Ten-year anniversary of CD3 δ deficiency

ABSTRACT

CD3 δ deficiency was first identified a decade ago by using differential expression libraries derived from thymocytes of patients with severe combined immunodeficiency. The phenotype was surprisingly severe unlike the mouse model or other human CD3 deficiencies known at that time.

The T-cell receptor (TCR) complex consists of a variable surface TCR heterodimer ($\alpha\beta$ or $\gamma\delta$), 2 invariant heterodimers that include the CD3 $\gamma\epsilon$ chain and the CD3 $\delta\epsilon$ chains, as well as a single invariant homodimer called ξ (Call et al. 2002). The variable chains recognize antigens, whereas the role of the invariant chains is to effectively transmit signals into the cytoplasm. This is done through a series of tyrosine phosphorylation events leading to activation of downstream signaling pathways including the PLC γ , PI3K, and MAPK pathways. These signals trigger cytoskeletal changes (actin assembly), secretion of growth factors, and expression of growth and cell contact receptors. This process culminates in differentiation, clonal expansion, or when necessary, apoptosis of T cells.

A decade ago, CD3 δ deficiency was first described in Roifman's laboratory (Dadi et al. 2003). Infants of Mennonite descent presented with typical features of severe combined immunodeficiency (SCID), yet they had a detectable thymus gland that was bigger than is usually seen in traditional cases of SCID (Roifman 2005). Evaluation of a thymus biopsy from the patient surprisingly revealed a gland heavily populated with thymocytes. Yet, although not completely dysplastic, the thymus had no visible Hassall's corpuscles, which is the hallmark of primary immunodeficiency.

In the pre-Whole Exome Sequencing era, there could be 2 potential routes to follow to define the genetic basis of this disease. One was the traditional linkage analysis method, which at that time required multiple subjects, and the other

was using the candidate gene approach. The number of subjects was very limited in this cohort and several candidate genes that had been tested were found normal. We therefore decided to undertake a novel approach.

Our method relied on the comparison of mRNA expression (expression libraries) between patient cells and controls. Usually this would have been a monumental task of sorting through too many variables with a low success rate of gene discovery. In this case, we hypothesized that by comparing 2 very "clean" cell types, i.e., age-matched thymocytes derived from patient thymus biopsy or from a normal thymus (infants who undergo thymectomy during heart surgery), the number of potential genes to be assessed could be manageable. Strikingly, significant immune-related mRNA expression variations were fewer than 15 gene products. CD3 δ was one of the possible candidates, yet it was not chosen as a first candidate for several reasons.

First, previous descriptions of other CD3 chain deficiencies were associated with a spectrum of clinical and immunological presentations ranging from leaky SCID (<10) to normal healthy subjects for complete CD3 γ deficiency (Arnaiz-Villena et al. 1992) or leaky SCID for CD3 ϵ deficiency (Soudais et al. 1993).

Second, the CD3 δ -null mouse appeared to be very leaky, similar to the human CD3 γ deficiency (Dave et al. 1997). In contrast, CD3 δ deficiency in our cohort resulted in complete absence of circulating T cells and

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a typical SCID phenotype. It was therefore a surprise to find the disease causing the mutation in the gene for CD3δ. This clearly indicated that in humans CD3δ, but not CD3γ, is critical for T-cell maturation and emigration out of the thymus. This is consistent with the finding that CD3δ can replace CD3γ but the reverse is ineffective (Zapata et al. 2004).

Third, the set of experiments leading to the discovery of CD3δ deficiency were possible only because of the availability of the patient's thymus tissue.

Complete CD3δ deficiency is fatal during infancy unless rescued with hematopoietic stem cell therapy (Marcus et al. 2011).

Our personal experience, as well as the experiences of others, indicates that using matched-related or unrelated donors is highly successful. Indeed, follow-up beyond 15 years post-transplantation reveals that all patients are well, and an assessment of the immune system shows a robust–normal immune reconstitution. In contrast, haplo-identical transplants failed in most attempts in these patients and should be avoided (Rieux-Laucat et al. 2006; Roberts et al. 2007; Marcus et al. 2011).

Recently, cases with partial CD3δ deficiency (Garcilán et al. 2014) have been described as well as deficiencies in other CD3 and TCR chains. This issue includes an excellent review by Marin et al. (p. 3) that summarizes all new discoveries.

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