CELL MIGRATION

Immunosurveillance by recirculating HSPCs

The functional significance of recirculating haematopoietic stem and progenitor cells (HSPCs) has been revealed. According to von Andrian and colleagues, it would appear that a pool of migratory HSPCs traffics from the bone marrow to survey non-lymphoid peripheral organs and provide an immediate means to boost the local supply of immune effector cells during infection.

Most adult HSPCs reside in specialized niches within the bone marrow; however, it has been known for some time that a population of these cells continuously recirculates between the bone marrow and blood. Despite speculations that this trafficking could be a mechanism to maintain equally full bone-marrow niches, the precise functional relevance of recirculating HSPCs had remained elusive until now.

The authors of the study surmised that, similar to tissue-resident lymphocytes, if HSPCs were to recirculate through non-lymphoid tissues they would also enter the lymphatic system to return to the blood. Indeed, lymph fluid collected from the thoracic duct contained a substantial number of bone-marrow-derived HSPCs that were capable of homing back to the bone marrow. Moreover, bone-marrow-derived HSPCs were found in many non-lymphoid tissues, including the lungs, the liver and the kidneys, at an estimate level of double the average number of HSPCs found in the blood. The average residency time of these HSPCs within non-lymphoid tissues was estimated to be at least 36 hours.

So, similar to lymphocytes, HSPCs continuously migrate to various non-lymphoid peripheral tissues. However, contrary to naive lymphocytes, which must first traffic through lymph nodes and Peyer's patches to reach lymph vessels, lymph-borne HSPCs do not accumulate in lymph nodes and can access lymph vessels in the absence of secondary lymphoid structures. This direct egress from non-lymphoid tissues to the draining lymph vessels was shown to be regulated by the sphingosine 1-phosphate receptor 1 ($S1P_1$), which is also responsible for controlling the egress of tissue-resident lymphocytes into lymphatics.

The study further showed that lymph-borne HSPCs had the same short-term and long-term multilineage reconstitution capacity as bone marrow-derived HSPCs, and could give rise to mature haematopoietic cells locally within non-lymphoid tissues. More importantly, tissue resident HSPCs, which express Toll-like receptors (TLRs) and their co-receptors, were capable of responding to TLR ligands such as lipopolysaccharide (LPS) by differentiating and proliferating into myeloid-cell lineages. Moreover, $S1P_1$ was downregulated in the presence of LPS, and LPS-treated HSPCs did not undergo chemotaxis down a gradient of S1P, suggesting that, in response to LPS recognition, HSPCs are retained in non-lymphoid tissues.

These findings indicate that recirculating HSPCs not only migrate from the bone marrow to the blood, but they also traffic to non-lymphoid tissues where they might detect situations such as tissue damage and infections and act as a rapid, versatile and local source to replenish tissue-resident immune cells.

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