B6-hTREM2

Strain Name：B6/JGpt-hTREM2^{em1Cin}/Gpt

Strain Type：Knockin

Strain Number：T056008

Background：C57BL/6JGpt

Description

Triggering receptor expressed on myeloid cells-2 (TREM2) is a transmembrane receptor of the immunoglobulin superfamily, highlighted as a major pathology-induced immune signaling hub. TREM2 interacting with a wide array of ligands, which encompass a wide array of anionic molecules, free and bound to the plasma membrane, including bacterial products, DNA, lipoproteins, and phospholipids. In physiology, TREM2 activity is restricted to a small number of niches, but in pathology, the TREM2 pathway becomes central for sensing tissue damage and restricting its spread [1].

Signal activation and regulation in TREM2 is a complex process that depends on tissue microenvironment and intracellular state. Current studies have shown that signal transduction in TREM2 is very complex. First, TREM2 binds to different ligands that regulate the direction of signal transduction in TREM2 and induce different effects [2]. For example, in Alzheimer's disease (AD) brains, TREM2 can directly interact with pathological β-amyloid (Aβ) oligomers form plaques, a hallmark of AD pathology [3]. Second, parallel cellular processes may regulate TREM2 signaling. Because TREM2 signaling seems to be most relevant in the context of tissue damage and pathology, it is important to consider the crosstalk between TREM2 signaling and other pathways activated by danger signals [4].

TREM2 plays an important physiological role in tissue development and/or maintenance, at least in the context of particular niches, the brain and bone, by controlling the function of TREM2-expressing myeloid cells: microglia and osteoclasts. TREM2 has been shown to play an important role in inducing phagocytosis, inflammatory resistance, and promoting cell survival [1]. Crossing mice deficient in TREM2 with models of neurodegeneration elucidated the specific roles of TREM2 in this context: promoting microglial survival and

their phenotypic transition to DAMs, a subtype restricting plaque growth by creating a physical barrier around Aβ aggregates. The importance of highlights TREM2 in neurodegenerative diseases, and the possibility of as potential therapeutic targets [5]. Secondly, accumulating evidence suggests a role of TREM2 in tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). A recent study found that TREM2 was significantly upregulated on peripheral blood monocytes and on TAMs in lung cancer patients and in tumor-bearing mice. TREM2 levels of macrophages around tumor cells showed a positive correlation with tumor progression. In addition, TREM2+ myeloid cells had a more potent inhibitory effect of T cell proliferation in vitro [6]. In addition, chronic low-level inflammatory states and accumulation of apoptotic bodies and protein aggregates are common features of obesity, fatty liver, and atherosclerosis. TREM2 plays a key role in the pathologic process by promoting phagocytosis and resisting inflammation to inhibit tissue damage.

TREM2 signaling is emerging as a signaling hub in AD, cancer, and metabolic diseases, with activation of TREM2 enhancing signal transduction and promoting the functional activity of macrophages. In tumors, the anti-inflammatory and immunosuppressive activity of TREM2 promotes tumor growth and immune escape. GPT constructed TREM2 humanized mice model on B6 and BALB/ C backgrounds, to evaluate the efficacy of monoclonal antibodies or small molecule drugs targeting the TREM2 signaling pathway, and to explore immunotherapy for myeloid cell-mediated diseases by exploring the function and regulatory mechanism of the central hub of TREM2 pathological signaling.

Strategy

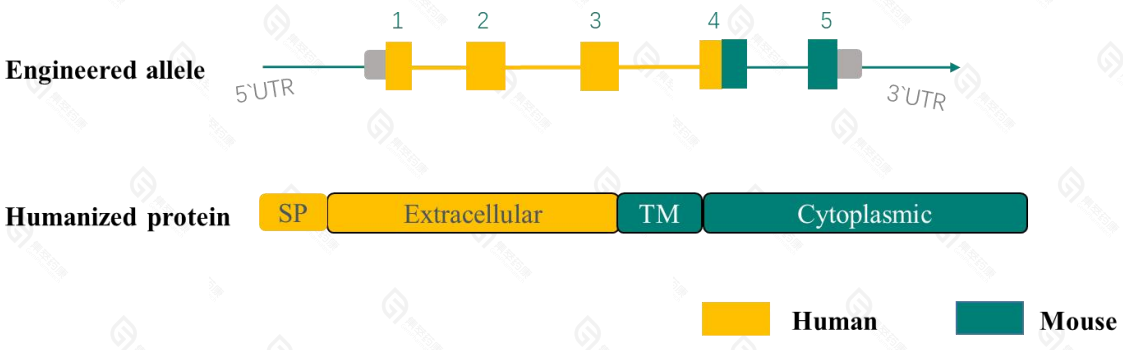

Fig.1 Schematic diagram of B6-hTREM2 humanized mice.

SP: Signal peptide, TM: Transmembrane

Application

1. Pharmacodynamic evaluation and mechanism of neurodegenerative diseases

2. Tumor immune efficacy evaluation and mechanism study

3. Pharmacodynamic evaluation and mechanism of metabolic syndrome

Data support

1. Human TREM2 mRNA expression analysis

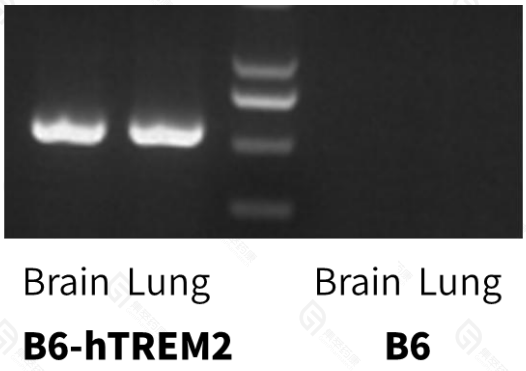

Fig.2 Detection of human TREM2 expression.
mRNA expression of human TREM2 was detected in the brain and lung of B6-hTREM2 but nor WT mice.

2. Human TREM2 Protein expression analysis

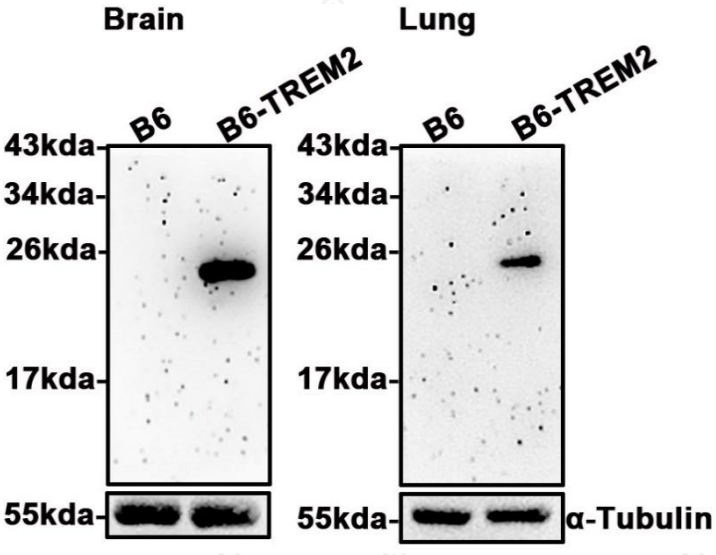

Fig.3 Detection of human TREM2 protein expression.

Human TREM2 expression were detected in the brain and lung of B6-hTREM2 but nor WT mice.

References

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