Immune effector cell-associated neurotoxicity syndrome

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a potentially serious complication that can occur after treatment with certain immunotherapies, particularly chimeric antigen receptor (CAR) T-cell therapy. This syndrome is characterized by neurological symptoms that can range from mild confusion and headache to more severe manifestations such as seizures, cerebral edema, and coma. ICANS is thought to result from an immune response triggered by the infused immune effector cells, leading to inflammation in the central nervous system.

The exact mechanisms underlying ICANS are not fully understood, but it is believed to involve the release of cytokines and other inflammatory molecules by activated immune cells, leading to disruption of the blood-brain barrier and subsequent neurological dysfunction. Prompt recognition and management of ICANS are crucial to prevent potentially life-threatening complications.

Vinnakota et al. examined the role of microglia using mouse models and cohorts of individuals with ICANS. CD19-directed CAR (CAR19) T cell transfer in B cell lymphoma-bearing mice caused microglia activation and neurocognitive deficits. The TGFβ-activated kinase-1 (TAK1)-NF-κB-p38 MAPK pathway was activated in microglia after CAR19 T cell transfer. Pharmacological TAK1 inhibition or genetic Tak1 deletion in microglia using Cx3cr1CreER:Tak1fl/fl mice resulted in reduced microglia activation and improved neurocognitive activity. TAK1 inhibition allowed for potent CAR19-induced antilymphoma effects. Individuals with ICANS exhibited microglia activation in vivo when studied by translocator protein positron emission tomography, and imaging mass cytometry revealed a shift from resting to activated microglia. In summary, we prove a role for microglia in ICANS pathophysiology, identify the TAK1-NF-κB-p38 MAPK axis as a pathogenic signaling pathway and provide a rationale to test TAK1 inhibition in a clinical trial for ICANS prevention after CAR19 T cell-based cancer immunotherapy [1)].

Treatment for ICANS typically involves supportive care, including close monitoring of neurological symptoms, administration of corticosteroids to reduce inflammation, and, in severe cases, interventions such as immunosuppressive therapy or intensive care management. Research is ongoing to better understand the risk factors, mechanisms, and optimal management strategies for ICANS in order to improve outcomes for patients undergoing immunotherapy

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