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Sommario/riassunto

The pathogenic mechanisms underlying primary T-cell disorders are mainly related to molecular alterations of genes whose expression is intrinsic to hematopoietic cells. However, since the differentiation process requires a crosstalk among thymocytes and the thymic microenvironment, molecular alterations of genes, involved in the differentiation and functionality of the stromal component of the thymus, may lead to a severe T-cell defect or failure of central tolerance, as well. The first example of severe combined immunodeficiency (SCID) not related to an intrinsic alteration of the hematopoietic cell but rather of the thymic epithelial component is the Nude/SCID phenotype, inherited as an autosomal recessive disorder, whose hallmarks are the T-cell defect and the absence of the thymus. The clinical and immunological phenotype is the human equivalent of the murine Nude/SCID syndrome, which represents the first spontaneous SCID identified in nude mice in 1966. For over 3 decades studies of immune system in these mice enormously contributed to the overall knowledge of cell mediated immunity, in the assumption that the athymia of these mice was solely responsible for the T-cell immunological defect. This syndrome is due to mutations of the transcription factor FOXN1, belonging to the forkhead-box gene family, which is mainly expressed in the thymus and skin epithelial cells, where it plays a critical role in differentiation and survival. An alteration of the thymic structure is also a feature of the DiGeorge syndrome (DGS),

which has been long considered the human counterpart of the nude mice phenotype. This syndrome is frequently associated to a deletion of the 22q11 region, which contains approximately 30 genes, including the TBX1 gene, which is responsible for most of the clinical features of DGS in humans and mice. In this syndrome common manifestations are cardiac malformations, speech delay, hypoparathyrodism and immunodeficiency, even though the immunological hallmarks of the T-cell defect in DiGeorge syndrome are profoundly different from those reported in human Nude/SCID. The divergence of the phenotype among these 2 entities raised the possibility that the FOXN1 transcription factor represents the real key stromal molecule implicated in directing the hematopoietic stem cell toward a proper T-cell fate. Thymic stromal component of the primary lymphoid organ is also required to negatively select the autoreactive clones, a process driven by the expression of tissue specific antigens (TSA) by medullary thymic epithelial cells (mTECs). The expression of genes encoding TSA antigens is mediated by autoimmune regulator (AIRE) gene, encoding a transcription factor expressed in mTECs. Molecular alterations of this gene are associated to autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), a rare autosomal disorder, which may be considered the prototype of an autoimmune disease due to the failure of central tolerance homeostasis. All these "experiments of nature" led to unravel novel pathogenic mechanisms underlying inherited disorders of immune system and, of note, to clarify the pivotal role of epithelial cells in the maturation and education process of T-cell precursors.