SLEEP

# Narcolepsy—a role for TRIB2 autoantibodies?

Increased levels of Tribbles homolog 2 (TRIB2) autoantibodies, which specifically target hypocretin neurons, have been observed in patients with narcolepsy, and high levels of these antibodies correlate with the severity of cataplexy.

Narcolepsy is a chronic sleep disorder linked with disturbances in the hypocretin (also known as orexin) system. In humans, studies suggest that narcolepsy is caused by loss of hypocretin-producing neurons, possibly through an autoimmune process. According to senior author Mehdi Tafti, however, "despite an intensive search, no autoantigens have ever been found in narcolepsy," leaving the autoimmune hypothesis open to speculation. Nevertheless, the existing data do support such a theory: the disease is strongly associated with a T-cell receptor α gene variant, and 95% of patients with narcolepsy with cataplexy carry the *HLA-DQB1*0602* allele, which has been linked to other autoimmune disorders such as multiple sclerosis.

Tafti's team used a transgenic mouse model of narcolepsy to screen for peptides that showed enrichment in hyprocretin neurons, hypothesizing that these peptides could be targeted by the autoimmune system and trigger narcolepsy. The researchers identified four candidate genes (*Igf2bp2*, *Slc12a6*, *Spin1* and *Trib2*) that exhibited increased expression in hypocretin neurons. TRIB2 has previously been confirmed as an autoantigen in autoimmune uveitis, a condition that can occur in association with narcolepsy.

> "...no autoantigens have ever been found in narcolepsy"

The investigators developed an enzyme-linked immunosorbent assay to detect antibodies against TRIB2 in serum and cerebrospinal fluid from patients with narcolepsy, in comparison with normal controls or patients with other neurological disorders, idiopathic hypersomnia or multiple sclerosis. Serum from patients with narcolepsy showed higher levels of TRIB2 autoantibodies than all the other patient groups tested. These autoantibody titers peaked within the first year after narcolepsy onset then decreased over the next 3 years, before stabilizing at markedly raised levels for up to 30 years. High TRIB2 autoantibody titers correlated significantly with both the frequency of cataplexy and the severity of sleepiness. Finally, serum samples with high TRIB2 antibody levels crossreacted with >86% of hyprocretin neurons in the mouse hypothalamus.

Tafti believes that patients diagnosed early with narcolepsy who have high serum TRIB2 autoantibody levels could benefit from immunotherapy: "the hope is to stop the autoimmune reaction as early as possible so that the remaining hypocretin neurons can recover." He adds that more research is needed to confirm that TRIB2 autoantibodies are indeed pathogenic.

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