Title: Activation of TLR3 augments the production of MMPs in human lung fibroblasts via inducible NOS dependent pathway

Body: Background: Viral infections cause exacerbations of airway diseases such as asthma and chronic obstructive pulmonary disease. Nitric oxide (NO) is excessively produced in the airways of these diseases via inducible NO synthetase (iNOS) expression. Matrix metalloproteinases (MMPs) are involved in airway remodeling and contribute to the progression of pulmonary diseases. However, the effects of viral infection on the production of iNOS and MMPs are unknown. Aims: We examined in vitro the effects of polyinosinic-polycytidylic acid (poly I:C), an analog of viral RNA and a ligand for toll-like receptor (TLR)3, on the production of iNOS and MMPs in human lung fibroblasts, and on the signal transduction. Methods: The productions of MMP-1, 2, 9 and iNOS were measured by zymography or western blotting after the cells were treated with poly I:C. The translocation of nuclear factor (NF)-κB p65 and interferon regulatory transcription factor (IRF)-3 into the nucleus were examined after the treatment. We also investigated the effects of N6-(1-iminoethyl)-lysine, hydrochloride (L-NIL), an iNOS inhibitor, caffeic acid phenethyl ester (CAPE), which is an NF-κB inhibitor, and knockdown of IRF-3 on poly I:C-mediated MMPs production. Results: Poly I:C augmented the production of MMP-1, 2, 9, and iNOS expression in fibroblasts. L-NIL reduced the poly I:C-augmented production of MMPs. The translocation of NF-κB p65 and IRF-3 into the nucleus was induced by poly I:C. CAPE and knockdown of IRF-3 suppressed the poly I:C-augmented production of MMPs and iNOS. Conclusions: The activation of TLR3 induced iNOS and, subsequently, MMPs production via both NF-κB and IRF-3 signaling in lung fibroblasts.