주제강연

Endothelial Cell 손상시 생존은 가능한가 ?
Can we induce therapeutic endothelial cell survival from insults-induced apoptosis in vitro and in vivo?

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The integrity and normal function of endothelium are indispensable for good health. In an adult human, the endothelial monolayer consists of an estimated 1 to 6 × 10^{13} cells that considered as a unit, form an approximately 1-kg heavy "organ". This "organ" plays a central role in the control of vascular tone, permeability, blood flow, coagulation, thrombolysis, inflammation, tissue repair, and growth. Damage to the endothelium can initiate thrombosis formation, neointimal hyperplasia, and atherogenesis. Therefore, maintaining a normal endothelial integrity in response to physical, biochemical and immune-mediated damage is important to prevent vascular diseases. Interestingly, angiopoietin-1 (Ang1) receptor, Tie2 is selectively expressed as an activated form in the endothelial cells of normal adult vessels, in which vasculogenesis and angiogenesis do not normally occur. We found that Ang1 is a strong survival factor for endothelial cells. We also demonstrated that Ang1 induced a signal transduction pathway leading to endothelial cell survival for the first time. The Tie2 receptor, PI 3'-kinase, and Akt are crucial elements in the signal transduction pathway leading to endothelial cell survival induced by the paracrine activity of Ang1. Given that Ang1 is a strong apoptosis survival factor without mitotic effect, constitutive expression of Ang1 in periendothelial cells may activate the Tie2 receptor, thereby acting as a paracrine factor that maintains normal integrity in non-proliferating endothelial cells. In fact, our *in vitro* experiments demonstrated that Ang1 prevented apoptosis in endothelial cells treated with several insults, including irradiation, oxidized LDL or clinical concentrations of mannitol. This effect was mediated through Tie2 receptor binding and PI 3'-kinase activation. In addition, Ang1 increases the survival of endothelial cells in response to lipopolysaccharide from Gram-negative bacteria. Ang1 also prevented apoptosis in endothelial cells of explanted porcine coronary arteries subjected to the same insults.

Generally, Ang1's antiapoptotic potency was similar or greater than that of VEGF and bFGF. These data suggest that systemic treatment with Ang1 could be beneficial in maintaining normal endothelial cell integrity during endothelial cell damage *in vivo*. Therefore, we conclude that the angiopoietin-Tie2 system is essential to the maintenance of normal endothelial survival and integrity. From this study, we coined the term 'Therapeutic endothelial cell survival (Therapeutic Endo-survival)' using Ang1. Although Ang1 could be the most potent, selective and safe agent for therapeutic endothelial cell survival, large-scale production of recombinant of Ang1 is hindered by aggregation and insolubility during production and purification of the protein. Recently, we invented small size of Ang1 variant, COMP/CC-Ang1/FD. COMP/CC-Ang1/FD is a soluble and more potent than native Ang1 for activating Tie2, enhancing endothelial cell survival in vitro. Furthermore, COMP/CC-Ang1/FD protects LPS- and irradiation- induced apotosis in micro-capillary endothelial cells of intestinal villi and lung in vivo and thereby increased survival rate. Therefore, COMP/CC-Ang1/FD would be very useful for therapeutic endothelial cell survival in the future.