Keratinocyte-mediated activation of TGFB maintains skin-recruiting memory CD8+ T cells

T Hirai1, Y Yang1,*, L Barbolin1,*, L Beura1, D Masopust1 and DH Kaplan1
1 Departments of Dermatology and Immunology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 2 Department of Dermatology, St. Luke’s International Hospital, Tokyo, Japan

Tissue-derived factors are critical for the development and persistence of skin-resident memory CD8+ T cells. Regulation of activation of TGFB by integrins α5β1, and α5β3 expressed on keratinocytes is required for residence of epidermal Treg that are lost in mice lacking the integrins (Itgb6/Itgb8-mice). However, whether skin-derived signals also affect recirculating memory cells that are only transiently in skin have been never noted. Here, we show that after resolution of skin vacuca virus (SVV) infection, antigen-specific circulating memory CD8+ T cells migrate into skin. Using CD8+ T cell specific Cre, Langerin-DTR mice and independent memory-matched psoriasis patient, while the counterpart with K17 silence cannot activate neither CD4+ or CD8+ T cells injected into taped WT and Langerin-DTR mice resulted in psoriatic-like skin inflammation of psoriasis. Inducing keratinocytes-directed, T cell mediated effector immune responses in skin is a major strategy in therapeutic drug development. To explore the cytokine environment within this nonlymphoid tissue shapes the differentiation state and function of CD8+ T cells, we analyzed tissue derived cytokines in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.

Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

T Yang1,*, X Zhang1, A Chen1, Y Xiao1, S Sun1, J Tan1, Y Cao1, J Chen2,*, L Li1* and K Huang1
1 Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2 Key Laboratory of Diagnostic Medicine designated by the Ministry of Education, Chongqing Medical University, Chongqing, China

Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypical fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-qPCR demonstrated that PGRN was also elevated in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.

Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

T Yang1,*, X Zhang1, A Chen1, Y Xiao1, S Sun1, J Tan1, Y Cao1, J Chen2,*, L Li1* and K Huang1
1 Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2 Key Laboratory of Diagnostic Medicine designated by the Ministry of Education, Chongqing Medical University, Chongqing, China

Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypical fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-qPCR demonstrated that PGRN was also elevated in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.

Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

T Yang1,*, X Zhang1, A Chen1, Y Xiao1, S Sun1, J Tan1, Y Cao1, J Chen2,*, L Li1* and K Huang1
1 Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2 Key Laboratory of Diagnostic Medicine designated by the Ministry of Education, Chongqing Medical University, Chongqing, China

Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypical fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-qPCR demonstrated that PGRN was also elevated in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.

Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

T Yang1,*, X Zhang1, A Chen1, Y Xiao1, S Sun1, J Tan1, Y Cao1, J Chen2,*, L Li1* and K Huang1
1 Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2 Key Laboratory of Diagnostic Medicine designated by the Ministry of Education, Chongqing Medical University, Chongqing, China

Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypical fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-qPCR demonstrated that PGRN was also elevated in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.

Progranulin promotes bleomycin-induced skin sclerosis by enhancing TGF-β/Smad3 signaling through up-regulation of TGF-β type I receptor

T Yang1,*, X Zhang1, A Chen1, Y Xiao1, S Sun1, J Tan1, Y Cao1, J Chen2,*, L Li1* and K Huang1
1 Department of Dermatology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2 Key Laboratory of Diagnostic Medicine designated by the Ministry of Education, Chongqing Medical University, Chongqing, China

Progranulin (PGRN) is an autocrine growth factor with multiple physiological and pathological functions. Previous reports demonstrated PGRN could increase dermal fibroblasts in wound healing and activate cancer associated fibroblasts in some cancers. Because systemic sclerosis (SSc) is a prototypical fibrosis-related disorder, here, we aimed to clarify the role and mechanism of PGRN in bleomycin (BLM)-induced model of SSc for the first time. We observed that the serum PGRN levels were increased in Chinese SSc patients compared with healthy controls. Immunohistostaining and RT-qPCR demonstrated that PGRN was also elevated in the lesion from mice model of BLM-induced dermal fibrosis. Additionally, in BLM-treated mice, PGRN deficiency not only attenuated dermal fibrosis but also decreased the differentiation of myofibroblasts. The reduced progression of skin sclerosis in PGRN-deficient mice was associated with decreased level of type I receptor (TIR I) and decreased level of p-Smad3 signaling via upregulation of TIR I. PGRN may be a new therapeutic target for SSc.