Karolinska Institutet

Institution för kvinnors och barns hälsa

Genetic studies of susceptibility to inflammation, autoimmunity, and hematological malignancy

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens Barnsjukhus.

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ABSTRACT

The immune system represents the body's defense against infectious organisms. Inborn defects of the immune system, called primary immunodeficiencies (PIDs), are a heterogeneous group of Mendelian disorders. Clinically, PIDs can cause isolated to broad susceptibility to pathogens, severe hyperinflammation, autoimmunity, allergy, and cancer. The studies in this thesis take advantage of the recent development in DNA-sequencing technologies and of our increased understanding of genetic variability to further explore the genetic architecture and phenotypic spectrum of hemophagocytic lymphohistiocytosis (HLH), an inborn error of lymphocyte cytotoxicity, and to elucidate the genetic factors behind autoimmunity and hematological malignancies in selected families.

Familial HLH (FHL) is a severe hyperinflammatory condition, genetically heterogeneous, caused by defective perforin-mediated lymphocyte cytotoxic activity. In **paper I** we use a high-throughput sequencing panel covering 12 HLH-related genes in 58 prospectively recruited patients with HLH and achieve a molecular diagnosis in 22 cases (38%). In **paper II** we show that perforin-deficiency due to biallelic *PRF1* missense variants is associated with broad intra-familial variability and clinical presentations seemingly unrelated to HLH, such as Hodgkin lymphoma. Using exome sequencing, in **paper III**, we identify biallelic pathogenic variants in *IFNGR1* and *INFGR2*, respectively, in two patients with HLH and disseminated mycobacterial infection. Previous studies have shown that HLH pathology is largely driven by IFN-γ. Instead, our findings suggest the existence of IFN-γ-independent mechanisms for the development of HLH. In **paper IV**, we uncover biallelic coding and non-coding variants in *RAB27A*, the gene responsible for Griscelli syndrome type 2 (GS2), in five unrelated patients with atypical HLH, normal pigmentation, and a functional defect suggestive of FHL. A complex structural variant disrupting the transcriptional start site (TSS) of one *RAB27A* transcript was shared among the patients. We show that the disrupted TSS is less predominantly used by melanocytes compared to lymphocytes, explaining the lack of hypopigmentation in these patients, otherwise present in GS2.

In **paper V** we report the beneficial effect of hematopoietic stem cell transplantation in a 14-year-old boy with LRBA deficiency and a seven-year history of severe autoimmmune disorders.

In **paper VI** we uncover germline heterozygous missense variants in *SAMD9L*, a gene located on 7q21, in two families with multiple individuals affected by cytopenia, immunodeficiency, myelodysplastic syndrome (MDS) with cytogenetic aberrations of chromosome 7, and neurologic disease. We show a gain-of-function (GOF) effect of the mutants, which inhibit cell proliferation. Germline *SAMD9L* GOF variants were lost in MDS cells and hematopoietic revertant mosaicism occurred frequently among less severely affected carriers. Our results indicate a strong selective advantage for hematopoietic cells that, through different somatic events, overcome the growth-inhibiting effect of germline *SAMD9L* GOF variants.

Taken together, these studies add to our understanding of the phenotypic and genetic spectrum of HLH, display the power of high-throughput sequencing in diagnostics of individuals affected by severe inflammation, autoimmunity, and hematological malignancies, and highlight *SAMD9L* as an important gene for regulation of hematopoietic cell proliferation.