Background: Upregulation of the innate immune response via the activity of Toll-like receptors and the NLRP3 inflammasome have been suggested as initiating events that can drive fibrosis in systemic sclerosis (SSc) (Pharmacol Ther. 2018;192:163). Lenabasum, a cannabinoid receptor type 2 agonist, is known to activate the resolution phase of acute human innate immune responses triggered through Toll-like receptor activation, favoring production of pro-resolving lipid mediators, reducing inflammatory infiltrates, and increasing bacterial clearance (Clin Pharmacol Ther. 2018;104:675). Given the potential importance of inflammasome activation in the pathogenesis of SSc, the question remained whether lenabasum inhibits inflammasome activation.

Objectives: Assess effects of lenabasum on IL-1 β and IL-18 production induced by inflammasome activation.

Methods: Primary human macrophages were derived from monocytes, stimulated with LPS and ATP to active inflammasomes and cultured with lenabasum. Levels of IL-1 β and IL-18 were measured in cell supernatants by ELISA. Separately, human PBMC were activated with 0.1 μ g/ml LPS $\pm$ 10 μ M lenabasum for 24 hours, and effects of lenabasum on the levels of IL-1 β and other pro-inflammatory cytokines were measured.

Results: Lenabasum significantly inhibited IL-1 β and IL-18 secretion by monocyte-derived macrophages, with IC₅₀ = 66.73 $\pm$ 3.92 nM and 349.23 $\pm$ 21.27 nM, respectively. A control inflammasome activation inhibitor, MCC950, which showed IC₅₀ = 18.33 $\pm$ 1.22 nM for IL-1 β inhibition and IC₅₀ = 21.43 $\pm$ 0.81 nM for IL-18 inhibition.

Conclusion: Lenabasum inhibits inflammasome activation, which could contribute to potential therapeutic efficacy in SSc and other autoimmune diseases.

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Figure

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AB0153

ADIPOSE-DERIVED STROMAL/STEM CELLS FROM SYSTEMIC SCLEROSIS PATIENTS SUCCESSFULLY EXERT A PARACRINE ANTI-FIBROTIC ACTIVITY AND INDUCE A PRO-ANGIOGENIC PHENOTYPE OF SCLERODERMA FIBROBLASTS IN VITRO

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Background: Adipose-derived stromal/stem cells (ADSCs) are multipotential non-hematopoietic progenitor cells with anti-inflammatory, immunomodulatory and regenerative effects. They have the advantage of accessibility and potent pro-angiogenic effects when compared with other stem cells, such as bone-marrow derived stem cells. Recent studies have shown that autologous fat grafting may be effective in the treatment of fibrotic and vascular complications in systemic sclerosis (SSc), despite a pro-fibrotic signature.

Objectives: Aim of the study was to better characterize the proliferative and secretory profile of ADSCs in normoxic and hypoxic conditions, and to evaluate the mechanisms by which ADSCs exert these observed clinical effects.

Methods: Adipose tissue samples were obtained by liposuction from 12 SSc patients and 10 healthy donors (HD). ADSCs were purified according to their adherence to the plastic and characterized to express specific MSC surface antigens by flow cytometry analysis. Proliferation of ADSCs from SSc patients and normal controls was evaluated in normoxic and hypoxic conditions. Fibroblasts and ADSCs derived from SSc patients were co-cultured in direct and indirect culture systems and compared to HD. Fibroblasts proliferation, mRNA expression and protein secretion of VEGF and known fibrotic mediators including TGF β -1, TGFR, CTGF, Collagen type I (Col I) were analyzed in the same conditions.

Results: Normoxic and hypoxic culture conditions did not modify the proliferation rate of both normal and SSc ADSCs. Hypoxia significantly increased mRNA expression of VEGF by HD and SSc ADSCs but had no effect on the mRNA expression of pro-fibrotic mediators, ie TGF β and TGFR. Normal and SSc fibroblast proliferation was significantly reduced in both co-culture systems ($p < 0.001$) and by treatment with normoxic and hypoxic conditioned medium (CM) ($p=0.001$ and $p=0.002$). In the same conditions, mRNA expression and protein secretion of TGF- β 1, CTGF and Col I were significantly reduced ($p = 0.003$, $p = 0.02$, $p=0.04$). These results were confirmed when normal and SSc fibroblasts were cultured in the presence of ADSCs normoxic and hypoxic CM ($p=0.02$ and $p=0.01$). Furthermore, a significant increase in mRNA expression and production of VEGF was observed in SSc fibroblasts cultured in the presence of normoxic and hypoxic CM ($p = 0.002$ and $p < 0.0001$, respectively).

Conclusion: We found that treatment with the medium from normoxic and hypoxic preconditioned ADSCs has an anti-fibrotic effect through both the inhibition of fibroblast proliferation and key mediators of fibrosis. The increased expression of VEGF by SSc fibroblasts in the presence of normoxic and, even more, hypoxic ADSCs CM, suggests that ADSCs can induce a paracrine pro-angiogenic phenotype, even in fibroblasts with a pro-fibrotic signature. Altogether these data show that ADSCs may exert their anti-fibrotic and pro-angiogenic effects on SSc fibroblasts by the secretion of paracrine factors, partly explaining the mechanisms underlining beneficial clinical results of fat graft in SSc patients.

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AB0154

MERTK AND THE RESOLUTION OF INFLAMMATION IN IGG4-RELATED DISEASE

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Background: IgG4-Related Disease (IgG4-RD) is characterized by fibrotic lesions, serum IgG4 elevation, and prompt response to glucocorticoids. B and T lymphocytes are considered the initiators of tissue inflammation in IgG4-RD, but the prominent stromal reaction observed at disease sites suggest that a dysregulation of processes involved in the resolution of inflammation could be pathologically relevant as well. Mer receptor tyrosine kinase (MerTK) and its ligands protein S (Pros1) have a pivotal role in the resolution of inflammation through the activation of a well-characterized signaling pathway that ultimately dampens the immune response and promotes the recovery of tissue function. MerTK and the processes involved in the resolution of inflammation have never been addressed in IgG4-RD.