Abstract

Inborn errors of immunity (IEI) are a heterogenic group of diseases of the immune system causing dysregulations of both innate and adaptive immunity. New altered immune-related genes are discovered every year, nowadays reaching over 400. (Tangye et al., 2020) Here three new autoinflammatory disorders of IEI patients are described.

Toll-like receptors (TLR) 7 and 8 are endosomal receptors in the innate immune response against external pathogens and endogenous autoantigens. A dysregulation in TLR7 and TLR8 in mice causes autoimmunity and inflammation, however, in humans, the immunopathology of TLR8 and TLR7 remains unclear. We identified a novel X-linked *c.1715G>T* mutation in *TLR8* that leads to autoimmune haemolytic anaemia and autoinflammation in male twins caused by dysregulation in TLR8 and TLR7 response especially in myeloid cells (low TLR8 protein expression, cross-reactivity of TLR8 for TLR7 ligands and enhanced TLR7 response).

Hematopoietic cell kinase (HCK) belongs to the Src family of kinases and is involved in myeloid cell migration, adhesion and degranulation. Kinase activity in the immune response must be strictly regulated. In HCK, this regulation is based on C-terminal inhibitory tyrosine, which when phosphorylated, HCK kinase activity is switched off. We identified a heterozygous mutation *c.1545C>A* in *HCK* where inhibitory tyrosine is missing and HCK is constitutively active. The main disease symptoms were cutaneous vasculitis and chronic pulmonary inflammation that progressed to fibrosis due to increased adhesion, migration and inflammatory capacity of myeloid cells.

Interferon alpha receptor subunit 1 (IFNAR1) is one of the two subunits of a dimer creating the interferon type I receptor. Type I interferon signalling plays a crucial role in antiviral immune response as well as preventing an excessive inflammatory response during viral infection. We identified a novel homozygous mutation *c.922C>T* in *IFNAR1* in a 15-month old boy who suffered a severe inflammatory reaction after live attenuated MMR vaccine administration due to a complete absence of IFNAR1 protein, therefore no interferon type I signalling in the patient.

Detailed characterization of novel mutations in *TLR8*, *HCK* and *IFNAR1* genes broadened the spectrum of IEI with autoinflammation. These studies can help in disease identification and treatment in similar cases.

Keywords

Inborn error of immunity, inflammatory disease, functional testing, Hematopoietic cell kinase, Toll-like receptor 8, Interferon alpha receptor