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Tse-Hua Tan

National Health Research Institutes, Taiwan

MAP4K3/GLK is a novel therapeutic target for IL-17A-mediated autoimmune disease

T-cell receptor signaling activates the kinase MAP4K3 (also named GLK) by inducing its direct interaction with the upstream adaptor protein SLP-76. Activated GLK directly phosphorylates and activates PKC-θ, which is required for NF-κB activation in T cells. Moreover, GLK-deficient mice show impaired Th17 differentiation and are resistant to IL-17A-mediated experimental autoimmune encephalomyelitis (EAE). Consistently, autoimmune SLE and rheumatoid arthritis (RA) patients show significantly increased GLK levels in T cells; the percentage of GLK-overexpressing T cells is correlated with autoimmune disease severity. Recently, we generated and characterized T-cell specific GLK transgenic (Lck-GLK Tg) mice and found that these transgenic mice spontaneously develop autoimmune diseases with an induction of systemic inflammation and an increase of autoantibodies (ANA, anti-dsDNA, rheumatoid factor). We found that GLK signaling specifically induced IL-17A transcription in the T cells of GLK transgenic mice. Moreover, the induction of serum IL-17A and autoantibodies in Lck-GLK Tg mice was abolished by treatment of a GLK inhibitor. The disease severity and serum IL-17A levels in EAE or collagen-induced arthritis mouse models were also attenuated by the GLK inhibitor treatment. In addition, GLK protein levels were also overexpressed in tumor tissues of lung cancer or hepatoma patients. The GLK overexpression was correlated with increased recurrence risks and poor recurrence-free survival rates of lung cancer and hepatoma. Collectively, MAP4K3/GLK is a novel diagnostic/prognostic biomarker and therapeutic target for cancer and IL-17A-mediated autoimmune diseases.

Biography

Tse-Hua Tan received his PhD degree in Molecular Biology at Princeton University and did his Postdoctoral research at Rockefeller University. He was a Full Professor and the Director of Immunology Fellowship Training Program at Baylor College of Medicine, Houston. He was a Research Scholar of the Leukemia & Lymphoma Society, USA. Currently, he is a distinguished Investigator and the Founding Director of Immunology Research Center in the National Health Research Institutes, Taiwan. He has made significant contribution in studying JNK siganling, apoptosis, and T-cell activation. He has published more than 116 papers with over 8,700 citations.

ttan@nhri.org.tw

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