INHIBITION OF GAS6/MERTK SIGNALING BY NOVEL MERTK ANTIBODY, 20A77, EXERTS SIGNIFICANT ANTI-TUMOR EFFICACY WITH LITTLE RETINAL DEGENERATION IN MICE

Atsushi Sawada*, Motomichi Togawa, Aki Takaoka, Toshikazu Inoue, Koji Nakamura. Chiome Bioscience Inc., Tokyo, Japan

Background Mer Receptor Kinase (MerTK) is a member of TAM (Tyro-3, AXL, MerTK) family of receptor tyrosine kinase and known as a macrophage receptor that mediates the efferocytosis. MerTK interacts with apoptotic cells through its ligands, Gas6 or protein S, and promotes the polarity of tumor-associated macrophages toward M2 phenotype. Recent studies have revealed that MerTK signaling is involved in the immune suppression in the tumor microenvironment and specific inhibition of MerTK signaling suppressed tumor progression. On the other hand, MerTK also plays an essential role in homeostasis of the retina through its ligands, Tubby and Tulp1 and the mutations in these genes cause retinal degeneration. Thus, blockage of MerTK signaling have a potential risk for the retinal toxicity.

Methods Anti-MerTK monoclonal antibodies which recognized both with mouse and human antigen were established by immunization of recombinant human MerTK proteins in MerTK-deficient mice. Isolated antibodies were analyzed their blocking activity against Gas-6 induced MerTK auto-phosphorylation by using MerTK-expressing cell-based assay. These antibodies were also analyzed their Inhibition activity of Tulp1-MerTK binding. The anti-tumor activity of isolated antibodies, 20A77 and 24A1, was evaluated in mouse colorectal CT26 bearing syngeneic mice model as monotherapy and in combination with anti-PD-1 antibody. In addition, retinal deficiency of 20A77 treated mice was analyzed histologically.

Results The isolated antibodies, 20A77 and 24A1, specifically recognized with both mouse and human MerTK and inhibited Gas6-dependent MerTK auto-phosphorylation. In contrast, these antibodies didn’t inhibit the Tulp1-MerTK binding. The treatment of either 20A77 or 24A1 antibody into CT26 bearing mice resulted in the reduction of the tumor growth. Tumor Infiltrated Lymphocyte (TIL) analysis revealed that the ratio of M1 polarized macrophage was increased in 20A77 treated mice. Moreover, the combination of anti-MerTK and anti-PD-1 antibody treatment indicated enhanced anti-tumor responses than any of single-agents of antibody treatment. Lastly, we analyzed the histological defect in the eyes of 20A77 treated mice. No deficiency of retina was detected in medical effective dose of 20A77 treated mice. However, increased amount of 20A77 treatment caused retinal degeneration.

Conclusions Novel anti-MerTK antibody, 20A77, which selectively inhibited GAS6-mediated MerTK signaling showed significant anti-tumor activity without retinal degeneration in a mouse model. Our results suggest that the strategy for ligand-selective inhibition of MerTK signaling by the specific antibody could become a novel treatment option with lower retinal toxicity for solid tumors.

REFERENCES