Institute of Transfusion Medicine

Genetics and Molecular Pathophysiology of Immunodeficiencies

Head: Hubert Schrezenmeier

Severe combined immunodeficiency (SCID) refers to a genetically and clinically heterogeneous group of disorders with defective cellular and humoral immune functions. Patients with SCID present in infancy and suffer from recurrent and persistent infections by opportunistic viral and fungal organisms. The common characteristic of all types of SCID is the absence of T cell-mediated cellular immunity due to a defect in T cell development or function. If present, B cells can be either primarily defective or merely deprived of adequate T cell signals. Without treatment, the disease is invariably lethal within the first year of life.

The most common classification of SCID cases relies on immunophenotyping according to the presence or absence of T, B and NK cells. Recent progress in the molecular characterization of SCID defects allows the definition and follow-up of more homogeneous cohorts according to the underlying genetic defect. The elucidation of the molecular defects in SCID patients has contributed to the understanding of very basic cellular mechanisms such as purine metabolism (ADA-, PNP-defect), signaling cascades (CD3 components, interleukine receptors and respective downstream factors), transcription factor behavior (MHCII-defects), Ca-channels (ORAI and STIM-deficiency), thymic T cell egress (CORO1A-defect), antigen receptor structure (TRAC-defect) and DNA repair (V(D)J recombination and NHEJ factors) (Fig. 1).

Very recently, we elucidated the molecular defect and part of the molecular pathophysiology of the most severe SCID entity: Reticular Dysgenesis, an aleukoytosis with sensorineural deafness. Deficiencies in the nuclear-encoded mitochondrial enzyme adenylate kinase 2 (AK2) affect leukocyte progenitor survival by increasing apoptotic propensity of the cells.

Although many genetic defects in SCID patients have now been detected, about 30% of SCID variants still lack a genetic diagnosis.
In collaboration with the bone marrow transplantation unit of the Clinic for Pediatric- and Adolescent Medicine (University Medical Center Ulm), novel SCID cases are constantly being identified by our group on the basis of clinical and immunological data.

The focus of our group is to analyse the underlying genetic defect of the SCID patients and to unravel the molecular pathophysiology of their lymphocyte defect. We make use of modern molecular tools including loss of heterozygosity screens and candidate gene/transcriptome/exomesequencing to identify the molecular basis of so far unresolved SCID cases. Functional complementation assays are performed with candidates from the molecular screen.

A better definition of the genetic, immunologic and phenotypic variability of these patients will help to define additional facets of the development and function of the human immune system and, in addition, will provide a faster road to diagnosis and potential therapy of this life-threatening disease.