The Editor's Choice

Abe R

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Inhibitory effect of kaempferol on skin fibrosis in systemic sclerosis by the suppression of oxidative stress

There is growing evidence that vasculopathy-induced hypoxia and oxidative stress enhance the process of fibrosis in systemic sclerosis (SSc). Kaempferol is a natural flavonoid widely found in various vegetables and fruits, and has been reported to have excellent antioxidant activity. Skiguchi A et al elucidated the effect of kaempferol on skin fibrosis and the mechanism of the inhibitory regulation of fibrosis by kaempferol. Kaempferol injection significantly inhibited bleomycin-induced dermal fibrosis in mice. The number of myofibroblasts, T-cells, and macrophages in lesional skin was significantly decreased by kaempferol injections. Kaempferol administration also significantly suppressed the bleomycin-induced oxidative stress signal in OKD48 mice. Additionally, mRNA levels of oxidative stress-associated factors, such as HO-1 and NOX2 in sclerotic skin were significantly decreased by kaempferol. Kaempferol also reduced apoptotic cells in the lesional skin of bleomycin-treated mice. Furthermore, the oxidant-induced intracellular accumulation of ROS in SSc fibroblasts was inhibited by kaempferol treatment. Administration of kaempferol might be an alternative treatment for skin fibrosis in SSc.

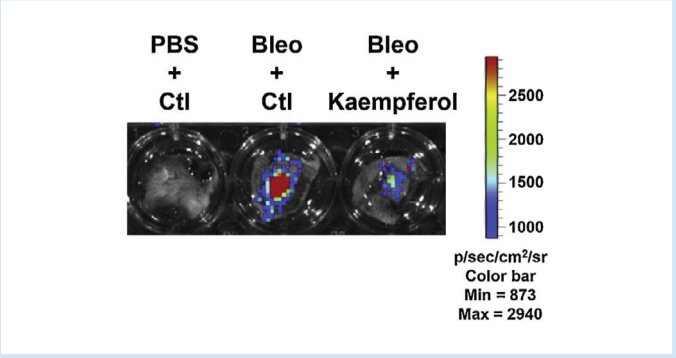

Fig. 2. Kaempferol injection reduced oxidative stress in the bleomycin-induced fibrotic skin *in vivo*. (A) Representative image of luminescence signals in the skin of OKD48 mice treated with subcutaneous injections of control PBS or bleomycin, and treated with intraperitoneal injection of kaempferol or control DMSO for 5 days. The color scale bar shows the photon counts (photon (p)/sec/cm²/sr).

The significance of tumor cells-derived MFG-E8 in tumor growth of angiosarcoma

Previous studies have indicated that MFG-E8 enhances tumor cell survival, invasion and angiogenesis. However, the role of MFG-E8 in angiosarcoma (AS) has not been clarified. Fujiwara C et al elucidated the mechanism of the regulation by MFG-E8 in AS and the association between MFG-E8 and clinicopathological features of AS. The expressions of MFG-E8 in murine and human AS cells were significantly higher than those in melanoma cells, macrophages and endothelial cells. Depletion of MFGE8 in murine AS cells by siRNA significantly inhibited the formation of capillary-like structures and migration, but not proliferation. Administration of anti-MFG-E8 Ab significantly inhibited tumor growth. Progression-free survival and overall survival time of the patients of AS with high expression of MFG-E8 were significantly shorter than those of AS with low expression of MFG-E8. AS-derived MFG-E8 might enhance tumor growth via angiogenesis and the induction of TAMs in autocrine/paracrine manner, and administration of anti-MFG-E8 Ab could be a therapeutic potential for AS.

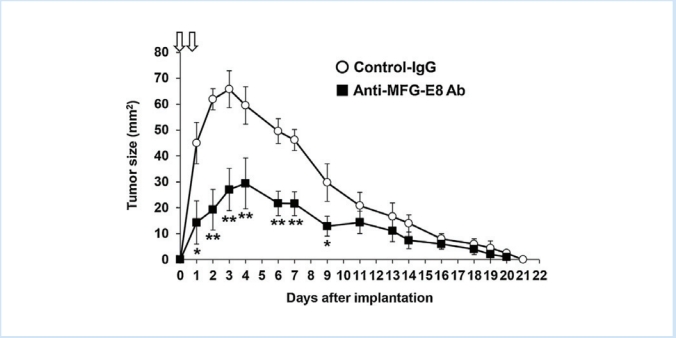

Fig. 3. Administration of anti-MFG-E8 antibody significantly inhibited the infiltration of TAMs and tumor growth of AS *in vivo*. (A) Tumor growth of AS tumors in mice injected with control-IgG or anti-MFG-E8 antibody. n = 5 mice in each group. Photographs of AS tumors in control-IgG or anti-MFG-E8 antibody injected mice at 2, 4, 6 and 9 days after implantation.

TNF-α and IL-17A induce the expression of lymphoepithelial Kazal-type inhibitor in epidermal keratinocytes

Serine proteases have important roles in skin barrier function and desquamation, and the aberrant expression or the dysfunction of serine proteases is associated with the pathogenesis of skin diseases. Serine protease activities are tightly regulated by serine proteases such as kallikrein-related peptidases (KLKs) and serine protease inhibitors such as lympho-epithelial Kazal-type related inhibitor (LEKTI). Sugihara S et al investigated the effects of the cytokines on the expression of LEKTI in epidermal keratinocytes. TNF-α and IL-17A significantly induced the expression of LEKTI in NHEKs. The immunohistochemical and tape-stripping analysis revealed that psoriatic skin lesions had higher LEKTI expression compared to normal skin and AD lesions. Trypsin- and chymotrypsin-like protease activities in the culture media were upregulated 3-5 days later but attenuated 6-7 days later period by these cytokines. In epidermal keratinocytes, the Th1&Th17 cytokines TNF-α and IL-17A induce the expression of serine protease inhibitor LEKTI, and it might occur to suppress the increase in the serine protease activities under inflammation.

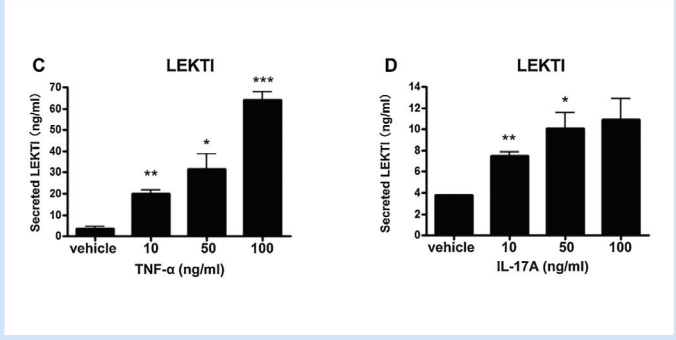

Fig. 1. TNF-α and IL-17A induce the expression of LEKTI in NHEKs. NHEKs were stimulated with TNF-α and IL-17A as 10, 50, 100 ng/ml and non-stimulated cells(vehicle) for 24 h (C, D)