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CD95-ligand contributes to abdominal aortic aneurysm progression by modulating inflammation

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Statement of the Problem: Abdominal aortic aneurysm (AAA) is one of a number of diseases associated with a prominent inflammatory cell infiltration, matrix protein degradation, and smooth muscle cell apoptosis. CD95 is an inflammatory mediator and an apoptosis inducer. How the CD95L/CD95 contributes to aneurysm degeneration remains largely unknown.

Methods & Results: By using the CaCl2 murine model of AAA, we found that both mRNA and protein levels of CD95L were increased in aneurysm tissue compared with NaCl-treated normal aortic tissue. To determine whether CD95L contributes directly to aneurysm formation, we used CD95L null (CD95L-/-) mice to examine their response to CaCl2 aneurysm induction. Six weeks after periaortic application of CaCl2, aortic diameters of CD95L-/- mice were significantly smaller compared to CaCl2-treated wild type controls. Connective tissue staining of aortic sections from CaCl2-treated CD95L-/- mice showed minimal damage of medial elastic lamellae which was indistinguishable from the NaCl-treated sham control. Furthermore, CD95L deficiency attenuates macrophage and T cell infiltration into the aortic tissue. To study the role of CD95L in the myelogeous cells in AAA formation, we created chimeric mice by infusing CD95L-/- bone marrow into sub-lethally irradiated wild type mice (WT/CD95L-/-BM). WT/CD95L-/-BM mice were resistant to aneurysm formation. Inflammatory cell infiltration was blocked by the deletion of CD95L on myeloid cells. The levels of caspase 8 in the aortas of CaCl2-treated wild type mice were increased compared to NaCl-treated controls. CD95L deletion inhibited caspase 8 expression. Furthermore, a caspase 8-specific inhibitor was able to partially block aneurysm development in CaCl2-treated aneurysm models.

Conclusion & Significance: These studies demonstrated that inflammatory cell infiltration during AAA formation is dependent on CD95L from myelogeous cells. Aneurysm inhibition by deletion of CD95L is mediated in part by down-regulation of caspase 8.

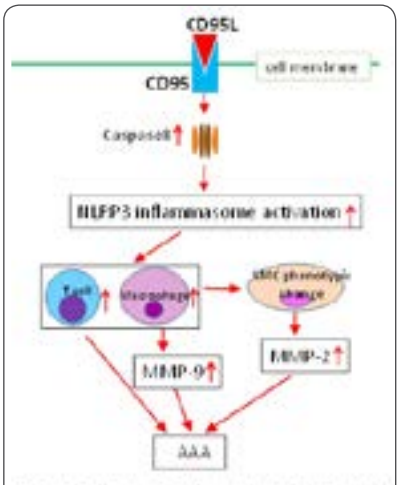

Figure 1. The pro-inflammatory mechanism of CD95L/CD95 – caspase 8 signaling in AAA.

Recent Publications

1. Batra R, Suh M K, Carson J S, Dale M A, Meisinger T M, Fitzgerald M, Opperman P J, Luo J, Pipinos I I, Xiong W and Baxter B T (2018) IL-1β (Interleukin-1β) and TNF-α (tumor necrosis factor-α) impact abdominal aortic aneurysm formation by differential effects on macrophage polarization. Arterioscler Thromb Vasc Biol. 38(2):457-463.
2. Dale M A, Xiong W, Carson J S, Suh M K, Karpisek A D, Meisinger T M, Casale G P and Baxter B T (2016) Elastin-derived peptides promote abdominal aortic aneurysm formation by modulating M1/M2 macrophage polarization. J Immunol. 196(11):4536-43.
3. Xiong W, Meisinger T, Knispel R, Worth J M and Baxter B T (2012) MMP-2 regulates Erk1/2 phosphorylation and aortic dilatation in Marfan syndrome. Circ Res. 110(12):e92-e101.
4. Xiong W, Mac Taggart J, Knispel R, Worth J, Persidsky Y and Baxter B T (2009) Blocking TNF-alpha attenuates aneurysm formation in a murine model. J Immunol. 183(4):2741-6.
5. Xiong W, Longo G M, Greiner T C, Zhao Y, Fiotti N and Baxter B T (2002) Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest. 110(5):625-32.

Biography

Wanfen Xiong is an Associate Professor at the University of Nebraska Medical Center. She received her PhD in Biochemistry and Molecular Biology. Since she completed her Postdoctoral training at Stanford University in 1999, she has worked to understand the etiology and mechanisms of aortic aneurysms. Through the study of a murine Marfan syndrome (MFS) model, she has shown that smooth muscle cells (SMCs) switched prematurely to a more mature contractile phenotype at postnatal day 7 in MFS mice. Her research interests are to understand the molecular mechanisms underlying early aneurysm development in Marfan syndrome and develop effective strategies to prevent aneurysm formation.

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