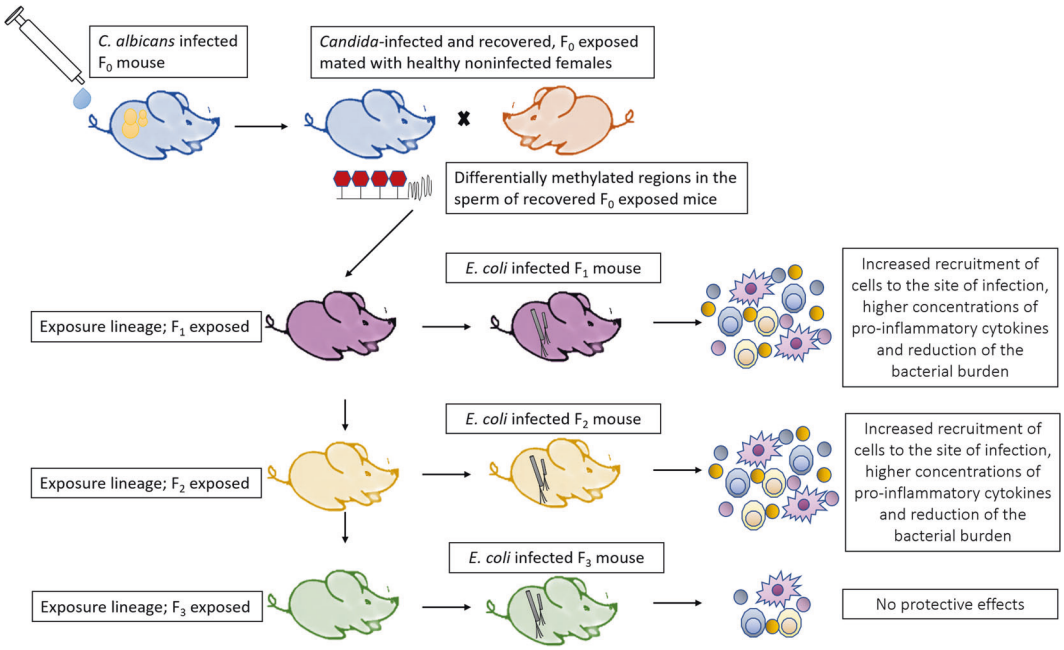

Fig. 1 Schematic representation of the inter- and transgenerational transmission of trained immunity.

In their reply, Katzmarski et al. highlight several papers strongly suggesting the existence of intergenerational transmission of trained immunity [9]. They speculate that, among other factors, the discrepant conclusions of the two independent studies could be caused by the respective housing, diet, and microbiome of the experimental animals.

Indeed, the composition of the mouse microbiome is significantly influenced by the characteristics of a given animal facility [10], which most likely can then seriously impact the results. This nicely completes the circle, as in our human ELA cohort, we were also able to demonstrate a triangular relationship among ELA, trained immunity, and long-term alterations in the microbiome [11]. Therefore, to further clarify the fascinating topic of transgenerational trained immunity to infectious diseases, which would clearly make sense from an evolutionary point of view and regarding mammalian adaptation to an environment rich in pathogens, better controlled experimental designs to account for microbiome variation need to be developed.

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COMPETING INTERESTS

MSD works as a consultant and an advisory board member at Theralution GmbH, Germany. The other authors declare no conflicts of interest.

ADDITIONAL INFORMATION

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