C57BL/6-hSTING1

Strain Name: C57BL/6JGpt-*Sting1*$^{em1Cin(hSTING1)}$*/Gpt*
Strain Type: Knock-in
Strain ID: T049781
Background: C57BL/6JGpt

Description

STING1 (Stimulator of Interferon Response cGAMP Interactor 1) gene, also known as Tmem173, enables 2', 3'-cyclic GMP-AMP binding activity, cyclic-di-GMP binding activity, and ubiquitin protein ligase binding activity. It is located in several cellular components, including the perinuclear region of the cytoplasm, autophagosome, and peroxisome. STING1 is involved in several processes, including defense response to other organisms, macroautophagy, regulation of upstream of interferon-beta and inflammatory response, and positive regulation of transcription by RNA polymerase II.

STING represents a highly attractive and promising target for cancer immunotherapy. Direct activation of STING in the tumor microenvironment leads to potent and systemic tumor regression[1]. Tumor-derived DNA can be engulfed by tumor-infiltrating DCs, promoting tumor-specific antigen presentation and cytotoxic T cell activation in a STING-dependent way[2]. Furthermore, activation of the STING signaling cell intrinsically improves differentiation and antitumor functions of Th1 and Th9 cells by increasing their respective production of interferon-gamma (IFN-γ) and interleukin-9[3]. In some cases, however, STING can also play pro-tumorigenic roles in the background of chronic inflammation. Chromosomally unstable tumor cells co-opt chronic activation of noncanonical NF-κB signaling downstream of STING to promote cell invasion and metastasis[4].

Overactivation of STING can trigger an undesirable inflammatory response and lead to autoimmune diseases. A gain-of-function mutation of this gene has been implicated in STING-associated vasculopathy with onset in infancy (SAVI). Patients develop widespread systemic inflammation due to increased levels of interferon beta (IFN-β). JAK inhibitors are considered to be a promising treatment according to several recent case reports[5,6]. Disturbed self-DNA metabolism caused by a mutation endonuclease gene, another rare genetic disorder, Aicardi–Goutières syndrome[7]. Similarly, familial chilblain lupus is a monogenic form of cutaneous lupus erythematosus caused by loss-

of-function mutations in the nucleases TREX1 or SAMHD1[8]. All these presentations in disease animal models can be associated with STING.

STING is also associated with neurological disorders. It is reported that a deficiency of STING signaling in the embryonic cerebral cortex leads to neurogenic abnormalities and autistic-like behaviors[9]. Interestingly, type I interferon signaling of STING has also been reported to control nociception in sensory neurons[10]. Thus, STING agonists may also alleviate chronic pain, including cancer pain. Furthermore, STING-mediated inflammation is also associated with several neurodegenerative diseases, including Parkinson's disease and amyotrophic lateral sclerosis (ALS).

GemPharmatech using gene editing technology to replace the full length of STING in B6 mice with the corresponding humanized gene fragment, and developed the B6-hSTING1 humanized mouse model, this strain is an ideal model for the efficacy and safety evaluation of drugs targeting STING.

Strategy

Fig.1 Schematic diagram of STING1 humanization strategy in B6-hSTING1 mice.

Application

1. Efficacy and safety evaluation for anti-STING drugs
2. Research on anti-tumor drugs
3. Research on autoimmune diseases
4. Research on neurological diseases

Supporting data

1. STING mRNA expression analysis

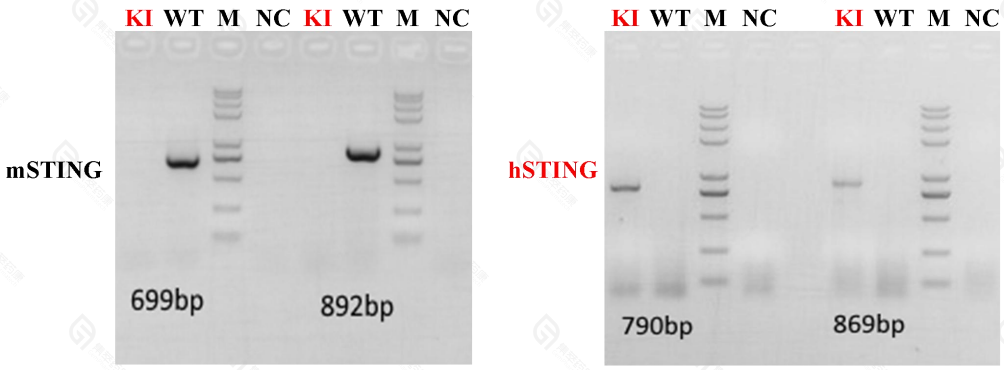

Fig 2. Expression of STING mRNA in B6-hSTING1 mice.

Specific analysis of the expression of STING gene in B6-hSTING1 mice using RT-PCR. Mouse STING mRNA was detectable only in spleen of wild-type mice，and human STING mRNA was detectable only in spleen of B6-hSTING1 homologous mice.

2. STING protein expression analysis

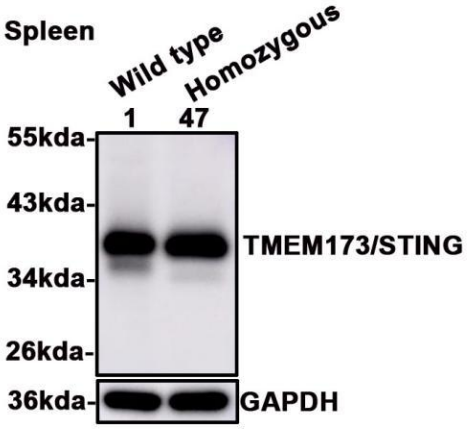

Fig.3 Detection of STING expression in B6-hSTING1 mice.

The cross-reaction antibody was used to detect the mouse endogenous and humanized STING expression. The expression of STING protein was detected in the spleen of both B6-hSTING1 homologous and B6 wild type mice by western blotting.

References

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