Abstract: P723

A novel CD147 inhibitor SP-8356 attenuates plaque progression and stabilizes vulnerable plaque in ApoE-deficient mice

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Aim: Plaque vulnerability is the crucial pathophysiological feature in atherosclerosis-related cardiovascular event such as myocardial infarction and stroke. CD147 has been suggested to play key roles in plaque vulnerability through interacting with cyclophilin A (CypA) and resultant activation of matrix metalloproteinase-9 (MMP-9). Here we report that the novel synthetic CD147 inhibitor SP-8356 ((1S,5R)-4-(3,4-dihydroxy-5-methoxystyryl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one) inhibits CD147/MMP-9 pathways and reduces plaque progression and stabilizes plaque vulnerability.

Methods: Advanced atherosclerotic plaque was induced in apolipoprotein E-deficient (ApoE KO) mice by partial ligation of the right carotid artery coupled with an atherogenic diet. SP-8356 (50 mg/kg) was orally given daily for 3 weeks. Histomolecular analysis was carried out on harvested carotid arteries.

Results: Surface plasmon resonance assay showed the specific binding of SP-8356 with CD147. SP-8356 inhibited CypA-CD147 interaction and MMP-9 activation. In ApoE KO mice model, SP-8356 inhibited plaque formation, reduced the number of macrophages, increased the number of vascular smooth muscle cells, increased the fibrous cap thickness, and increased the collagen type I contents in fibrous cap. SP-8356 also reduced the apoptotic cells in the plaque lesion.

Conclusions: Owing to its improvement of plaque stability and inhibitory effect on plaque development, SP-8356 could be a potential therapeutic drug candidate for atherosclerosis and related clinical manifestations.