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Vulnerable Plaque: State of the Art

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DATE : 18 May 2015, Monday ***(including Q & A session)***
TIME : 0930 – 1100
VENUE : SCM809
LANGUAGE : Mandarin
FACILITATOR : Dr. YU Zhiling

Abstract of the Seminar

Atherosclerotic plaque vulnerability is an essential mechanism involved in the pathogenesis of acute coronary syndrome. In this presentation, recent advances in the basic and clinical research on vulnerable plaque in our laboratory will be addressed. First, we have developed several animal models of vulnerable plaque including a rabbit model of plaque rupture and thrombosis, a rabbit model of intraplaque hemorrhage and a mouse model of plaque rupture and thrombosis. These models have been used successfully in delineating the molecular mechanisms of and therapeutic targets for plaque instability. Second, we have discovered a number of novel mechanisms mediating plaque formation and progression: (1) nicotine promotes the formation of abdominal aortic aneurysm by activation of AMPKα2 and MMP-2; (2) cold exposure triggers the conversion of white adipose tissue to brown adipose tissue with consequent lipolysis and increased serum levels of LDL-C, which enlarges plaque size and enhances plaque instability; (3) TNF-α inhibits P4Hα(I) via activating ASK1-JNK-NonO signaling pathways thereby leading to decreased collagen synthesis and vascular remodeling; (4) hepcidin promotes plaque destabilization by exaggerating inflammatory cytokine release, intracellular lipid accumulation, oxidative stress, and apoptosis in the macrophages with iron retention;(5) PC-PLC promotes plaque instability by enhancing the recruitment of inflammatory monocytes/macrophages through increasing endothelial expression of ICAM-1, VCAM-1 and MCP-1. Third, we have reported several novel biomarkers of plaque vulnerability:(1) –69C>G polymorphisms of TrkB gene is significantly associated with coronary artery disease(CAD) and TrkB –69C homozygotes with decreased TrkB expression shows an increased risk for CAD, suggesting that TrkB has a protective role; (2) NPR-C is a novel susceptibility gene to CAD in a large Chinese Han population; (3) two-dimensional and three-dimensional plaque strain is a novel predictor of plaque rupture and ischemic stroke in animals and patients; (4)plaque eccentric index, plaque area, high-sensitive CRP and plaque acoustic density are independent predictors of plaque rupture in rabbits, and carotid intimal-medial thickness, coronary arterial remodeling index and high sensitive CRP are independent predictors of plaque rupture in patients with unstable angina; Finally, we revealed a series of novel therapeutic targets for vulnerable plaque:(1) dominant-negative mutation of MCP-1 significantly inhibits plaque and systemic inflammation and reduces the incidence of plaque rupture;(2)overexpression of ACE2 attenuates early atherosclerotic lesions and stabilizes vulnerable plaque via down-regulating ERK-p38、JAK-STAT and Ang II-ROS-NF-κB pathways while up-regulating PI3K-Akt pathway in vessels;(3) Ang-(1–7) dose-dependently attenuates early atherosclerotic lesions via inhibiting ERK/P38 and JAK/STAT pathways and increasing the expression of SM22α and AT2R, and enhances the stability of mature plaque via suppressing the expression of pro-inflammatory cytokines and MMPs;(4) In a mouse model of diabetes and atherosclerosis, gene silencing of TRIB3 gene effectively activates Akt signaling, reduces insulin resistance and macrophage apoptosis and limits the growth of lipid core, resulting in a stabilized plaque;(5)adoptive transfer of Tregs dose-dependently inhibits the release of inflammatory factors and MMP-2 and MMP-9 and increases the expression of P4Hα(I) in plaque, and reduces plaque vulnerability index and these effects are found to be mediated by TGF-β and IL-10;(6) adoptive transfer of Tregs dose-dependently reduces local infiltration of macrophages and CD4+T cells and release of inflammatory factors and MMP-2 and MMP-9, increases the production of IL-10 and TGF-β1, leading to a lower incidence and severity of abdominal aortic aneurysm;(7) traditional Chinese medication Tongxinluo dose-dependently lowers the serum level of LDL-C, attenuates local inflammation and oxidative stress, decreases the number of vascular vasa vasorum and reduces the incidence of plaque rupture in animal models.

****Welcome****