**The Role of IL-18 in Abdominal Aortic Aneurysm Formation**

Buddhila Wickramasinghe (19208625)

Advisor – Anthony (Bill) Vinh

**Running head**: Abdominal aortic aneurysms

Abdominal aortic aneurysms (AAA) are defined as the permanent dilation of aortic vessel wall that occurs predominantly in the infrarenal region (1, 2). Although the condition is asymptomatic, rupture of the progressively dilated vessels could be fatal (1-4). AAA remains a pathological condition with surgical repair as the only available treatment option. As surgery is associated with significant complications, extended recovery periods and reduced durability, there is a serious need for pharmaceutical treatments to prevent aneurysmal growth and rupture (1-3).

Although molecular mechanisms of AAA formation are not well established, known details suggest that it is closely associated with macrophage infiltration, subsequent inflammation of the vessel wall (1, 2, 5) and production and activation of various cytokines and proteases (4). Macrophages can be activated via inflammasomes which are multimeric receptor molecules that process the activation of various pro-inflammatory cytokines and regulate inflammation in chronic disease conditions (6, 7). Evidently, inhibition of NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasomes by MCC950 was able to decrease hypertension and renal inflammation in vivo (7, 8). Oligomerization of NLRP3 inflammasomes stimulated by several pathogen- and danger- associated molecular signals such as lipopolysaccharides (9), reactive oxygen species, microcrystals and high concentrations of salt, leads the conversion of pro-caspase-1 into active caspase-1 (6-8). Consequently, caspase-1 proteolytically cleaves pro-interleukin (IL)-18 into active IL-18 (7-9) which then leaves the native cells and promotes inflammation in neighbouring cells by recruiting macrophages to the site (7, 8). As IL-18 is linked with several disease states including atherosclerosis and is a vital marker of cardiovascular death (5), its contribution towards AAA pathogenesis is worth investigating.

A study conducted by Suehiro et al. (2019) on IL-18 knocked out (KO) and wild type (WT) mice describes how IL-18 is associated with AAA formation. Both groups of mice have been subcutaneously infused with Angiotensin II (Ang II) to induce AAA. Findings suggest a higher prevalence of AAA development associated with elevated IL-18 levels in WT mice compared to IL-18 KO mice. Subsequently, the observation of significantly attenuated macrophage infiltration in abdominal aortas of the IL-18 KO mice than that of WT mice proposes that IL-18 manifests macrophage infiltration in abdominal aortas during the formation of AAA. Osteopontin (OPN), an extracellular matrix (ECM) protein known to regulate inflammatory cell recruitment and adhesion (5) was also observed to be overexpressed in WT mice compared to IL-18 KO mice. This confirms the reported idea that IL-18 controls the expression of OPN and OPN in turn, contributes to AAA pathogenesis (10) by inducing the production of matrix metalloproteases (MMP) that encourage the breakdown of ECM (5). Therefore, IL-18 could be an attractive therapeutic target for the disease.

In summary, since AAA progression and rupture has higher rates of morbidity and mortality, and surgery is the only treatment available, there is a serious need for an optimal medical therapy. AAA development is associated with macrophage infiltration and inflammation and IL-18 is believed to be a centre player owing to its role in increasing OPN expression, macrophage infiltration and MMP activation. Therefore, further studies should be dedicated to understanding the role of IL-18 more thoroughly in favour of developing medical treatments based on IL-18 inhibition.

**References**

1. Davis FM, Daugherty A, Lu HS. Updates of Recent Aortic Aneurysm Research. Atertio Thromb Vasc Biol. 2019;39(3):e83-e90.

2. Lu H, Daugherty A. Aortic Aneurysms. Atertio Thromb Vasc Biol. 2017;37(6):e59-e65.

3. Golledge J, Norman PE. Current status of medical management for abdominal aortic aneurysm. Atherosclerosis. 2011;217(1):57-63.

4. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. Lancet. 2005;365(9470):1577-89.

5. Suehiro C, Suzuki J, Hamaguchi M, Takahashi K, Nagao T, Sakaue T, et al. Deletion of interleukin-18 attenuates abdominal aortic aneurysm formation. Atherosclerosis. 2019;289:14-20.

6. Latz E. The inflammasomes: mechanisms of activation and function. Curr Opin Immunol. 2010;22(1):28-33.

7. Krishnan SM, Ling YH, Huuskes BM, Ferens DM, Saini N, Chan CT, et al. Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension. Cardiovasc Res. 2018;115(4):776-87.

8. Krishnan SM, Dowling JK, Ling YH, Diep H, Chan CT, Ferens D, et al. Inflammasome activity is essential for one kidney/deoxycorticosterone acetate/salt‐induced hypertension in mice. British Journal of Pharmacology. 2016;173(4):752-65.

9. Gracie JA, Robertson SE, McInnes IB. Interleukin-18. J Leukocyte Biol. 2003;73(2):213-24.

10. Bruemmer D, Collins AR, Noh G, Wang W, Territo M, Arias-Magallona S, et al. Angiotensin II–accelerated atherosclerosis and aneurysm formation is attenuated in osteopontin-deficient mice. The Journal of Clinical Investigation. 2003;112(9):1318-31.