NLGN4X

Neuroligin 4, X-linked (NLGN4X) is a gene located on the X chromosome, and it encodes a protein called Neuroligin 4X. Neuroligins are a family of cell adhesion molecules that play a crucial role in the formation and regulation of synapses, which are the junctions between nerve cells (neurons) that allow them to communicate with one another. NLGN4X is primarily associated with the development and function of synapses in the brain.

Here are some key points about NLGN4X:

Gene Structure: NLGN4X is located on the long arm of the X chromosome. It is part of a family of neuroligin genes, with other members like NLGN1, NLGN2, and NLGN3, each of which plays a role in synaptic function.

Function: Neuroligin 4X is a cell adhesion molecule found in neurons. It is involved in the formation and maintenance of synapses, particularly excitatory synapses, by binding to neurexins, which are another class of synaptic cell adhesion molecules found on the surface of neighboring neurons. The binding of neuroligins to neurexins helps ensure proper synaptic connections.

Neurodevelopment: NLGN4X is crucial for brain development, and it plays a role in shaping the connectivity and function of neural circuits. Proper neuroligin function is essential for normal cognitive and behavioral development.

Association with Autism Spectrum Disorder (ASD): Mutations or variations in the NLGN4X gene have been identified in individuals with autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder characterized by difficulties in social communication and repetitive behaviors. Some mutations in NLGN4X can disrupt synaptic function and are thought to contribute to the risk of developing ASD.

Synaptic Plasticity: NLGN4X, like other neuroligins, is involved in synaptic plasticity, which is the ability of synapses to strengthen or weaken in response to neural activity. This plasticity is crucial for learning and memory.

Research: Scientists are actively studying NLGN4X and other neuroligins to better understand their roles in synaptic function and how genetic variations in these genes may influence brain development and contribute to neurodevelopmental disorders like ASD.

Understanding the function of genes like NLGN4X and their relationship to brain development and neurological disorders is an important area of research in the field of neuroscience and genetics. It provides insights into the underlying mechanisms of brain function and may lead to the development of targeted therapies for conditions like ASD.

Neuroligin 4 X-linked (NLGN4X) harbors a human leukocyte antigen (HLA)-A2-restricted tumor-associated antigen, overexpressed in human gliomas, that was found to induce specific cytotoxic T cell responses following multi-peptide vaccination in patients with newly- diagnosed glioblastoma.

Methods: T cell receptor (TCR) discovery was performed using droplet-based single cell TCR sequencing of NLGN4X-tetramer-sorted T cells post vaccination. The identified TCR was delivered to Jurkat T cells and primary human T cells (NLGN4X-TCR-T). Functional profiling of NLGN4X-TCR-T was

performed by flow cytometry and cytotoxicity assays. Therapeutic efficacy of intracerebroventricular NLGN4X-TCR-T was assessed in NOD scid gamma (NSG) major histocompatibility complex (MHC) I/II knockout (KO) (NSG MHC I/II KO) mice bearing NLGN4X-expressing experimental gliomas.

Results: An HLA-A *02-restricted vaccine-induced T cell receptor specifically binding NLGN4X131-139 was applied for therapeutic use. Reactivity, cytotoxicity, and polyfunctionality of this NLGN4X-specific TCR is demonstrated in various cellular models. Intracerebroventricular administration of NLGN4X-TCR-T prolongs survival and leads to an objective response rate (ORR) of 44.4 % in experimental gliomas-bearing NSG MHC I/II KO mice compared to 0.0 % in control groups, respectively.

Conclusion: NLGN4X-TCR-T demonstrates efficacy in a preclinical glioblastoma model. On a global scale, we provide first evidence for the therapeutic retrieval of vaccine-induced human TCRs for the off-the-shelf treatment of glioblastoma patients [1)].

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Krämer C, Kilian M, Chih YC, Kourtesakis A, Hoffmann DC, Boschert T, Koopmann P, Sanghvi K, De Roia A, Jung S, Jähne K, Day B, Shultz LD, Ratliff M, Harbottle R, Green EW, Will R, Wick W, Platten M, Bunse L. NLGN4X TCR transgenic T cells to treat gliomas. Neuro Oncol. 2023 Sep 16:noad172. doi: 10.1093/neuonc/noad172. Epub ahead of print. PMID: 37715782.