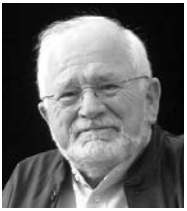
JPSプレナリーレクチャー　JPS Plenary Lecture

3/19（Wed） Room A　13:30 ～ 14:30

［座長］ 飯野 正光（東京大学大学院医学系研究科細胞分子薬理学教室）
［Chair］ Masamitsu Iino（Dept. Pharmacol., Grad. Sch. Med., The Univ. Tokyo）

JPSPL The Endothelial Saga: From Function to Dysfunction



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Endothelium-dependent dilatations are due mainly to the release of nitric oxide (NO) which is formed by the constitutive endothelial NO synthase (eNOS). NO diffuses to the underlying vascular smooth muscle and stimulates soluble guanylyl cyclase with the resulting production of cyclic GMP. The release of NO from the endothelium can be mediated by both pertussis toxin-sensitive G_i- (e.g. α_2-adrenergic agonists, serotonin) and insensitive G_q- (adenosine diphosphate, bradykinin) proteins. The ability of the endothelial cell to release NO can be down-regulated by oxidative stress and increased presence of oxidized low density lipoproteins (LDL). It is reduced chronically by aging, smoking, environmental pollution and in hypertension and diabetes. Following injury or apoptotic death, the endothelium regenerates. However, in regenerated endothelial cells, there is an early selective loss of the pertussis-toxin sensitive mechanisms of NO-release. Functional studies suggest that abnormal handling of LDL because of increased oxidative stress play a key role in this selective loss. Genomic analysis demonstrates the emergence of fatty acid binding protein-A (A-FABP)) in regenerated endothelial cells. To verify the role of oxidative stress and A-FABP in the genesis of coronary atherosclerosis, endothelial regeneration was induced in the coronary artery of pigs treated chronically with BMS309403 (A-FABP inhibitor) or apocynin (anti-oxidant) for 28 days before functional examination and histological analysis of the coronary arteries (with native or regenerated endothelium). Both the antioxidant treatment and inhibition of A-FABP normalized the diminished G_i-protein mediated relaxations to serotonin and reduced the intima-medial thickening caused by endothelial regeneration. These treatments did not affect the response to bradykinin or endothelium-independent agonists (detaNONOate and isoproterenol). These experiments confirm the crucial role of oxidative stress and of the emergence of A-FABP in the initiation of endothelial dysfunction and subsequent coronary atherosclerosis.