11.

T-CELL RECEPTOR COMPLEX DEFICIENCY

Jose R. Regueiro and Maria J. Recio

CONCISE DESCRIPTION AND BRIEF HISTORICAL OVERVIEW

Mature T lymphocytes detect the presence of antigens by way of a variable surface heterodimer (either αβ or γδ) termed the T-cell receptor (TCR, Fig. 11.1). In humans, TCR molecules form a complex with two invariant heterodimers called CD3γε and CD3δε and a single invariant homodimer termed CD247 (also called ζζ) (Call et al., 2002). These invariant proteins participate in assembly and surface expression of the whole TCR complex, and in the delivery of intracellular signals that drive T-cell maturation or apoptosis in the thymus, and T-cell activation, proliferation, and effector function or anergy/apoptosis after antigen recognition (Malissen et al., 1999). During early T-cell development, other invariant chains such as the pre-TCR may assist immature TCR ensembles. CD3 and CD247 chains lack intrinsic enzymatic activity for signal transduction. Rather, they relay on conformation- and phosphorylation-dependent recruitment and activation of a number of cytosolic and transmembrane protein tyrosine kinases (PTK) and adaptors such as Zap-70, Fyn, Lck, TRIM, LAT, SLP-76, SIT, and Nck (Schraven et al., 1999). Most TCRαβ-bearing T cells recognize processed peptides associated with major histocompatibility complex (MHC) molecules, whereas the ligands of TCRγδ-bearing T cells are still debated, but include unprocessed bacterial phosphoantigens in humans (Hayday, 2000).

Because of the central role of T cells in adaptive immune responses and the central role of the TCR complex in T-cell selection and function, the description in 1986 of a human familial CD3 expression deficiency in a child with immunodeficiency, but also in his healthy sibling, was in many ways surprising (Regueiro et al., 1986). Four years later, a second CD3 expression deficiency was reported in a healthy child (Thoenes et al., 1990). As it turned out, the former was due to a complete CD3γ deficiency (Arnaiz-Villena et al., 1992) and became the first primary TCR complex immunodeficiency for which the genetic basis was elucidated, while the latter was caused by a partial CD3ε deficiency (Soudais et al., 1993). Further CD3, CD247, and TCR deficiencies followed (Table 11.1), which, keeping with the initial observations, can be classified as complete or partial (also termed leaky) according to the absence or presence of residual levels of the affected protein.

TCR complex deficiencies in humans are very rare autosomal recessive diseases characterized by a selective TCR complex expression defect frequently associated with peripheral blood T, but not B or natural killer (NK), lymphocytopenia and severe combined immunodeficiency disease (SCID) symptoms. TCR complex deficiencies are caused by a range of severe or leaky mutations in the genes encoding for TCR complex chains (to date other than TCRβ, TCRγ or TCRδ). Mutation databases have been established for most of them (http://bioinf.uta.fi/base_root/index.php), as well as diagnostic support websites (http://bioinf.uta.fi/IDdiagnostics).

CLINICAL AND PATHOLOGICAL MANIFESTATIONS

Reported cases of TCR complex deficiencies have steadily grown to close to 30 patients in 16 families (see Table 11.1), half of them CD3δ deficiencies. Age of onset is generally within the first year of life, essentially with SCID features such as recurrent respiratory infections, chronic diarrhea, and failure to thrive. Chronic pyogenic infections, dysmorphic features, or bone abnormalities were not reported. Unless hematopoietic stem cell transplantation is performed, most

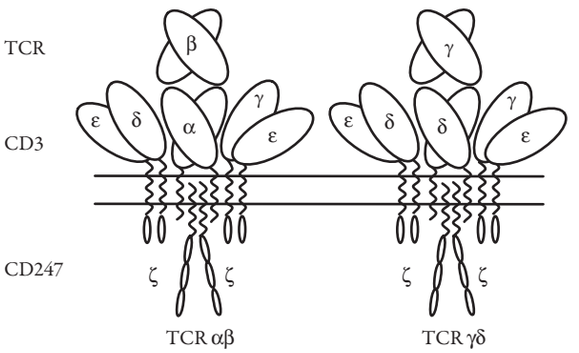

Figure 11.1 *TCR complex isotypes.* Variable TCR heterodimers bind antigens, while invariant CD3 heterodimers (γε and δε) and CD247 homodimers (also called ζζ) undergo conformational changes and recruit intracellular enzymes (such as Fyn, Lck, and Zap) to initiate signal transduction.

patients die early in life as a consequence of viral infections. Omenn syndrome features (hypereosinophilia, hyper-IgE, dermatitis) have been reported in partial CD3δ, CD247, or TCRα defects. In a few cases, notably in complete CD3γ deficiency and in a partial CD3ε deficiency, certain individuals do not show features of immunodeficiency and have reached their third decade in good health without intervention.

LABORATORY FINDINGS

The most consistent laboratory finding is a selective T lymphocytopenia. It may be severe ($T^{\downarrow}B^{+}NK^{+}$ immunophenotype), as observed in complete CD3ε or CD3δ defects, with less than 2% peripheral blood T cells, or mild ($T^{+/\downarrow}B^{+}NK^{+}$), as observed in complete CD3γ or CD247 defects and in most partial TCR complex defects (with >20% T cells, Table 11.2). Overall lymphocytopenia (<3,000 cells/μL in children) is common in the former group, although exceptions due to compensatory B and NK expansions have been reported.

T-lymphocyte functions (anti-CD3 or phytohemagglutinin responses) and B-lymphocyte functions (antibody production following infection or vaccination) are absent when no T cells are detected, although Ig levels may be normal. These functions may be preserved or even normal in partial defects. Autoimmunity and/or immune dysregulation laboratory features may be present, particularly in such leaky defects (see information about Omenn syndrome above).

When T lymphocytes are present, the following laboratory findings have been reported:

1. A TCR complex expression defect is always observed, with 2- to 100-fold less TCR on patient versus normal control T cells using standard CD3ε-specific monoclonal antibodies. It may be severe (more than 10-fold), as observed in CD247 or (partial) CD3ε defects, or mild (less than 5-fold), as observed in CD3γ or (partial) CD3δ or TCRα defects. Thus, a different hierarchy for invariant chain dependence can be proposed for T-cell selection (CD3ε ≥ CD3δ > CD3γ ≥ CD247, see above) as compared with TCR complex expression when some T cells are selected (CD3ε ≥ CD247 > CD3δ ≥ CD3γ). This suggests differential signaling versus structural roles of the different chains during T-cell development.
2. Both αβ and γδ T cells can be detected, but with a restricted repertoire, with few qualifying as recent thymus emigrants (measured using TCR Rearrangement Excision Circles or $CD45RA^{+}CD27^{+}$ T cells). However, notable exceptions have been observed, such as partial CD3δ and TCRα defects, which show a $T\alpha\beta^{\downarrow}T\gamma\delta^{+}B^{+}NK^{+}$ immunophenotype with a fairly normal γδ T-cell compartment (Morgan et al, 2010, Gil et al, 2011).
3. In rare cases, two T-cell populations are detected: one with impaired TCR complex expression and a second with normal TCR complex expression (Rieux-Laucat et al., 2006). Somatic mutations that reverted to wild type in certain T-cell clones were found to explain these findings (see the section on mutations analysis below).

Table 11.1 **TCR COMPLEX DEFICIENCIES**

TCR COMPLEX DEFICIENCIES				REFERENCESA		NUMBER OF	
PROTEIN	GENE	CHR.	OMIM	COMPLETE	PARTIAL	FAMILIES	PATIENTS
CD3γ	*CD3G*	11	186740	1–5		3	5
CD3δ	*CD3D*	11	186790	6–9	10	7	16
CD3ε	*CD3E*	11	186830	7	11	2	4
CD247[b]	*CD247*	1	186780	12	13	2	2
TCRα	*TRAC*	14	186880		14	2	2
					Total	16	29

[a] [1] Arnaiz-Villena et al., 1992;[2] Sanal, 1996;[3] van Tol et al., 1997;[4] Allende, 2000;[5] Recio, 2007;[6] Dadi, 2003;[7] de Saint Basile et al., 2004;[8] Takada, 2005;[9] Marcus et al., 2011;[10] Gil et al., 2011;[11] Soudais, 1993;[12] Roberts, 2007;[13] Rieux-Laucat et al., 2006; [14] Morgan, 2011.

[b] Also known as TCRζ or CD3ζ

MOLECULAR BASIS

The lack of any invariant TCR complex chain has a profound impact on αβ TCR, pre-TCR, and γδ TCR expression and function. As these receptors are required for T-cell development, T lymphocytopenia ensues in patients, and adaptive immunity is impaired. Different invariant chains show different effects on T-cell selection, as shown in Figure 11.2, supporting the hierarchy indicated above (CD3ε ≥ CD3δ > CD3γ ≥ CD247). TCRα strictly associates to CD3δε dimers, whereas TCRβ has been shown to interact with γε as well as δε dimers before CD247 associates to the TCR complex (Call et al., 2002). This may explain the differential effect of the lack of CD3δ or ε, as compared to CD3γ (or CD247), on T-cell development, which is blocked in complete CD3δ or ε deficiency, but only impaired in human CD3γ or CD247 deficiency.

Table 11.2 **TCR COMPLEX DEFICIENCIES: CLINICAL AND IMMUNOLOGICAL DATA**

CD3γ

Family	*1*			*2*	*3*	
Nationality	Turkey				Spain	
Patient/sex	P1 M	P2 M	P3 M	P4 M	P5 M	
Consanguineous?	YES				NO	
Mutation	Early protein truncation (EPT)					
Diagnosis at (m)	3	7	48	12	48	
Present age[1]	†9 m	†20 m	18 y	†32 m	28 y	
BMT[2]	No	ID	No	No	No	
Lymphopenia (% T cells)	29	39	40	35	43	
Cause of death[3]	Sepsis	Pneumonia	AW	Pneumonia	AW	

[1] 2009 †=exitus at; y (years); m (months)

[2] ID (HLA-matched sibling)

[3] AW (alive and well)

CD3ε

Family	*1*			*2*	
Nationality	French				
Patient/sex	P1 M	P2 F	P3 M	P4 F	
Consanguineous?	NO	YES			
Mutation	Exon 7 skipping (EPT)	Early protein truncation			
Diagnosis at (m)	24	?	1	birth	
Present age[1]	20 y	†5 m	†3 m	†2 m	
BMT[2]	No	No	No	H	
Lymphopenia (% T cells)	63%	?	?	<1%	
Cause of death[3]	AW	Pneumonitis	CMV	ADV	

[1] 2009 y (years); m (months); ND (not done)

[2] H (haploidentical)

[3] AW (alive and well); ADV (adenovirus); CMV (cytomegalovirus)

CD3δ

Family	*1*					*2*		*3*	*4*		*5*	*6*
Nationality	Canada Mennonites					France			Japan		Ecuador	
Patient/sex	1 F	2 M	3 M	4 F	5?	6 F	7 F	8 M	9 F	10 M	11 M	12 M
Consanguineous?	YES								NO			
Mutation	Early protein truncation (exon 2/3)								Exon 3 skip		Exon 2 skipping	
Diagnosis at (m)	0	2	2	?	?	3	0	5	3	0	14	4
Present age[1]	8 y	†2 m	†3 m	>17 y[4]	?	†5 m	†6 m	†6 m	†3 m	3 y	19 m	†5 m
BMT[2]	MUD	No	No	MUD	MUD	No	H	H	MUD	CB	H	MUD
Lymphopenia (% T cells)	0.1–0.6%			?	?	<1%		0%	1.7%	0.1%	14%	30%
Cause of death[3]	AW	ADV	CMV	AW	AW	CMV	Asperg	EBV	CMV	AW	AW	CMV?

[1] y (years); m (months)

[2] MUD (marrow unrelated donor); H (haploidentical); CB (cord blood)

[3] AW (alive and well); ADV (adenovirus); CMV (cytomegalovirus); EBV (Epstein-Barr virus); Asperg (Aspergillus)

[4] Had a healthy baby in 2008

(continued)

Table 11.2 (CONTINUED)

	CD247		TCRα	
Family	*1*	*2*	*1*	*2*
Nationality	Caribbean	Hawaii	Pakistani	
Patient/sex	P1 M	P2 F	1 F	2 M
Consanguineous	?	NO	YES	
Mutation (*leaky*)	Early truncation	Late insertion	Exon 3 skipping	
Diagnosis at (m)	4	10	15	6
Present age	8 y	10 y	?	?
BMT	Haploidentical	Haploidentical	Haploidentical	Haploidentical
Lymphopenia (% $CD3^{dull}$ T cells)	4–17%	63%	21%	50%
Cause of death	Alive & well	Alive & well	Alive & well	Alive & well

FUNCTIONAL ASPECTS

TCR complex function obviously cannot be studied in patients with TCR complex defects that block T-cell development. When some T cells are present, meaningful comparisons with normal individuals are difficult because T-cell subset representation and surface TCR complex expression are altered. Nonetheless, it is clear that normal TCR signaling is possible in vivo, since selection took place in those patients and in some cases (CD3γ, partial CD3ε) normal antibody responses indicate intact helper T-cell functions. T-cell lines from patients have been difficult to derive. Our studies in human CD3γ-deficient primary T cells, interleukin (IL)-2-dependent T-cell lines, and Herpesvirus saimiri- or HTLV-I-transformed T lymphocytes indicated that CD3γ contributes to but is not required for the regulation of TCR trafficking in resting and antigen-stimulated mature T lymphocytes (Torres et al., 2003). Despite its effects on TCR complex expression (likely due to impaired recycling), CD3γ is dispensable for several TCR-induced mature T-cell responses, such as calcium flux, cytotoxicity, up- or downregulation of several surface molecules, and proliferation and synthesis of certain cytokines (TNFα). In contrast, phorbol myristate acetate-induced TCR complex downregulation and TCR-induced synthesis of other cytokines (IL-2) as well as adhesion and polarization were severely impaired (Arnaiz-Villena et al., 1992; Pacheco-Castro et al., 1998; Perez-Aciego et al., 1991; Torres et al., 2002). The lack of CD3γ causes a stronger impairment of αβTCR expression in $CD8^+$ than in $CD4^+$ T cells in humans and in mice. We have shown that this is due to biochemical differences in the intracellular control of αβTCR complex assembly, maturation, or transport between the two lineages, which result in conformational lineage-specific differences regulated by activation or differentiation both in normal and in CD3γ-deficient primary T cells (Zapata et al., 1999, 2004). More recently, we have reported that the lack of CD3γ in humans caused a stronger impairment of CD3 expression in αβ than in γδ T cells (Siegers et al., 2007), whereas the opposite is true in partial CD3δ deficiency (Gil et al, 2011).

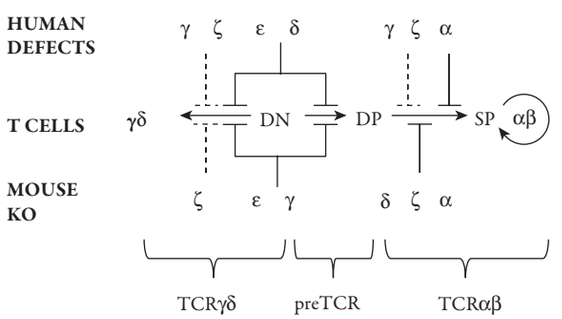

Figure 11.2 Leaky (dashed) or severe (solid) block of early T-cell differentiation caused by complete invariant TCR complex chain defects in humans or mice. αβ T-cell development is simplified in two steps: (1) pre-TCR-mediated double-negative (DN) CD4–CD8– to double-positive (DP, $CD4^+CD8^+$) transition and (2) αβ TCR-mediated positive/negative selection and generation of single-positive (SP) $CD4^+$ and $CD8^+$ αβ T cells. γδ T cells develop from DN thymocytes. CD247 is depicted as ζ for brevity.

MUTATION ANALYSIS

Mutation analysis was started by probing T-cell RNA with *CD3*, *CD247*, or *TRAC*-specific sequences. For some CD3δ defects, microarray analysis of thymocyte RNA revealed low specific transcript levels. In all cases, cDNA was synthesized and used to amplify and sequence TCR complex genes. This revealed the presence of point mutations or small deletions (Fig. 11.3), which could be traced with mutation-specific oligonucleotides, restriction enzymes, or direct sequencing. Small deletions were due to splicing site mutations, which were identified on genomic DNA by sequencing relevant exon boundaries. As a consequence, no or very few specific proteins of the TCR complex could be detected biochemically.

In a partial CD247 deficiency, reversion of some T-cell clones to normal expression was observed in vivo as a consequence of additional mutations in T-cell precursors (Rieux-Laucat et al., 2006).

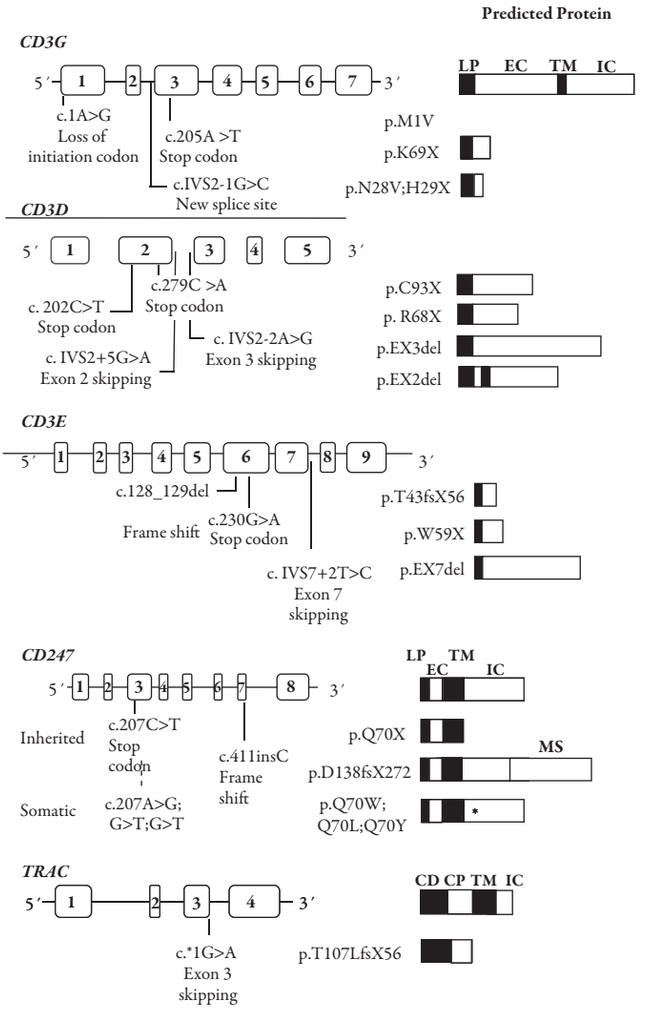

Figure 11.3 Mutations reported in genes encoding for TCR complex chains and predicted proteins. LP, leader peptide; EC, extracellular; TM, transmembrane; IC, intracellular; CD, constant domain; CP, connecting peptide; UT, untranslated.

STRATEGIES FOR DIAGNOSIS

Definitive: Male or female patient with surface TCR complex expression defect, selective peripheral blood T lymphocytopenia ($T^-B^+NK^+$ or $T^{+/-}B^+NK^+$ phenotype), and mutations in a TCR complex gene (such as *CD3G, CD3D, CD3E, CD247*, or *TRAC*).

Probable: Male or female patient with surface TCR complex expression defect and selective peripheral blood T lymphocytopenia ($T^-B^+NK^+$ or $T^{+/-}B^+NK^+$ phenotype)

Spectrum of disease: From SCID (common) to healthy (rare, overlooked?). Complete CD3ε or CD3δ defects show the $T^-B^+NK^+$ phenotype, whereas complete CD3γ or CD247 defects and partial defects tend to show the $T^{+/-}B^+NK^+$ phenotype. T-cell revertants with normal TCR complex expression due to somatic mutations may be present.

Differential diagnosis: With patients showing $T^-B^+NK^+$ or $T^{+/-}B^+NK^+$ phenotypes, such as those with defects in IL7Rα, FOXN1, Coronin-1A, Zap70, MHC class I or II, PNP, ADA, or DiGeorge syndrome

Testing for the percentage of $CD3^+$ lymphocytes may not be enough to detect TCR complex deficiencies, particularly when some T cells are present. Analyzing the mean fluorescence intensity is mandatory, as well as using a range of TCR-, CD3-, and CD247-specific monoclonals. The expression defect follows the CD3ε ≥ CD247 > CD3δ ≥ CD3γ hierarchy with a wide fold-difference range.

Biopsy specimens from lymphoid tissues should be thoroughly studied (Arnaiz-Villena et al., 1991; Dadi et al., 2003; Morgan et al., 2011) and T cells preserved if possible (Pacheco et al., 1998; Perez-Aciego et al., 1991) and analyzed by immunoprecipitation (Perez-Aciego et al., 1991; Thoenes et al., 1992) and molecular biology techniques (Arnaiz-Villena et al., 1992; Soudais et al., 1993).

MODE OF INHERITANCE, CARRIER DETECTION, AND PRENATAL DIAGNOSIS

TCR complex deficiencies are autosomal recessive disorders. Heterozygotes are healthy and cannot be easily distinguished from normals by standard laboratory tests, although half-normal CD3 expression levels have been reported by flow cytometry (Brooimans et al., 2000; Muñoz-Ruiz et al., 2013) or biochemistry (van Tol et al., 1997). Thus mutation analysis must be performed in each case, as explained above. Restriction fragment length polymorphism (RFLP) analysis using TaqI and a *CD3E* probe (50% heterozygosity) or polymorphic markers may help to define *CD3GDE* haplotype inheritance for carrier detection and/or prenatal diagnosis, since recombination within the *CD3* gene complex is rare.

TREATMENT AND PROGNOSIS

Unless the patient is transplanted, the prognosis is very poor for those with complete defects except CD3γ and for most partial defects (see Table 11.2). Matched related, haploidentical mismatched related (MMRD), matched unrelated (MUD), and mismatched unrelated donors have all been used for hematopoietic stem cell transplantation, with bone marrow, peripheral blood, or cord blood as sources. The recipients generally underwent myeloablative conditioning. The largest series consisted of patients with CD3δ defects; they showed a superior outcome using MUD as compared to MMRD (Marcus et al, 2011). Viral infections (herperviruses) are the most common cause of death among transplanted patients. Successfully transplanted patients have been shown to lead a normal life up to 18 years posttransplantation.

A few patients had no immunodeficiency symptoms and thus did not receive hematopoietic stem cell transplantation (CD3γ, partial CD3ε), reaching their third decade in good health. In those cases prophylactic intravenous immunoglobulin (IVIG) with (Le Deist et al., 1991) or without (van Tol et al., 1997) antibiotics were used, or antibiotics only when symptoms developed (Allende et al, 2000). The observation

that most antibody responses were normal in vivo in one case prompted a comprehensive vaccination program, excluding attenuated live viruses. No secondary effects were recorded. Thus, this approach may be helpful for other TCR complex-deficient patients on a preventive basis. Bronchial asthma in one case was treated with ketotifen and cromolyn sodium between 3.5 and 7 years of age (Sanal et al., 1996), followed by salbutamol sulfate and sodium chromoglycate to manage his nonatopic hyperreactive airway, including eformoterol with occasionally inhaled steroids. Gene therapy protocols were tested in vitro (Sun et al., 1997). However, transfer of CD3γ into mature T cells may disrupt their intrathymic fine tuning (Pacheco-Castro et al., 2003). Thus, lymphoid progenitors may be better targets in this case, although the selective advantage of transduced over untransduced T cells remains to be established.

ANIMAL MODELS

Single as well as multiple TCR complex deficiencies have been created in mice through gene targeting (Malissen et al., 1999; Mombaerts et al., 1992). Ablation of any invariant TCR complex protein essentially blocked T-cell development, although at different intrathymic checkpoints, and to a different extent (see Fig. 11.2). Indeed, all invariant TCR complex proteins, except CD3δ, are required for T-cell selection at the pre-TCR (TCRβ) checkpoint, with the following hierarchy: CD3ε > CD3γ > CD247. However, all invariant TCR complex chains, including CD3δ, are required for T-cell selection at the TCRαβ checkpoint and for αβTCR surface expression. Interestingly, CD3δ is also dispensable for γδ T-cell selection and for γδTCR surface expression in mice, but not in humans (Dadi et al., 2003). This is due to a differential stoichiometry of the γδTCR between the species (Siegers et al., 2007). The mouse surface γδTCR does not incorporate the CD3δ subunit; thus, its stoichiometry is TCRγδCD3εγεγζζ rather than TCRγδCD3εδεγζζ, as observed in humans (see Fig. 11.1). The murine models are similar to human CD3 deficiencies in some aspects (ε > γ in αβTCR expression, no peripheral T cells when CD3δ is lacking) but not in others (peripheral blood T-lymphocyte numbers are clearly higher in humans lacking CD3γ). Thus, peripheral lymphoid expansion mechanisms may differ between species. CD3 gene inactivation in mice, even when kept in pathogen-free facilities, may cause pathological manifestations, including enteropathy in ζ/η- or CD3δ-deficient mice, which resemble those observed in some CD3γ- or CD3δ-deficient humans.

CONCLUDING REMARKS

The TCR complex is first expressed and used by T cells early during their intrathymic development. Accordingly, complete TCR complex deficiencies strongly impair early T-cell differentiation events in humans, generally causing SCID. TCR complex deficiencies provide insights into the redundant and unique roles of these transmembrane molecules for TCR complex assembly and signal transduction and thus for T-cell selection and antigen recognition, which are not always recapitulated by murine models.

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