Editorial Commentary

IL-33 in murine abdominal aortic aneurysm: a novel inflammatory mediator awaiting clinical translation

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Abdominal aortic aneurysm (AAA) affects approximately 5% of the high-risk general population consisting of men between the ages of 60–75 (1). Histopathologically, AAA are characterized by degradation of the extracellular matrix (particularly elastin), medial smooth muscle cell (SMC) depletion or apoptosis, and inflammation (2,3). Very little is known about risk factors for AAA expansion, once an aneurysm has been detected. Increasing aneurysm size and smoking have been associated with faster aneurysm growth, while diabetes has been associated with slower growth (4). The role of inflammation in AAA has been tested and explored for decades. Studies of human AAA have demonstrated the presence of inflammatory cells in all layers of the aortic aneurysm wall as well as in the associated mural thrombus (5). Understanding the function of these inflammatory cells has been the focus for many research groups. Baxter's group has proposed that AAA formation and progression is associated with an imbalance in M1/M2 macrophage polarization, resulting in a preponderance of pro-inflammatory M1 macrophages and relative deficiency of anti-inflammatory M2 macrophages (6,7). Others have demonstrated that AAA are associated with a deficiency of regulatory T cells (T_{reg}) (8,9). The chronic inflammatory state is further supported by the presence of circulating pro-inflammatory cytokines, such as IL-6, IL-1β, tumor necrosis factor-α (TNF-α) and interferon-gamma (IFN-γ) in patients with AAA (10). In animal models of AAA, inhibition of IL-1β (6) and TNF-α (11) have been associated with protection from AAA formation, decreased macrophage infiltration, and preservation of elastin layers.

IL-33 is a recently described member of the IL-1 cytokine family with pleotropic pro- and anti-inflammatory effects (12). Unlike most other cytokines, IL-33 is not secreted (13). Rather, it is constitutively expressed in the nuclei of different cell types, where it functions as a chromatin-associated nuclear cytokine. At the time of cell injury, IL-33 is released into the extracellular space, thus acting as a nuclear alarmin. As an extracellular protein, IL-33 can interact with its receptor ST2, which is expressed primarily on T_H2 cells, but also T_{reg} cells, macrophages and neutrophils, leading to formation of a heterodimeric signaling complex involving the adaptor protein myeloid differentiation primary response protein 88 (MyD88) and IL-1 receptor accessory protein (IL1RAP). Formation of the signaling complex leads to activation of MAPK and NF-κB pathways (12,13). In inflammatory cells, stimulation by IL-33 has been demonstrated to drive M2 macrophage polarization as well as expansion of T_{reg} cells (13).

In the recent report entitled "IL (Interleukin)-33 Suppresses Abdominal Aortic Aneurysm by Enhancing Regulatory T-Cell Expansion and Activity" published in *Arteriosclerosis, Thrombosis, and Vascular Biology* (14), Li and colleagues demonstrated that IL-33 induced an ST2-dependent regulatory T cell expansion and an anti-

inflammatory response associated with decreased AAA size in murine models of AAA (14). Using the calcium phosphate mouse AAA model, the authors observed increased expression of IL-33 and its receptor ST2 in murine AAA. Overexpression of IL-33 led to smaller AAA, decreased infiltration of CD3+ cells and macrophages, and a shift in cytokine production consistent with increased M2 macrophage polarization. Using DEREG transgenic mice with inducible T_{reg} cell depletion, Li and colleagues demonstrated that regulatory T cells were required for the protective effect of exogenous IL-33 on AAA growth.

Interestingly, the data presented by Li and colleagues shows increased total IL-33 expression in the mouse AAA model and increased nuclear expression of IL-33 in aortic fibroblasts (based on the immunofluorescent staining). However, the interaction of IL-33 with ST2, leading to T_{reg} cell expansion and M2 macrophage polarization, occurs after IL-33 has been released from cells, presumably as a result of cell injury or cell necrosis. Therefore, it remains to be shown if and how increased expression of IL-33 in the mouse AAA is related to the demonstrated beneficial effects of exogenous IL-33. Along the same lines, without studies examining the effect of IL-33 deficiency in AAA, we do not have a clear picture of the role of endogenous IL-33 in AAA formation in the mouse model, and the effect of IL-33 deficiency may or may not impact AAA development. For example, in studies of IL-33 in murine models of atherosclerosis, Miller and colleagues reported that treatment with exogenous IL-33 significantly reduced atherosclerotic plaque development in high fat diet-fed ApoE-/- mice (15). However, an independent study examining the effect of endogenous IL-33 or ST2 deficiency showed no impact on plaque development in a slightly different mouse atherosclerosis model (16).

Similar to many mechanistic studies based on mouse AAA models, the present work must be evaluated in the context of limitations associated with animal models. There are currently three widely used mouse models for the study of AAA: the elastase perfusion model (17), the periadventitial calcium chloride or calcium phosphate model (18,19), and the angiotensin II infusion model (20). All of these models result in aneurysmal dilatation of the aorta characterized histologically by disruption of the medial layer of the arterial wall accompanied by an inflammatory response (21). Previous investigations on the role of IL-33 in atherosclerosis have demonstrated the variability that can arise through use of different animal models (15,16). Although Li and colleagues demonstrated that the protective effect of exogenous IL-33 could be observed in 2 distinct murine AAA models, it is important to remember that murine AAA models are chemically induced, and although histopathologically may share characteristic features with human AAA, human AAA arise from a combination of complex genetic and environmental risk factors, none of which have yet been completely understood.

The report by Li and colleagues contributes to the growing literature supporting the role of regulatory T cells in AAA development. In the angiotensin II mouse AAA model, injection of T_{reg} cells was protective of AAA formation (9). Similarly, patients with AAA have been found to have decreased proportion of functional regulatory T cells (8,9). The present study suggests that exogenous IL-33 may induce expansion of T_{reg} cell population, which may protect against AAA expansion. The challenge, however, resides in translating these findings into clinical interventions. Although the pro-inflammatory milieu of human AAA is well-documented, identifying an anti-inflammatory therapy remains elusive, despite the wealth of experimental data from animal models. Although targeted inhibition of IL-1β was effective in the mouse (6), a recent clinical trial (NCT02007252) of canakinumab, an IL-1β neutralizing antibody, in patients with small AAA was terminated after interim analyses showed that there was no effect of the study drug on AAA growth over 12 months. Similarly, although doxycycline, a known inhibitor of matrix metalloproteinases, has been demonstrated to slow mouse AAA expansion (22), the effect of doxycycline in slowing human AAA growth is still under investigation (23).

The work by Li and colleagues raises important questions for future studies. IL-33 is released by injured cells but not by apoptotic cells, so further study of IL-33 may shed light on mechanisms of SMC depletion and cell injury in the aortic wall. As mentioned earlier, the role of endogenous IL-33 in AAA remains unexplored. Lastly, although IL-33 has been demonstrated in human atherosclerotic plaque, no studies to date have demonstrated upregulation of IL-33 (or ST2) either in human AAA tissue or as a circulating factor in patients with AAA. These initial clinical studies are crucial, since IL-33 expression in mouse cells differs from expression in human cells (13). The authors are to be congratulated on their initial work suggesting a therapeutic role for IL-33-mediated regulatory T cell expansion in AAA growth. Of interest will be the follow-

up studies to explore the role of IL-33 deficiency in mouse AAA models and test whether any of these findings are translatable to humans. Better understanding of the complex relationship between immune responses and AAA expansion is a challenging problem, but may ultimately hold the key to medical management of AAA.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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