Symposium VI:
S6-1
House dust mite allergen Der f 1 can activate latent TGF-β, leading to the expression of profibrogenic genes

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Abstract
Rationale: It remains uncertain whether the protease activity of a major mite allergen Der f 1 affects airway remodeling in asthma. Transforming growth factor (TGF)-β, a key cytokine for airway remodeling, is secreted as a latent complex (latent TGF-β) in which TGF-β is non-covalently associated with the latency-associated peptide (LAP). LAP proteolysis is required for the release of TGF-β from the latent complex and its binding to the receptors.

Objective: This study investigated whether Der f 1 can cleave LAP via its proteolytic activity and activate latent TGF-β, thereby leading to expression of profibrogenic genes.

Methods: The effects of Der f 1 on the activation of latent TGF-β in vitro and in vivo were examined by the detection of TGF-β activity using TGF-β signaling reporter cells and mice, real-time PCR for TGF-β target gene expression, and histological examination.

Measurements and Main Results: Der f 1 cleaved LAP and induced the activation of latent TGF-β in vitro, which was inhibited by E-64, a cysteine protease inhibitor. The intratracheal or intranasal exposure of Der f 1 to mice induced TGF-β activity in the bronchoalveolar lavage (BAL) fluid, expression of TGF-β, Smad7, and type I and IV collagen mRNAs in the lung, and subepithelial fibrosis which was inhibited by E-64. The Smad promoter activity increased in the lung of Der f 1-challenged TGF-β/Smad signaling-reporter mice.

Conclusions: Der f 1 can induce the activation of latent TGF-β via its protease activity, leading to expression of profibrogenic genes involved in airway remodeling in asthma.

S6-2
Role of Endothelial Progenitor Cells for Organ Regeneration

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Recently the regenerative potential of stem cells has been under intense investigation. In vitro, stem and progenitor cells possess the capability of self-renewal and differentiation into organ-specific cell types. In vivo, transplantation of these cells may reconstitute organ systems, as shown in animal models of diseases. In contrast, differentiated cells do not exhibit such characteristics. Human endothelial progenitor cells (EPCs) have been isolated from the peripheral blood of adult individuals, expanded in vitro and committed into an endothelial lineage in culture. The transplantation of these human EPCs has been shown to facilitate successful salvage of limb vasculature and perfusion in athymic nude mice with severe hindlimb ischemia, while differentiated endothelial cells (human microvascular endothelial cells) failed to accomplish limb-saving neovascularization.

These experimental findings call into question certain fundamental concepts regarding blood vessel growth and development in adult organisms. Postnatal neovascularization has been previously considered synonymous with proliferation and migration of pre-existing, fully differentiated ECs resident within parent vessels, i.e. angiogenesis. The finding that circulating EPCs may home to sites of neovascularization and differentiate into ECs in situ is consistent with “vasculogenesis”, a critical paradigm for establishment of the primordial vascular network in the embryo. While the proportional contributions of angiogenesis and vasculogenesis to postnatal neovascularization remain to be clarified, our findings together with the recent reports from other investigators suggest that growth and development of new blood vessels in the adult is not restricted to angiogenesis but encompasses both embryonic mechanisms.

Furthermore, recent studies indicate optional role of EPCs for organ regeneration, including anti-inflammatory and anti-fibrotic effects for the preparation of organ regenerations. I will discuss this issue in the symposium.

Reference