Title

Therapeutic agent for fibrosis and inhibitor of nuclear accumulation of phosphorylated Smad

Background and Purpose of Research

Idiopathic pulmonary fibrosis (IPF) is a disease the symptoms of which includes shortness of breath caused by excessive fibrotic response of lung interstitial tissue. Available data are said to suggest that the prevalence rate of IPF would be such that ten to twenty people of ten thousand people are affected, but the number of potential patients is assumed to be more than tenfold. Because the cause of the disease is unknown, and there is no established medical treatment, IPF is designated as an intractable disease in Japan. Pirfenidone and Nintedanib are the two therapeutic agents that are approved in Japan. Ehilst these conventional therapeutic agents help managing the forced vital capacity, they are not capable of extending survival in patients. As such, there is need for a therapeutic agent based on novel approaches. The purpose of this research is to provide a therapeutic or preventive for fibrosis based on new mechanism of action.

Summary of Research Results

Transforming growth factor- β 1(TGF β 1) binds to receptor, and promotes phosphorylation activity of Smad (an intracellular signaling molecule), which leads to nuclear accumulation of the phosphorylated Smad, thereby induces expression of collagen and α -smooth muscle actin (α -SMA), which cause fibrosis. Researchers focused on sphingolipid which exists abundantly in cell membrane lipid raft which forms scaffold of the binding of TGF β 1 to receptor, and investigated into what reference it bears to TGF β 1 signaling. The investigation revealed that glucosylceramide (GlcCer) synthase inhibitor or lactosylceramide (LacCer) synthase inhibitor blocks the synthase of GlcCer or LacCer, which is contained in the sphingolipid, and inhibits nuclear accumulation of phosphorylated Smad, thereby suppresses expression of collagen and α -SMA, which cause fibrosis. A new mechanism of action was found in the field of therapy and prevention of fibrosis.

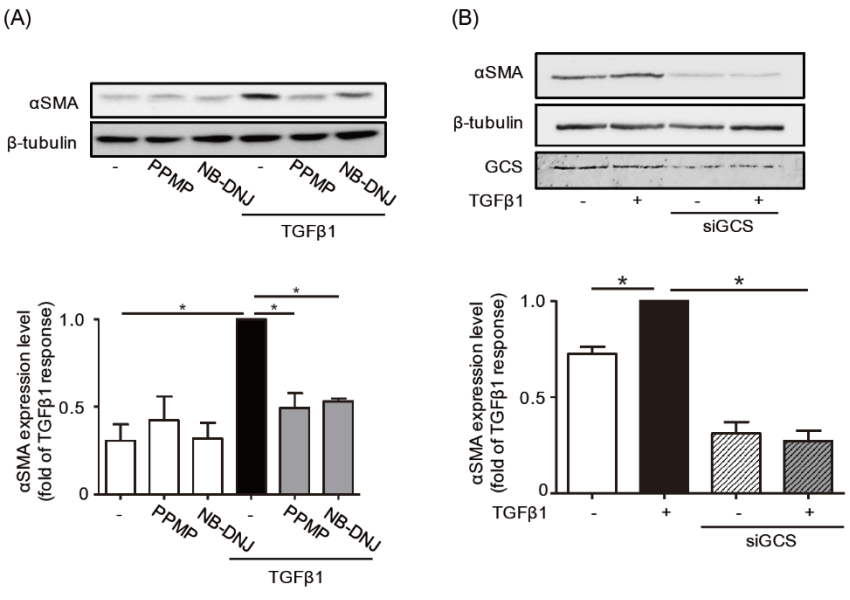

Fig. 1; (A) PPMP and N-Butyldeoxynojirimycin (NB-DNJ), which are GlcCer synthase inhibitor and

LacCer synthase inhibitor, blocked induction of expression of α-SMA by treatment of TGF β 1. (B) Knockdown of GlcCer synthase by adaptation of siRNA demonstrated that treatment of TGF β 1 did not lead to induction of expression of α-SMA.

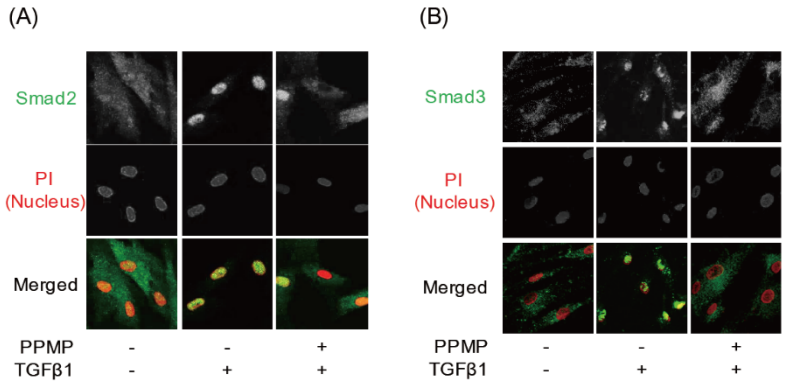

Fig.2; Immunostaining of cells provided illustration of localization of Smad 2 and Smad 3 after 3 hours of TGF β 1 treatment. PPMP inhibited nuclear accumulation of Smad.

Patent Status

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Advantages

Inasmuch as the mechanism of action involving synthesis expression of fibrosis-related protein caused by phosphorylated Smad does not vary from tissue to tissue, the use of this therapeutic agent for fibrosis is not limited to lung, but also is applicable to kidney, liver, heart, skin, bone marrow, pancreas, eyes, and so forth.

Applications

Therapy and prevention of fibrosis.

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