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Novel Monogenic Autoinflammatory Diseases

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Heterozygous *OAS1* gain–of–function variants cause an autoinflammatory immunodeficiency (Magg et al., 2021)

Six unrelated individuals presented with recurrent fever, rash, diarrhoea, failure to thrive and viral-like airway infection. All had normal T cell count, low B cell count and hypogammaglobulinemia. Exome sequencing (ES) identified four *de novo* missense variants (p.Ala76Val, p.Cys109Tyr, p.Val121Gly, and p.Leu198Val) in the *OAS1* gene. OAS1 (oligoadenylate synthetase 1) is a type 1-interferon inducible protein, which initiates an antiviral response against viral double-stranded RNA. Human induced pluripotent stem cell model demonstrated that the gain of function variants in *OAS1* resulted in unprovoked excessive synthesis of a second messenger 2[2032?]-5[2032?]-oligoadenylate (2-5A), which in turn resulted in activated RNAse-L mediated cleavage of cellular RNA, leading to apoptosis of B cells and monocytes. B cell apoptosis caused hypogammaglobulinemia and the dysfunction of macrophages and monocytes lead to activation of pro-inflammatory pathways. This new disorder was named as OAS1-associated Polymorphic Autoinflammatory Immunodeficiency (OPAID).

Gain–of–function variants in *SYK* cause immune regulation and systemic inflammation in humans and mice (Wang et al., 2021)

The authors ascertained three individuals from two unrelated families. The affected child in the first Chinese family had fever, rash, non-bloody diarrhoea, arthritis, failure to thrive, and perianal fistulas, and succumbed to recurrent infections at 3 years of age. The proband in the second Ashkenazi Jew family developed colitis, arthritis and rash, at 2 weeks of age. Her 35-year-old father also had fever, rash and diarrhoea as a child. ES identified monoallelic variants in *SYK* gene. Patient 1 had a *de novo* c.1649C>A, p.Ser550Tyr variant and patients 2 and 3 had c.1649C>T, p.Ser550Phe variant in *SYK*. SYK is a critical signalling molecule expressed in peripheral mononuclear cells (PBMC), B cells and intestinal epithelium. The variants in the patients resulted in phosphorylation of tyrosine residues at position 525/526 causing constitutive activation of SYK. Similar results were reproduced in transfection studies using HEK293 cells and human SW480 colonic epithelial cells. CRISPR-cas9 edited mice showed that heterozygous mice developed arthritis and bone erosion. The affected mice when treated with a SYK specific inhibitor, R406, showed improvement. Bone marrow transplantation in affected mice showed resolution of disease. This study provides evidence for the role of *SYK* gain-of-function variants in causing inflammation and immune dysregulation in humans and the potential use of SYK as a therapeutic target.

Somatic mutations in *UBA1* and severe adult–onset autoinflammatory disease (Beck et al., 2020)

ES was performed on three men who had severe inflammatory syndrome with onset between fifth to seventh decades. They had alveolitis, chondritis, and skin lesions, haematological abnormalities like thrombocytopenia, macrocytic anemia and thromboembolic phenomena. A novel, apparently heterozygous variant, at codon 41(methionine-41), in *UBA1* gene, which is on the X chromosome, was identified in them. All three men had a

normal karyotype. Hence, somatic mosaicism was suspected. Sanger sequencing to screen additional patients for variants in *UBA1* identified 25 males with one of the three variants in codon 41 (p.Met41Val, p.Met41Thr or p.Met41Leu). The neutrophils and monocytes of patients had increased proportion of mutant cells. However, mature lymphocytes had more of wild type variant. Transcriptome analysis of peripheral blood cells of these patients showed evidence for activation of innate immune pathways. *UBA1* gene encodes the major E1-activating enzyme, which is required for initiation of ubiquitination signalling. By analysing the expression of UBA1 Met41 variants in human embryonic kidney cells, the authors identified a new isoform of UBA1, which they termed as UBA1c, which had reduced catalytic activity. These findings were recapitulated in the cells from the participants. CRISPR-cas9 edited zebra fish models were used to study the effect of *UBA1* variants on systemic inflammation. The authors thus described a new autoinflammatory syndrome, which they named as VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic).

Mutations that prevent caspase cleavage of *RIPK1* cause auto–inflammatory disease (Lalaoui et al., 2020)

Seven individuals from three unrelated families presented with recurrent fever and lymphadenopathy, which began in early childhood and continued to adulthood. ES in affected individuals from the three families identified heterozygous missense variants in *RIPK1* gene at the key aspartate residue (p.Asp324Asp, p.Asp324Tyr, and p.Asp324His). RIPK1 (Receptor Interacting Protein Kinase 1) is a key regulator of innate immune signalling pathway like NF-kappa B and MAPK (Mitogen-Activated Protein Kinase) inflammatory pathway. The optimum activity of RIPK1 is maintained by posttranslational modification and caspase-8 mediated cleavage. In normal circumstance, caspase mediated cleavage of RIPK1 prevents activation of inflammatory pathways and necroptosis. RIPK1 cleavage resistant mice model demonstrated that the variants in the key aspartate residue in RIPK1 resulted in resistance to caspase-8 and activation of the proinflammatory pathways. This novel condition was named as 'Cleavage-resistant RIPK1-Induced Autoinflammatory' (CRIA) syndrome.

References

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