Title: Role of interferon-γ in tumor necrosis factor-α-mediated increase of lung microvascular endothelial cells

Body: Background: Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease in which tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are overexpressed and have been suggested to play pathogenic roles. The effect of these agents on angiogenesis in the lung tissues of COPD is unknown. Objective: To examine the effects of these mediators on lung endothelial cells (ECs). Methods: Nrf2 knockout mice were exposed to cigarette smoke (CS) for 4 weeks, and the down-regulated genes referring to vascularity in the whole lung were identified by microarray analysis. To confirm the protein levels, which were indicated in the microarray data, co-cultivation of lung fibroblasts with ECs in the presence of TNF-α and IFN-γ was performed, thereafter ECs were submitted to an examination of protein levels expression using immunoblotting or immunocytochemistry. Results: Microarray analysis data have shown that the mRNA expression of angiomotin-like protein 1 (AmotL1) decreased in response to CS when compared to no exposure to CS. TNF-α enhanced vascular endothelial growth factor (VEGF) production by cultured lung fibroblasts, however, vascularity was decreased when treated with IFN-γ. In addition, IFN-γ induced tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors on ECs and attenuated the expression of AmotL1 localized to endothelial cell-cell junctions. Conclusions: These results suggest that IFN-γ acts as anti-angiogenesis by regulating the expression of TRAIL receptors and AmotL1 on ECs, which were induced by the enhanced VEGF production by TNF-α-stimulated lung fibroblasts.