SARS Coronavirus Papain-like Protease Induces Egr-1-mediated Up-regulation Of TGF-β1 in Pro-fibrotic Responses

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Background/Objective

SARS coronavirus (SARS-CoV) papain-like protease (PLpro), a deubiquitinating enzyme, reduces interferon (IFN) induction via inactivation of IRF3 and NF-κB. Our prior studies demonstrate SARS-CoV PLpro suppressing type I IFN signaling through down-regulation of ERK1, and increasing the TGF-β1 production through ubiquitin proteasome, and p38 MAPK pathways in human promonocytes (J Gen Virol 2011; 92:1127-40; Proteomics 2012,12: 3193-205).

Method

This study investigates the molecular mechanisms of TGF-β1 promoter activation induced by SARS-CoV PLpro in human lung epithelial cells and mouse lung tissues.

Result

In human lung epithelial A549 cells, SARS-CoV PLpro up-regulates the expression of TGF-β1 and pro-fibrotic genes (vimentin, glial fibrillary acidic protein, and type I collagen) in concentration- and time-dependent manners. Dual luciferase reporter assays indicated that the promoter region of TGF-β1 promoter between -175 to -60, the Egr-1 binding site, was identified as responsible for PLpro-induced activation of TGF-β1 promoter. Subcellular localization anlaysis of transcription factors showed the consistent finding in that PLpro triggered nuclear translocation of Egr-1, but not NF-κB and Sp-1 in A549 cells. Gene silence of Egr-1 by siRNA significantly reduced the expression of PLpro-induced TGF-β1 and pro-fibrotic genes. Furthermore, the inhibitor of the TGF-β1 receptor, SB-431542, selectively inhibited the mRNA expression of pro-fibrotic genes and latent TGF-β1 convertases. Meanwhile, mouse model by direct pulmonary injection with recombinant plasmids demonstrated PLpro expression in lung tissues induced up-regulation of TGF-β1, pro-fibrotic genes, and inflammatory cytokines.

Conclusion

The results revealed that SARS-CoV PLpro significantly triggered Egr-1 mediated activation of TGF-β1 promoter, correlating with up-regulation of pro-fibrotic responses in vitro and in vivo.