Editorial Commentary

Lost in translation: do animal studies add value to the management of abdominal aortic aneurysms?

Doireann Patricia Joyce[1], Stewart Redmond Walsh[1], Tze Tec Chong[2], Tjun Yip Tang[2]

[1]Department of Vascular Surgery, Galway University Hospital, Galway, Ireland; [2]Department of Vascular Surgery, Singapore General Hospital, Singapore

Correspondence to: Tjun Yip Tang, MD, FRCS (Gen), FAMS. Consultant Vascular & Endovascular Surgeon, Associate Professor Duke-NUS Medical School, Department of Vascular Surgery, Singapore General Hospital, Level 5, Academia, 20 College Road, Singapore 169856. Email: tang.tjun.yip@singhealth.com.sg.

Provenance: This is an invited article commissioned by the Section Editor Lei Zhang (Department of Vascular Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China).

Comment on: Li J, Xia N, Wen S, *et al.* IL (Interleukin)-33 Suppresses Abdominal Aortic Aneurysm by Enhancing Regulatory T-Cell Expansion and Activity. Arterioscler Thromb Vasc Biol 2019;39:446-58.

Submitted Apr 21, 2019. Accepted for publication Apr 26, 2019.
doi: 10.21037/jtd.2019.04.110
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.110

The work outlined by Li *et al.* (1) in their recently published work demonstrated a protective effect of IL-33 in a murine model of abdominal aortic aneurysm (AAA). Through a series of elegant experiments, the authors found that both the administration of exogenous IL-33 and overexpression of IL-33 in transgenic mice blunted AAA growth. Two separate models were used in this research. The first consisted of calcium phosphate ($CaPO_4$) induction by applying $CaCl_2$ followed by phosphate buffered saline (PBS) to the infrarenal aorta. Control mice were treated with sodium chloride (NaCl) alone. The second murine model involved the induction of AAA through exposure of the infrarenal aorta to 100% porcine pancreatic elastase versus heat-inactivated elastase in control mice.

A number of key observations were made with regard to the $CaPO_4$ model. First, IL-33 levels (in both the 10- and 18-kDa active forms) were found to be elevated in adventitia fibroblasts from AAA compared to NaCl treated mice. Increased expression of the IL-33 receptor ST2 in AAA lesions compared with controls was also detected on immunoblot analysis. $CD45^-$ cells were found to be major IL-33 expressors in AAA. Exogenous IL-33 (administered intraperitoneally) was found to reduce aortic wall dilatation, increased aortic wall deposition and protected the aortic wall elastica from fragmentation. Similar results were noted in IL-33 transgenic mice. Exogenous $CD4^+Foxp3^+$ regulatory T-cell (Treg) numbers contained in the blood and spleens of $CaPO_4$-induced AAA mice increased following IL-33 treatment. These observations were mirrored in IL-33 transgenic mice when compared with non-transgenic (NTG) mice. This IL-33 Treg expansion was detected only in wild type, but not ST2-deficient $ST2^{-/-}$ mice, indicating that the protective effects of IL-33 occur due to proliferation of Tregs which is, in turn, mediated by ST2. Tregs isolated from IL-33 mice enhanced ability to inhibit smooth muscle cell expression of MCP-1 and IL-6, in addition to reducing expression of MMP-2 and MMP-9. Tregs from this group were also found to increase M2 macrophage polarization than controls. Next, the authors demonstrated that IL-33 did not prevent AAA formation in $CaPO_4$-treated mice after depletion of Tregs through a reduced ability to suppress aortic wall elastic fragmentation and promotion of collagen deposition.

The porcine pancreatic elastase model produced similar results including the ability for IL-33 to reduce aortic diameter size and aortic wall elastic fragmentation and to increase collagen deposition. In addition, treatment with IL-33 reduced intra-lesional infiltration of T-lymphocytes and macrophages, inflammatory cytokine production, MMP-2 and MMP-9 production and lesion cell apoptosis.

Based on the findings outlined above, the authors propose recombinant IL-33 therapy and overexpression of

endogenous IL-33 as a means of stemming the growth of AAA or indeed preventing it altogether. These suggestions, may however, be considered overly ambitious for a variety of reasons. First, small sample sizes were utilized in each study group with a maximum number of 15 mice employed. As such, one could consider the drawing of such conclusions to be both unfounded and premature. In the human setting, sample sizes this low would not be accepted outside of a pilot study. While the findings described here may well be reproducible, further validation work is undoubtedly required prior to translation into humans.

Next, the implications of exogenous IL-33 therapy or upregulation of this interleukin in the human setting have yet to be elucidated. Li *et al.* (1), performed histological analysis which did not show adverse effects on lung, liver, kidney or heart following IL-33 administration or overexpression. Despite this, extensive safety profiling will be required before this therapy could be considered to be either safe or efficacious for use in human studies. While the authors of this work should be commended for undertaking extensive research into the potential role of IL-33 in AAA, their findings may merely represent the groundwork on which further studies can be built.

Cite this article as: Joyce DP, Walsh SR, Chong TT, Tang TY. Lost in translation: do animal studies add value to the management of abdominal aortic aneurysms? J Thorac Dis 2019;11(Suppl 9):S1277-S1278. doi: 10.21037/jtd.2019.04.110

Acknowledgements

None.

Footnote

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

References

1. Li J, Xia N, Wen S, et al. IL (Interleukin)-33 Suppresses Abdominal Aortic Aneurysm by Enhancing Regulatory T-Cell Expansion and Activity. Arterioscler Thromb Vasc Biol 2019;39:446-58.

