SCIENCE FOR THE BENEFIT OF HUMANITY

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Modified Anti-TNFR Antibodies for Improved Treatment of Tumors

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Technology Summary

Proliferative diseases, such as non-Hodgkins lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) are currently treated by combinations of chemotherapy, monoclonal antibodies, immunotherapy, and radiation. However, there remains a particular need for the development of therapeutic antibodies with both specificity and reduced toxicity to the patient. One approach is to target members of the Tumor Necrosis Factor Receptor (TNFR) superfamily, such as CD40, for the design of engineered agonistic antibodies. There has been a steady effort to develop anti-CD40 antibodies that can act as an activating ligand for CD40 and mount an immune response against neoplastic diseases by stimulating apoptosis and T-cell responses. The main limitation here is the non-selective toxicity caused by the release of cytokines by the activated T-cells. Therefore, there remains a need to develop an anti-CD40 immunotherapy that can act against a specific tumor target.

Our scientists have discovered that the activation of the immune response by agonistic CD40 antibodies requires the engagement of the inhibitory IgG Fc receptor FcγRIIB. They engineered an anti-CD40 antibody with a modified Fc region that has 30-fold increased binding affinity to FcγRIIB, and this antibody showed a 10-fold increase in the tumor-specific cytotoxic T-cell response in lymphoma and melanoma models. This modified antibody is also active against $CD40^{+}$ and $CD40^{-}$ tumors. The absolute requirement for FcγRIIB engagement provides a significant advance in the future rational design of antibody-based therapeutics, especially those targeting the TNFR superfamily.

Advantage

The improved engagement of the FcγRIIB receptor by the anti-CD40 chimeric antibody greatly enhances immune stimulatory effect of the antibody. This modification can be applied to other agonistic TNFR superfamily antibodies.

Area of Application

Therapeutic TNFR antibodies to treat human and veterinary diseases, including cancer.

Stage of Development

Chimeric antibodies have been tested in humanized mouse models for lymphoma and melanoma.

Lead Inventor

Jeffrey V. Ravetch

Patent Information

PCT patent application WO 2012/087928 and US patent application US-2014-00108021-A1

References

Li, F. and J.V. Ravetch, 2011. *Science*, 333:1030.

Smyth, M.J. and M.H. Kershaw, 2011. *Science*, 333:944 (comment).