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NMDAR-targeted CAAR-T cell therapy

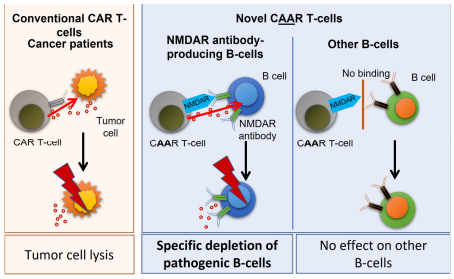
NMDA receptor, CAAR, chimeric autoantibody receptor, encephalitis

INVENTION NOVELTY

Pathogenic autoantibodies against the Anti-N-Methyl-D-Aspartate (NMDA) receptor (NMDAR) are responsible for the most common autoimmune encephalitis, a rare disease increasing in prevalence. NMDAR autoantibodies might also be at the origin of further neurologic diseases, e.g. autism and dementia. Current immunosuppressive treatment of NMDAR encephalitis like apheresis and rituximab aim to remove pathogenic autoantibodies, but its effects are non-specific. Immune suppression with rituximab depletes B cells, the source of pathogenic autoantibodies, but at the cost of removing B cells globally including immunoprotective B cells. Apheresis reduces the level of autoantibodies but does not remove the B cells.
It was surprisingly found that T cells engineered with a chimeric autoantibody receptor (CAAR) target B cells expressing NMDAR-specific autoantibodies on their surface. It could be demonstrated that the NMDAR-CAAR T cells selectively eliminate anti-NMDAR memory B cells and inhibit disease-causing autoantibody production.

VALUE PROPOSITION

This NMDAR-CAAR strategy could provide a highly selective treatment for a severe neurological autoimmune disease with reduced side effects, faster remission, and better long-term prognosis. The results will pave the way for clinical trials of CAAR-T cell therapy in NMDAR encephalitis and can be expanded to a broader spectrum of autoantibody-mediated diseases.



Chimeric autoantibody receptor strategy

TECHNOLOGY DESCRIPTION

In contrast to chimeric antigen receptors, which recognize and bind their target through an extracellular antibody fragment, CAARs use the autoantigen to direct the cytotoxicity of T cells expressing the CAAR to only those B cells that produce NMDAR antibodies, leaving protective B cells unaffected. NMDAR-CAARs consist of an extracellular multi-subunit NMDAR autoantigen fused to fused to a CD8 hinge and an intracellular 4-1BB/CD3ζ signaling domain. NMDAR-CAARs recognized a large panel of autoantibodies from NMDAR encephalitis patients. Sera of patients with NMDAR encephalitis bound to NMDAR-CAAR transduced Jurkat cells, while none of healthy control sera showed any binding. NMDAR-CAAR engineered primary T cells of healthy donors could be activated by target cells expressing NMDAR-reactive autoantibodies. In a passive transfer mouse model of an anti-NMDAR B cell line, application of NMDAR-CAAR T cells led to the depletion of anti-NMDAR B cells and sustained reduction of autoantibody levels without notable off-target toxicity.

COMMERCIAL OPPORTUNITY

NMDAR-CAAR T cell therapy could avoid the chronic immunosuppression from current treatments while creating comparable or even enhanced efficacy. Expanding the CAAR T cell approach to all autoimmune encephalitides and other autoimmune-mediated diseases not only broadens its applicability, but provides new, possibly curative treatment options for these difficult-to-treat conditions.

DEVELOPMENT STATUS

Based on multiple monoclonal antibodies, the binding domain of NMDAR-CAAR has been optimized to recognize the broadest possible repertoire of antibodies. The lead NMDAR-CAAR construct detected most of the monoclonal antibodies tested.

PATENT SITUATION

Patents are pending in US, EP, JP, CN and CA, with priority of June 5, 2019.

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