Transcription Coactivator MED1 Protects Against Atherosclerosis by Modulation of Macrophage Polarization

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Mediator 1 (MED1), a key subunit of the Mediator complex, interacts with several nuclear receptors and transcription factors to direct gene-specific transcription. It is well-known that MED1 play important roles in lipid metabolism. However, the role and underlying mechanisms of MED1 in atherosclerosis remains unclear. Here, macrophage-specific MED1 knockout ($MED1^{\Delta Mac}$) mice were generated to investigate the contribution of MED1 on atherogenesis in vivo. We demonstrate that among mice deficient in apolipoprotein E (Apoe), the additional loss of macrophage MED1 ($MED1^{\Delta Mac}/ApoE^{-/-}$) exhibited significantly larger atherosclerotic lesions in the whole aortic tree and aortic root compared with $MED1^{fl/fl}/ApoE^{-/-}$ littermates on either the chow or the western diet, and these effects were also found in low-density lipoprotein (LDL) receptor-deficient ($LDLR^{-/-}$) mice reconstituted with bone marrow from $MED1^{\Delta Mac}$ mice. Peritoneal macrophages from $MED1^{\Delta Mac}/ApoE^{-/-}$ mice had significantly increased expression of gene markers for M1-like macrophages, including IL-1β, IL6,COX2, iNOS, Gro1, MCP1 and TNFα, etc, whereas decreased levels of anti-inflammatory genes for M2-like macrophages, such as Arg1, Mrc1, Retnla, Chi3l3 and PPARγ. Over-expression of MED1 using adenovirally-driven MED1 (Ad/MED1) in $MED1^{fl/fl}/ApoE^{-/-}$ macophages repressed the proinflammatory gene expression. Re-expression of MED1 using Ad/MED1 counteracted the high level of inflammatory gene in $MED1^{\Delta Mac}/ApoE^{-/-}$ macophages. Furthermore, gene expression profiling and PCR array showed that MED1-deficient macrophages exhibited the increased M1 targets and decreased M2 targets. These data demonstrate that MED1 expression by macrophages has anti-atherogenic effects via regulation of macrophage polarization. MED1 may be considered as a potential therapeutic target to treat atherosclerosis.

Disclosure Block:
L. Bai: None. **E. Liu:** None.