Objectives: To explore the effect of nicotine on matrix metalloproteinases (MMPs) and RANKL expression from RA-FLS and its possible intracellular signaling mechanism.

Methods: Synovial tissues were obtained from 45 patients with active RA as well as 11 osteoarthritis (OA) and 11 noninflammatory orthopedic arthropathies (Orth.A) patients for control. The expression of AChR in synovial membrane and cultured FLS were detected by immunohistochemistry staining and Western blot. RA-FLS were treated in vitro with different concentrations of nicotine and its effect on RA-FLS viability was evaluated by cell counting kit-8. After nicotine pre-treatment on TNF-α stimulated RA-FLS, the expression of MMP-2, MMP-3, MMP-9, TIMP-1, TIMP-2, RANKL, and OPG in culture supernatant were measured by ELISA, while the change of AP-1 pathway including c-Fos and c-Jun were detected by quantitative real-time PCR and Western blot.

Results: Immunohistochemical analyses showed intense endocytoma staining for AChR in RA-FLS mainly in lining layer. The percentage of both lining and sublining AChR expressing cells were significantly higher in RA than that in OA or Orth.A (figure 1A). Further western blot showed significantly higher expression of AChR7 in RA-FLS than that in Orth.A-FLS (p<0.003, figure 1B). Nicotine (0.1 μM–50 μM) showed no cytotoxicity on RA-FLS proliferation. Pretreatment with 50 μM nicotine for 24 hours significantly promoted the secretion of MMP-3 and RANKL but inhibited TIMP-1 secretion in TNF-α stimulated RA-FLS (all p<0.05, figure 1C). Further, 25 μM and 50 μM nicotine treatment for 24 hours upregulated both mRNA and protein expression of c-Fos and c-Jun. Furthermore, c-Fos and c-Jun positive cells were significantly more in RA than that in OA or Orth.A (figure 1D).

Conclusions: Nicotine can promote MMP-3 and RANKL expression through overexpressed AChR in RA-FLS which might be involved in the pathogenesis of osteogenesis and bone destruction in RA.

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IGURATIMOD AMELIORATES BLEOMYCIN-INDUCED ALVEOLAR INFLAMMATION AND PULMONARY FIBROSIS IN MICE BY SUPPRESSING EXPRESSION OF MMP-9

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Background: Interstitial lung disease (ILD) occurs in 15% of patients with connective tissue diseases (CTD) and is difficult to manage (1). Despite advances in management strategies, CTD-ILD has a significant adverse effect on quality of life and is still a leading cause of mortality, highlighting an urgent need for optimal treatment regimens. It is known that inflammatory cytokines play an important role in alveolitis and the development of pulmonary fibrosis (2). Iguratimod (IGU) has a reported effect on preventing the inflammatory processes by inhibiting the production of various inflammatory cytokines (3).

Objectives: To investigate the potential therapeutic efficacy of IGU on mouse model of bleomycin (BLM) induced pulmonary fibrosis.

Methods: A total of 75 C57BL/6 mice were randomly and evenly divided into control group, BLM (5 mg/kg) group, BLM +IGU (90 mg/kg) group, BLM +methylprednisolone (MP, 10 mg/kg) group and BLM +pirtfenide (PF, 100 mg/kg) group. The mice were sacrificed on day 7, day 14, day 28 respectively. The lung tissue was examined by Hematoxylin and eosin staining and Masson staining to evaluate the degree of alveolitis and fibrosis, and plasma cytokines were measured.

Results: Histopathological results showed that IGU attenuated BLM-induced alveolar inflammation and decreased collagen deposition in lung tissue from day 7 till day 28. Both the pathological alveolitis scores and fibrosis scores in drug treated group (IGU group, MP group and PF group) were decreased dramatically compared with BLM group on day 7, day 14 and day 28 respectively (p<0.05). There were no statistical significances among those three groups. Cytokine profile showed that IGU decreased the level of tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6 and matrix metalloproteinase (MMP-9) which were up-regulated by BLM on day 7, day 14 and day 28 respectively (p<0.05). Furthermore, there is a strong correlation between the severity of the pulmonary fibrosis and the plasma MMP-9 levels (r=0.22, p<0.001).

Conclusions: IGU was effective in suppressing BLM-induced alveolar inflammation and pulmonary fibrosis, and it has the equal anti-inflammatory and anti-fibrotic effects as MP or PF. The therapeutic effects by IGU may be attributed to the inhibition of MMP-9 either directly or indirectly. Therefore, IGU presents as a promising agent for pulmonary fibrosis treatment.

REFERENCES: