Aryl hydrocarbon receptor: a novel target for the anti-inflammatory activity of statin therapy

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Statin therapy is associated with an attenuation of the systemic inflammatory response. Aryl hydrocarbon receptor (AhR) is believed to play an active role in the control of inflammation. Specific statins promote the transcription of Cyp1a1, which induction involves AhR activation1. We investigated whether AhR might be involved in the anti-inflammatory effect of statins treatment.

We performed luciferase assay to test the ability of murine hepatocytes overexpressing AhR and the xenobiotic responsive elements (XRE) and the ability of murine embryonic fibroblast AhR KO, transfected with different mutants of AhR to activate receptor in response to statins. Lipopolysaccharide (LPS)-treated RAW 264.7 macrophage cells were tested for the expression of AhR and for pro-inflammatory/anti-inflammatory response to different statins. Activated AhR WT and KO macrophages were tested for the expression of M1 and M2 markers and for pro-inflammatory/anti-inflammatory cytokines production. Luciferase assays showed that atorvastatin and pravastatin activated AhR, but no AhR mutants. LPS treatment of RAW 264.7 cell line induced AhR. Exposure of RAW 264.7 to both pravastatin and atorvastatin concomitantly to LPS reduced IL-6 production and increased IL-10 secretion. Atorvastatin and pravastatin potentiated arginase expression and anti-inflammatory response in activated macrophages in AhR dependent manner.

These data show that atorvastatin and pravastatin activate AhR, attenuate the inflammatory response induced by LPS and promote M2 phenotype in AhR dependent manner. AhR might represent a mediator of the anti-inflammatory effects of statin treatment.

1Hu W., et al, Mol Pharmacol. 2007 Jun;71(6):1475-86