Understanding Mechanisms underlying Monogenic Autoinflammatory Diseases may lead to Targeted Treatment

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Monogenic autoinflammatory diseases (MAD) are characterized by fever, systemic and/or organ-specific inflammation due to mutations of genes involved in innate immunity.

Mechanisms underlying MAD have been clarified over the last 20 years to involve that of inflammasomes with IL-1β activation, NF-kB-activation with dysfunctional ubiquitination, interferonopathies, cytokine signaling and protein-folding disorders.

The prototypic MAD due to inflammasomopathies with IL-1β activation includes familial Mediterranean fever (MEFV mutation) and cryopyrin-associated periodic syndromes (NLRP3 mutation). Other IL-1β activation disorders include Majeed syndrome (LPIN2 mutation), NLRC4-MAS (NLRC4 mutation), MKD/HIDS (MVK mutation), PAPA (PSPTIP1 mutation), FKLC (NLRP1 mutation) & PFIT (WDR1 mutation). Blockade of IL-1 with anakinra or canakinumab is the treatment of choice, except for FMF for which colchicine is the drug of first choice. For NLRC4-MAS, addition of IL-18 blockade is necessary.

NF-KB activation disorders include Blau syndrome (NOD2 mutation) and ubiquitination disorders, which include HA20 & otulipenia (insufficient deubiquitination), HOIL-1 & HOIP deficiency (impaired ubiquitination). These MAD generally respond well to TNF-α blockade probably because of activation of NF-kB pathways by TNF-α receptors.

Interferonapathies include SAVI (GOF mutations in dsDNA sensor STING), AGS (multiple genes/proteins defects in intracellular sensing of nucleic acids) and PRAAS-CANDLE (multiple proteasome genes/proteins defect). Patients with SAVI are being treated with inhibitors of JAK, TBK1 and IKKE which are signaling molecules of type 1 interferon pathway.

Cytokine signaling disorders driving autoinflammation include DIRA (defect in IL-1 receptor antagonist), DITRA (defect in IL-36 receptor antagonist) and IL-10/IL-10R deficiency. These MAD have been treated with both TNF-α and IL-1 blockade with variable responses. IL-17 blockade has been used for DITRA. HSCT has been performed for IL-10R deficiency with successful outcome.