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Surprising potential immune system modulators – cannabinoids

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Endogenous cannabinoid system is a subtle modulator of neurons and different peripheral cells activity. Two main endogenous cannabinoids, ananamide and 2-arachidonoylglycerol (2-AG) synthetized either in peripheral tissues or in postsynaptic part of neuronal synapses act upon CB1 receptors (localized rather in central nervous system, in presynaptic parts of neuronal synapses) and CB2 (localized in peripheral tissues – gastrointestinal, immune cells, reproductive organs, adipose tissue). These main cannabinoid receptors are coupled with Gi protein. Activity of endogenous cannabinoid system in peripheral tissue causes inhibition of T-cells proliferation, promotion of antiinflammatory Treg cells differentiation and decrease in proinflammatory cytokines production in macrophages. Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main exogenous cannabionoids of plant origin – phytocannabinoids, THC acts rather on CB1 receptors in central nervous system whereas CBD – on CB2 receptors in peripheral tissues. Therefore, CBD is considered as potential immune system modulator that decreases local immune system activity. In different investigations, CBD was considered as a potential drug in treatment of COVID-19, autoimmune diseases or even cancer. These investigations were undertaken rather on animal model, however, in COVID-19 CBD was investigated in human randomized CANDIDATE study. Although current guidelines approved the use of THC or CBD in symptomatic treatment in some specific conditions (e.g., therapy of muscle spasticity in multiple sclerosis) and cannabinoids also present potentially negative effects, their potential as subtle but effective immune system modulators is still to be elucidated.

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Genetic factors in autoimmunity: the common and the uncommon

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Autoimmune diseases arise from a complex interplay between genetic predisposition and environmental influences. As famously summarized by Fathman, autoimmunity can be considered a combination of "genetics and bad luck." Advances in genomic technologies have significantly improved our understanding of the genetic architecture underlying these conditions. Family aggregation, segregation, linkage, and association studies – culminating in genome-wide association studies (GWAS) – have identified numerous susceptibility loci involved in innate immunity, T- and B-cell signaling, apoptosis, autophagy, ubiquitination, and phagocytosis. Many of these genetic variants are shared across multiple autoimmune diseases, highlighting common pathogenic pathways.

Among genetic determinants, the human leukocyte antigen (HLA) region remains the strongest contributor to disease susceptibility, explaining up to 50% of the genetic risk in some disorders. Nevertheless, HLA alleles are neither necessary nor sufficient for disease development, indicating the involvement of additional genetic factors and gene–gene interactions. Structural variations, such as complement gene copy number differences (particularly C4A and C4B), have also been associated with diseases like systemic lupus erythematosus. Moreover, next-generation sequencing and phenome-wide association studies are expanding our capacity to identify rare variants and genotype–phenotype correlations.

Genetic predisposition is further modulated by sex-related differences, endogenous retroelements, and interactions with environmental factors such as smoking and the microbiome. Together, these elements form a multifactorial "mosaic" that explains the heterogeneity, clinical manifestations, and prognostic variability.