Effects of Janus kinase (Jak) inhibitors on macrophage polarization in a mouse model of systemic sclerosis

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Background:

Systemic sclerosis (SSc) is a rare autoimmune disorder associated with immune dysregulation, vasculopathy and chronic inflammation leading to subsequent fibrosis of the skin and visceral organs such as lung in which pro-inflammatory (polarized M1) and pro-fibrotic (polarized M2) macrophages play a key role. To date, there is no disease-modifying drug for SSc patients and the identification of new therapeutic options is a priority.

Macrophage activation in pro-inflammatory phenotype is the result of interferon receptor activation by interferon gamma and involvement of JAK1/JAK2/Phospho-STAT1 pathway.

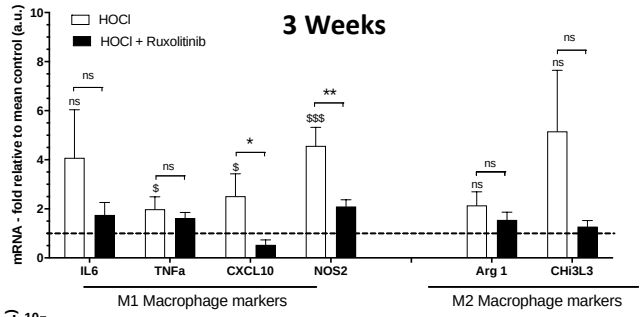
Macrophage activation in pro-fibrotic phenotype is the result of IL-4 or IL-13 receptor activation resulting in JAK1/JAK3/Phospho-STAT6 and JAK1/JAK2/Tyk2 Phospho-STAT6 pathway activation respectively.

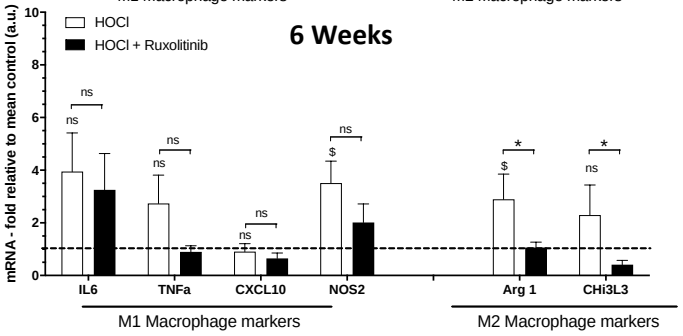
Objectives: To evaluate the effect of ruxolitinib (a Jak2/1 inhibitor) in a mouse model of SSc by highlighting the effects on macrophage polarization and fibrosis.

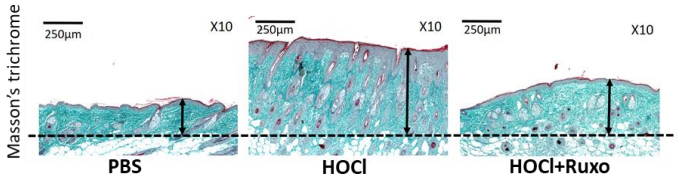
Methods:

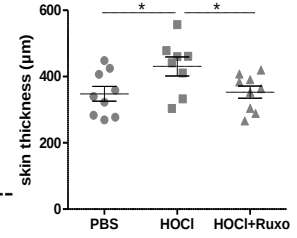
In vivo experiments: **Experimental model of SSc** was induced by intra-dermal injection of 200 µl hypochlorous acid (HOCl, extemporaneously prepared) 5 days/week for 6 weeks in female C57BL/6J mice used at 8 weeks of age. Control mice received injection of PBS. A volume of 100 µl of **Ruxolitinib** (40 mg/kg) or solvent (0.5% weight/volume carboxymethylglucose in NaCl 0.9%) was administrated by oral gavage twice a day.
A skin biopsy was performed after 3 and 6 weeks.

Skin analysis

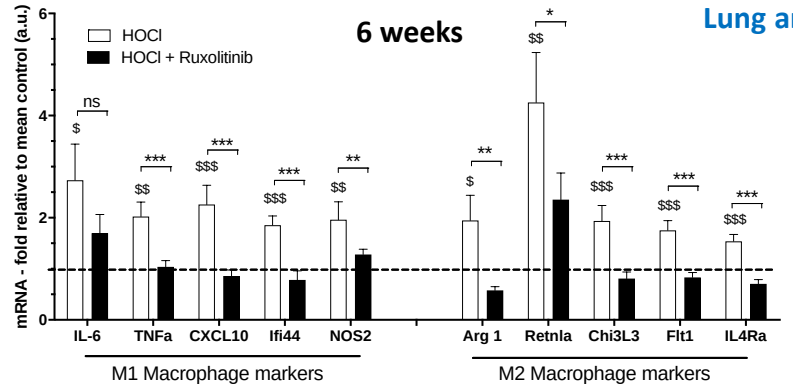




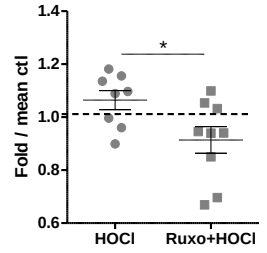


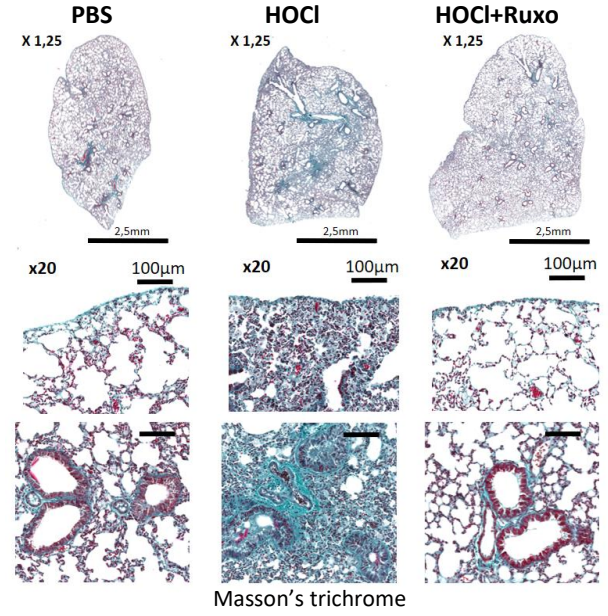


Lung analysis

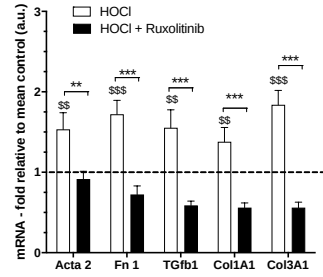


Hydroxyproline content per lung lobe





mRNA expression of fibrotic markers



Conclusion :

Ruxolitinib prevents the development of skin and lung fibrosis in a mouse model of systemic sclerosis, and significantly reduced the expression of key polarization markers of both M1 (pro-inflammatory) and M2 (pro-fibrotic) macrophages.
Our results support the notion that JAK-STAT signaling pathway play an important role in pathogenesis of SSc and sheds new light on Jakinibs as a pontential candidates for treatment of SSc and other fibrotic disorders in humans.