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Journal club

NEW BEGINNINGS

Back in 2002, during my struggling Ph.D. years, I was trying to map the potential immunogenicity of a dystrophin transgene to facilitate its use in gene therapy for Duchenne muscular dystrophy. While exploring the mechanisms that control immune-mediated rejection of transgenes, I became fascinated by dendritic cells (DCs) and their potential roles in transgene rejection. I remember vividly the day I stumbled across a paper by Merad *et al.* detailing a unique and striking feature of Langerhans cells (LCs), the supposedly 'bona fide' DCs of the epidermis.

In this study, the authors elegantly showed that, in contrast to other DCs, epidermal LCs renewed locally throughout life under steady-state conditions with minimal contribution from blood precursors. Using congenic bone marrow transplantation (BMT), they showed that LCs remained of host origin throughout life whereas most other leukocytes, including lymphoid organ DCs, were replaced by donor-derived haematopoietic precursor cells. This was a striking finding as two decades earlier Katz and Frelinger had shown that LCs were repopulated by haematopoietic precursors after allogeneic BMT. However, what they hadn't realized is that allogeneic BMT triggers inflammatory graft-versus-host skin lesions, inducing the death of tissue-resident LCs and promoting their replacement by bone marrow-derived cells. By contrast, congenic BMT does not induce skin inflammation, thus allowing for steady-state maintenance of LCs. Merad *et al.* consolidated their findings using parabiotic mice and unequivocally established that adult LCs renew locally, independently of circulating precursors. Their study completely revisited the existing LC paradigm and challenged the concept that LCs are bona fide DCs.

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This study inspired me to join the nascent Merad laboratory in 2004 to work on DC development and maintenance in tissues, which to me was the key to understanding tissue tolerance. Importantly, this study highlighted the uniqueness of the LC as a macrophage–DC hybrid that can be considered a macrophage 'by nature' and a DC 'by nurture'. Furthermore, it laid the ground conceptually and experimentally for revisiting the Van Furth mononuclear phagocyte system dogma, which proposed that all macrophages arise from circulating blood monocytes. Looking back, my life would have been different if I had missed this paper, hence my advice to young scientists to never miss a Journal Club and to read outside the box!

Florent Ginhoux
*Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), SINGAPORE 138648*
Florent_Ginhoux@immunol.a-star.edu.sg

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ORIGINAL RESEARCH PAPER Merad, M. *et al.* Langerhans cells renew in the skin throughout life under steady-state conditions. *Nat. Immunol.* **3**, 1135–1141 (2002)