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Study reveals direct regulatory role of serotonin in rheumatoid arthritis

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RA Symptoms and Pathology Worse in Mice Missing Enzyme Needed for Serotonin Synthesis, According to Report in The American Journal of Pathology

For the first time, serotonin (5-hydroxytryptamine, 5-HT) has been directly implicated in the pathophysiology of rheumatoid arthritis (RA). Although 5-HT is predominantly known as a neurotransmitter within the central nervous system, new evidence points to additional important functions for serotonin in the periphery. A report in The American Journal of Pathology shows that experimentally-induced RA in serotonin-deficient mice is worse than disease reported in controls and that some effects of RA can be reduced by serotonin or its agonists (compounds that activate serotonin receptors).

These findings may lay the groundwork for new treatment approaches for RA. "Our study highlights that 5-HT has a direct immunoregulatory role in arthritis. The development of treatments targeting 5-HT or 5-HT receptors could represent an exciting prospect to regulate the immune response in RA and open new perspectives to improve the therapeutic options for patients," explained co-lead investigator Marie-Christine de Vernejoul of BIOSCAR, INSERM UMR_S1132 of the Hôpital Lariboisière, Unité Mixte de Recherche (UMR) 1132, Université Paris Diderot (Paris, France).

The investigators used a mouse model of RA known as collagen-induced arthritis (CIA) that produces features similar to that of human RA. Disease manifestations include cartilage and bone destruction, as well as the activation of cells responsible for bone resorption, known as osteoclasts. They compared the effects of CIA in normal mice to those in mice genetically bred with a deficiency in tryptophan hydroxylase-1, a key enzyme needed for serotonin production in peripheral tissues.

The investigators found that both the number and activity of osteoclasts were higher in 5-HT-deficient mice with arthritis. In addition, more bone resorption was detected both at the affected joints and at remote sites.

The serotonin-deficient mice with arthritis also showed changes in certain cell-signaling molecules known as cytokines (higher IL-17, higher TNF-α, and lower IL-4) in their paws. Specifically, they displayed a shift in the balance between T cell subtypes, especially regulatory T cells and Th17 lymphocytes.

"Altogether, our data show that 5-HTdeficient mice are characterized by a relative, dampened expansion of Treg associated with an enhanced shift toward a Th17 phenotype, a situation previously described in patients with arthritis," noted co-lead investigator Francine Côté of the Laboratory of Cellular and Molecular Mechanisms of Hematological Disorders and Therapeutic Implications Institut Imagine INSERM U1163/CNRS ERL 8254, Hôpital Necker (Paris, France).

Subsequent experiments using cell cultures showed that the balance between Th17/Treg cells could be normalized by the addition of 5-HT or 5-HT receptor agonists, revealing a direct regulatory role of serotonin in RA. These novel data suggest a new therapeutic target that could be important for this disabling disease.

Source:
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