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Getting down and dirty: Germ-exposed lab mice as a model of the adult human immune system

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‘dirty’ mice would be a valuable addition to the toolbox of the transplant immunologist....

The power to track and delineate single elements of the immune system, including those involved in allograft rejection and tolerance, is largely derived from inbred laboratory mouse strains. This facile and flexible approach has effectively enabled the translation of laboratory findings into clinical application. However, many examples exist where therapies that work in mice fail to have similar efficacy in humans. This inconsistency has been attributed to evolutionary separations between mice and humans¹, reduced exposure of laboratory mice to microbial pathogens² and the biological consequences of inbreeding³. Recently, there has been a greater appreciation for the microbiota and for microbial exposure in regulating immune functions suggesting that laboratory mice living in abnormally hygienic barrier facilities may not reflect all relevant aspects of the adult human immune system.

Recent work published by Masopust and colleagues in *Nature* tested the impact of the microbial environment on the cellular composition of the immune system in inbred laboratory mouse strains⁴. Tissue distribution and phenotype of lymphoid cells in laboratory mice raised under specific pathogen free (SPF) conditions were compared to feral and pet store mice as well as human blood and tissue.

Antigen-experienced (memory) T cells were almost entirely comprised of the central memory subtype in laboratory mice and represented a minority of all T cells. Moreover, the analysis of blood and nonlymphoid tissue in laboratory mice revealed a lack of systemic and tissue-resident memory T cells and ten-fold lower serum immunoglobulin levels compared to adult humans. The lack of stimulation by specific pathogens and possibly commensals may impact naïve immunity in SPF mice resembling immune responses seen in human newborns rather than adults. In contrast, mice either captured in the wild or bought from a pet store reflected the adult human immune system consistently with the presence of differentiated effector and tissue-resident memory T cells in addition to clinically

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comparable amounts of innate immune cells and appropriate levels of serum antibodies. To assess if the observed differences were the result of “nature versus nurture”, Masopust and colleagues co-housed laboratory mice with pet store mice and observed that laboratory mice developed a mature immune system when co-housed for 4 weeks. Indeed, exposure to commensals and pathogens rendered co-housed mice more resistant to subsequent infections with *Listeria monocytogenes* or *Plasmodium berghei*, and generated an improved effector T cell response to lymphocytic choriomeningitis virus.

With evidence suggesting environmental alterations of phenotypic immune signatures, the authors then went on to analyze the immune transcriptome in detail and reported on significant overlaps between metagenes that were upregulated in pet store or co-housed mice compared with SPF laboratory mice. Comparable changes were observed in the transition of the human immune transcriptome from newborns to adults. Interestingly, these transcriptional differences included both adaptive and innate immune responses, suggesting that the innate immune system also ‘matures’ upon exposure to pathogens. This finding supports recent reports on innate immune memory⁵ highlighting that a complex immune system requires complex stimuli.

Overall, this study illustrates that inconsistencies between mice and human studies could be attributed to a lack of microbial diversity in laboratory mice raised under SPF conditions. Indeed, many of the events that influence the human microbiome are not necessarily reflected by the way of life of a laboratory mouse. Clearly, immunological triggers such as the ‘baptism’ in the complex microbial environment of the female reproductive tract immediately after birth, environmental exposure to commensals and pathogens, or dietary habits which influence the host microbiome are missing. In support of this complexity, it has been recently shown that gut microbiota derived short-chain fatty acids regulate amount and function of colonic regulatory T cells that protected against experimentally induced colitis in mice⁶.

The influence of microbial exposure and the microbiota itself on alloimmunity has attracted attention in the field of transplantation. Virus-specific memory T cells that are cross-reactive with allogeneic cells have recently been shown to impact allograft outcomes². Moreover, a significant influence of commensal bacteria on graft rejection has been demonstrated⁷. These findings highlight the importance of previous microbial exposure on transplantation outcome and implicate that the commensal flora is shaping alloimmunity. Many studies in bone marrow and solid organ transplantation, suggest that the lack of microbial diversity is linked to infections and graft-versus-host-disease after transplantation^{8,9}.

With this recent work by Masopust and co-workers, the microbial exposure and commensal bacteria story has been extended to influencing immune system maturation and its complexity. In order to better model allogeneic transplant outcomes in laboratory mice and to tease out the molecular mechanisms that contribute to rejection *versus* tolerance, ‘dirty’ mice would be a valuable addition to the toolbox of the transplant immunologist. After all, memory T cells, which are a major constituent of clinical alloreactivity¹⁰, are vastly underrepresented in laboratory mice housed under SPF conditions.

Starting to understand the complexities of immunology as an intricate network of various disciplines represents exciting challenges and opportunities. Indeed, a reductionist approach may not reflect relevant aspects of the human immune system. At the same time, we wish to point out that the results by Masopust and co-workers are not necessarily arguing against the use of SPF mice which remain an indispensable discovery tool in immunology. Instead, ‘dirty’ mice may serve as supplements to our current models investigating the immune system and testing promising immunomodulatory strategies.

Reintroducing ‘nature’ into laboratory mice will undoubtedly open up new questions and have us question old answers as complex pathologies will be met with complex and more ‘human-like’ models.

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