Innate lymphoid cells (ILCs) represent a novel family of developmentally related hematopoietic effectors with central roles in innate immune responses to infections, lymphoid organogenesis, intestinal homeostasis, and wound healing. The prototypes of the ILC family are natural killer cells and lymphoid tissue–inducer cells. In 2010, 4 independent laboratories have identified previously unrecognized ILC populations that promote the development of CD4+ T-helper type 2 (Th2) cell–dependent immunity and inflammation at mucosal sites. These cell populations, now collectively termed group 2 ILC2, include natural helper (NH) cells, multipotent progenitor type 2 cells, and nuocytes or innate type 2 helper cells.\(^7\) They are retinoic-acid-receptor-related orphan receptor-γ-independent Lin−CD90+CD127+GATA3+ and require Id2, interleukin (IL)-7, retinoic-acid-receptor-related orphan receptor-α, and the common cytokine receptor γ chain. ILC2 cells are capable of producing Th2 cytokines, most notably IL-5 and IL-13 but not IL-4, in response to IL-25 and IL-33, 2 predominantly epithelial cell–derived cytokines whose increased expression at mucosal surfaces is associated with exposure to allergens or helminth parasites. Recent characterization of ILC2 cell biology has underscored their major role in asthma, allergies, and parasitic infections, but nothing was known about the role of ILC2 cells in atherosclerosis. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Perry et al provide the first insight into the possible role of NH cells in this disease. This group demonstrates for the first time that NH cells are induced to coexpress IL-13 during type 2 inflammation.

Further studies are required to fully elucidate whether ILC2, in peripheral tissues, which secrete IL-5 constitutively and inactivated eosinophils. Recently, Nussbaum et al have shown that serum IL-5 levels are maintained by long-lived ILC2 resident in peripheral tissues, which secrete IL-5 constitutively and are induced to express IL-13 during type 2 inflammation. Further studies are required to fully elucidate whether ILC2, including NH cells, instead of Th2 cells, are antiatherogenic. The transcription repressor Id2 was previously reported to be essential for the differentiation of all innate lymphocytes, but this is the first report about the mandatory role of Id3 in IL-5 production by NH cells, which seems to be independent of hypercholesterolemia of apoE mice because C57BL/6 displays the same phenotype.\(^6\) NH cells have been found in a newly identified lymphoid structure associated with adipose tissues in the mouse peritoneal cavity.\(^3\) These fat-associated lymphoid clusters are present in both human and mouse mesentery. Perry et al have now identified NH cells also in the periadventitial tissue that surrounds vessels.
One important unresolved issue raised by this study concerns the origin of IL-33. Perry et al treated apoE−/− mice with recombinant IL-33, but this cytokine is likely to be produced naturally in vivo because apoE−/− mice treated with soluble ST2, a decoy receptor that neutralizes IL-33, develop more atherosclerosis. IL-33, a member of the IL-1 family, possesses a chromatin-binding domain in its N terminus and is constitutively expressed in the nuclei of endothelial cells and epithelial cells of tissues exposed to the environment. Similar to other IL-1 family members, IL-33 does not possess any signal peptide. The nuclear IL-33 is released by necrotic cells after tissue injury and trauma. Atherosclerotic plaques are particularly enriched in endothelial microparticles derived from apoptotic/necrotic endothelial cells. It is tempting to hypothesize that IL-33 is released from apoptotic/necrotic plaque neovessels.

In summary, the new identification of a role of ILCs in atherosclerosis will allow a better understanding of the complex interactions between the innate and adaptive immune systems in the development and progression of this disease. In particular, it should shed new light on the controversial issue about the role of type 2 immune responses.

Disclosures

None.

References


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Innate Lymphoid Cells: New Players in Atherosclerosis?
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