

C57BL/6-Tnk1 mut

Strain Name: C57BL/6-Tnk1^{em1Cin(S502E)}/Gpt

Strain Type: Knock-in

Strain ID: T056722

Background: C57BL/6JGpt

Description

The biological function and regulation of TNK1, a non-receptor tyrosine kinase that acts as an activator of innate immunity and inflammation through NF- κ B activation, STAT1 activation, and proinflammatory cytokine release, is unknown [1]. 14-3-3 release of TNK1 allows TNK1 to aggregate in ubiquitin-rich puncta and become active. However, TNK1 binding to 14-3-3 requires phosphorylation of the proline-rich structural domain S502, and mutations in S502 result in a reduction of TNK1 binding to 14-3-3 protein to near background levels. 14-3-3 controls TNK1 accumulation on ubiquitin clusters. The increased stability of TNK1 lacking UBA, coupled with increased TNK1 aggregation due to 14-3-3 binding site deletion, may provide a high enough local concentration of TNK1 Δ UBA-AAA to promote kinase oligomerization and activation, leading to tumor growth. Thus TNK1 is a ubiquitin-binding and 14-3-3 regulatory kinase that targets and blocks tumor growth [2].

The model is a point mutation, and in comparison to the human protein sequence, murine Tnk1 S498 is equivalent to human TNK1 S502. The murine Tnk1 (S498E) mutation results in reduced phosphorylation of the binding site to the 14-3-3 protein, which fails to activate ubiquitination and thus promotes tumor growth. This model can be used to evaluate the tumor suppressive effect of drugs targeting mutations at this locus.

Strategy



Figure 1 Schematic representation of the Tnk1(S498E) point mutation strategy in C57BL/6-Tnk1 mut mice

Application

1. Validation of the anti-tumor effects of drug molecules targeting TNK1 (S502E).
2. Anti-tumor research.

Data Support

1. Gene identification data of C57BL/6-Tnk1 mut mice

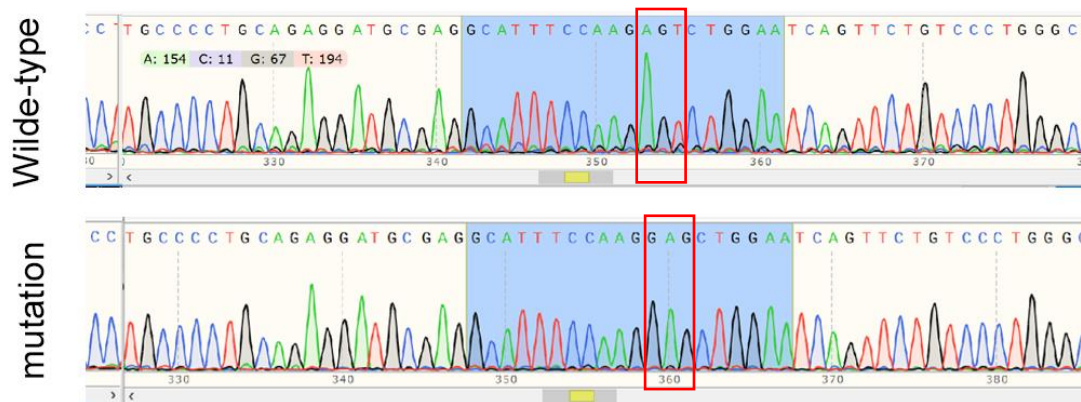


Figure 2 Gene identification results of C57BL/6-Tnk1 mut mice

Genetic identification assay of C57BL/6-Tnk1(S498E) mice showed that the S498 locus was successfully mutated from AGT base to GAG base in C57BL/6-Tnk1(S498E) mice compared to wild-type C57BL/6.

References

- [1] Armacki, M, et al. Thirty-eight-negative kinase 1 mediates trauma-induced intestinal injury and multi-organ failure. J. Clin. Invest. 128, 5056–5072 (2018).
- [2] Chan TY, Egbert CM, Maxson JE, et al. TNK1 is a ubiquitin-binding and 14-3-3-regulated kinase that can be targeted to block tumor growth. Nat Commun. 2021 Sep 9;12(1):5337.

