REVIEW
Inborn errors of immunity and immunodeficiencies: Antibody-mediated pathology and autoimmunity as a consequence of impaired immune reactions

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B-cell tolerance to self-antigen is an active process that requires the temporal and spatial integration of signals of defined intensity. In common variable immune deficiency disorders, CTLA-4 deficiency, autoimmune lymphoproliferative syndrome, or in collagen VII deficiency, genetic defects in molecules regulating development, activation, maturation, and ECM composition alter the generation of B cells, resulting in immunodeficiency. Paradoxically, at the same time, the defective immune processes favor autoantibody production and immunopathology through impaired establishment of tolerance. The development of systemic autoimmunity in the framework of defective BCR signaling is relatively unusual in genetic mouse models. In sharp contrast, such reduced signaling in humans is clearly linked to pathological autoimmunity. The molecular mechanisms by which tolerance is broken in these settings are only starting to be explored resulting in novel therapeutic interventions. For instance, in CTLA-4 deficiency, homeostasis can be restored by CTLA-4 Ig treatment. Following this example, the identification of the molecular targets causing the reduced signals and their restoration is a visionary way to reestablish tolerance and develop novel therapeutic avenues for immunopathologies.

Keywords: B-cell receptor · autoantibodies · autoimmunity · extracellular matrix · inborn errors of immunity

See accompanying Commentary by Ehl and Thimme.

Introduction

Autoantibodies are immunoglobulins specific for self-antigens. Autoantibodies are found also in healthy individuals [1], but they are not linked to pathology. Autoantibodies can be pathogenic for
several reasons (reviewed in [2]). For instance, disease can be driven by the specificity of the antibody leading to activation or inhibition of the target protein, like in Grave’s disease or in myasthenia gravis, respectively. Additionally, autoantibodies can drive inflammation and pathology by forming immune complexes and activating complement, in tissues such as skin or kidneys, like in systemic lupus erythematosus (SLE). Autoantibodies recognizing self-antigens can also bind Fc receptors activating innate immune cells to phagocytose the targets or can induce the killing of the target by NK cells such as in antibody-dependent cytotoxicity. Therefore, the pathogenicity of the autoantibodies (reviewed in [2]) can be mediated by their variable region and specificity, but also by their constant part. In both cases, the availability and binding to the self-antigen will be essential to induce pathology.

Tolerance limits the generation and pathogenicity of autoantibodies. The primary antibody repertoire generated in the BM bears the intrinsic risk of the occurrence of self-reactive specificities. Indeed, central tolerance mechanisms avoid that self-reactive B cells with high affinity for self-antigen leak out of the BM [3]. However, the mechanisms of central tolerance are not fully understood. It has been shown that the primary repertoire is largely polyreactive and able to recognize antigens (including self-antigens) at low affinity [4]. In periphery during maturation from transitional to naive cells, an additional step of selection for self-reactive specificities occurs [5]. Clonal deletion or receptor editing of self-reactive B cells are not the only mechanisms suggested to control primary repertoire self-reactivity. In new concept of adaptive tolerance [6], affinity-matured autoreactive IgM generated by activation of B cells by polyvalent autoantigen complexes can bind the autoantigen and protect it from degradation and consequent presentation to T cells. In adaptive tolerance, the complexity of the antigen (monovalent vs. multivalent) can influence generation and expansion of pathogenic autoantibodies. In fact, monovalent antigen by binding to IgD increases the threshold of B-cell receptor (BCR) activation and prevent self-reactive naive B-cell activation [7]. Polyvalent antigens can well induce activation of IgD and IgM and promote GC maturation of the cells. Furthermore, the GC itself contributes to B-cell selection and tolerance, principally by limiting T-cell help [8, 9].

Break of tolerance to self-antigens is traditionally thought to be the result of hyperactivation of the immune system. In complex models of autoimmunity such as rheumatoid arthritis (RA) or SLE, enhanced lymphocyte activation, augmented innate immunity responses, and increased cytokine secretion have been involved in immunopathology. Based on this knowledge, the current therapeutic approaches are centered on immunosuppression. Several of these approaches are currently used in the clinic, including general immune suppression targeting both T and B cells by using steroids or mycophenolate, inhibition of specific inflammation mediators such as tumor necrosis factor (TNF) or interleukin-1 (IL-1), or broader ablation of cytokine-mediated effects by inhibitors of the cytokine signaling pathways, for example, by Janus kinases (JAKs) inhibitors. These approaches are efficient in inducing and/or maintaining disease remission, but often do not revert the underlying immunopathology.

The studies of inborn errors of immunity clearly showed that not only hyperactivation but also defects in immunological processes result in break of tolerance, generation of autoantibodies, and consequent immunopathology [10–12]. Based on this rationale, the therapeutic approach to these diseases should also consider reconstruction of the deficient process or the missing signal rather than only focusing on immune suppression. Prototypical examples of this immunological paradox are failures in B-cell antigen receptor (BCR) activation and downstream signaling cascades, like Cavelin 1 deficiency in mouse models [13], human inborn mutations in the kinase BTK in patients suffering from X-linked agammaglobulinemia [14], alterations of expression of the kinase LYN in patients with SLE [15], or defects in BCR signaling in patients with common variable immunodeficiency (CVID) [16]. Additional examples are disturbed T–B cell interaction outside and within the GC as observed in Fas [17] or CTLA-4 deficiency [18, 19], or disturbed extracellular matrix (ECM)-upheld architecture and signaling in secondary lymphoid organs such as in the case of collagen VII deficiency [20–22]. The common denominator of all these conditions is the presence of autoantibodies (Fig. 1, Table 1), indicating a loss of tolerance in the B compartment. We will discuss below how pathogenic antibody generation can be the result of an impaired immune reaction, and how restoration might be the therapeutic avenue to reinstate homeostasis. Briefly, we will focus on how pathogenic antibodies can be a consequence of the alteration of the following steps: (1) BCRs intrinsic signals (Fig. 1A), (2) signals after antigen encounter (Fig. 1B), and (3) interactions with the ECM (Fig. 1C).

**Impaired B-cell selection as consequence of reduced BCR activation**

BCR signaling strength is crucial for the selection of the primary naïve repertoire and the recruitment of B cells to the GC or to mount extrafollicular responses. In complex models of autoimmunity such as in SLE or RA, increased BCR signaling is associated with a break of tolerance and the subsequent generation of autoantibodies [23]. In fact, enhanced activity and/or expression of elements of the BCR signaling cascade such as BTK [24] and PI3K [25, 26] have been reported. Mouse models of autoimmunity are also mainly associated with scenarios of enhanced signaling such as ablation of receptors and signaling molecules known to repress BCR signals like CD22, Fcγ receptor IIb, SHP1 or PTPN22, or mutations in the phosphatase CD45 (reviewed in [27]). However, in several human inborn errors of immunity, impaired BCR signaling is closely linked to antibody-mediated immunopathology highlighting the need of novel studies addressing this enigmatic immunological paradox.

The plasma membrane of B cells is highly compartmentalized, and a special ordered structure that separates IgM and IgD BCRs has been repetitively observed [28–32] (reviewed in [33]). The IgM- and the IgD-BCRs reside in different membrane compartments with distinct protein and lipid composition. The functional consequences of disrupted membrane compartmentalization were recently demonstrated in Caveolin 1-deficient mice, in which the
disturbed distribution of IgM and IgD results in reduced BCR signaling [13] (Fig. 1). Surprisingly, these mice developed autoantibodies and spontaneous germinal centers when aging. Moreover, immature B cells showed a skewed primary BCR repertoire that was enriched for self-reactive specificities pointing out to a break in central tolerance. The association between impaired BCR signaling and autoimmunity is a very rare finding in animal models. Mice harboring mutations in genes encoding key components of the BCR signaling machinery have been deeply studied; however, these mutations mainly suppress B-cell development or autoimmunity in disease-prone mouse models rather than exhibit a break in tolerance. In addition to Caveolin 1-deficient mice, one of the few examples in which impaired BCR signaling leads to systemic autoimmunity is the lupus-prone NZM2410-derived allele of Slamf6, which results in weaker BCR signaling than the C57BL/6 allele does in immature B cells [34].

BCR signaling in patients with inborn errors of immunity: Lessons learned for disease targeting

In sharp contrast to mouse models, reduced BCR signaling as a cause of B-cell tolerance break is much more common in humans with inborn errors of immunity presenting with antibody deficiency, such as CVID disorders. This rare genetic syndrome has been associated with defects in components of the BCR signaling complex such as CD19, CD20, CD81, or CD21, but also with other molecules important for T-dependent B-cell activation and B-cell survival [35]. About 25% of CVID patients develop autoantibody-mediated cytopenias. Autoantibody generation in these patients is associated with reduced responses to BCR activation [36, 37].

In the same line, patients with BTK mutations carry an antibody repertoire enriched in autoreactive clones [14]. Why is the reduction of BCR activation more often associated with the generation of autoantibodies in humans? And why do mice models fail to recapitulate human phenotypes?

One possibility is that autoimmunity in the settings of reduced BCR signaling needs genetic modifiers that are not present in monogenic mouse models. Indeed, the majority of CVID patients are likely carrying polygenic traits predisposing to disease. In line with this, disease onset and severity of autoimmunity in the Caveolin 1-deficient mice was more evident in a mixed genetic background [13]. Such correlations raise the possibility that a break in central tolerance as consequence of BCR-associated defects is necessary, but not sufficient to cause autoimmunity. Thus, additional alterations in peripheral B-cell tolerance, Table 1. Disease models discussed in text with description of the defective immunological process and the potential therapeutic approach complementing the deficient immunological process

| Disease model       | Impaired immunological process                                                                 | Potential treatment approach                          |
|---------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------|
| CVID                | Reduced/defective B-cell receptor signaling                                                   | Restoration of signaling                               |
| CTLA-4 deficiency   | Impaired T-B interaction                                                                      | CTLA-4 Ig replacement                                 |
| LRBA deficiency     |                                                                                               |                                                       |
| ALPS (Fas deficiency)| Defective B-cell activation, differentiation, and apoptosis                                   | Modulation of PI3K signaling (mTOR inhibitors)        |
| Dystrophic epidermolysis bullosa (DEB) | Disturbed immune-supporting ECM                                                              | Reconstitution of ECM through gene- or protein-replacement or biologics and small molecules |
abnormal T cells, disturbed Toll-like receptor (TLR) 7 or TLR9 signaling [38, 39], intrinsically disturbed T-B cell interactions, and/or as consequence of disturbed architecture of the secondary lymphoid organs might contribute to the immunopathology. Indeed, Caveolin 1 deficiency in other immune cells, in addition to B cells, favors the development of immunopathology in aged mice [13]. Remarkably, T cells deficient in Caveolin 1 exhibited altered TCR and TGFβ1 signaling and generation of regulatory T cells after allogeneic hematopoietic cell transplantation [40].

Alternatively, pre-BCR and BCR signaling during early B-cell development plays a more prominent role in humans compared to mice. Clinical reports have indicated that patients having SCID due to defects in IL-7R signaling have detectable peripheral blood B cells [41–43]. In contrast, mutant mice with defects in IL-7 or in components of the IL-7R exhibited a complete blocked B-cell development [44–46]. Thus, B-cell development and establishment of central tolerance in humans more profoundly depends on the quality of the pre-BCR and BCR signaling, and therefore, decreasing the strength of this signaling might subvert central tolerance mechanisms such as receptor editing and negative selection, allowing thus the escape of autoreactive clones into the periphery driving autoantibody production.

In the framework of this immunological paradox, the reconstitution of BCR signaling would contribute to restoration of the homeostasis. However, to take this therapeutic approach, it is necessary to identify the exact mechanism underlying the failure in central tolerance without generally increasing BCR signaling with the risk of inducing a break in peripheral tolerance that would again result in immunopathology. Taken together, the development of B-cell autoimmunity seems to happen at the extremes of BCR signal strength; too little signal induces breaks in central tolerance while too much signal might break peripheral tolerance [47]. Indeed, modulating BCR signaling with small molecules is a promising approach [48, 49]. In fact, BTK targeting seems a promising approach in MS [50]. In other diseases, the outcome of the clinical studies is less straightforward [51], suggesting that in some cases combinatorial treatment may be beneficial. Nevertheless, a better understanding of the role of BCR signaling in autoantibody generation is mandatory to design novel therapeutic approaches. However, a major challenge remains to spot how to restore a physiological range of BCR signal strength allowing intact B-cell tolerance.

**Impaired B-cell selection upon antigen encounter**

Autoantibodies are secreted by plasmablasts and plasma cells that have escaped peripheral tolerance check-points. For example, immature B cells are prone to cell death when stimulated via the BCR by a self-antigen, but signals such as BAFF, TLR, or CD40L signaling may rescue them and guide them into the memory compartment [52]. Linked to this, increased availability of self-antigen, such as in defective clearance of apoptotic cell in SLE [53], can contribute to break of tolerance. The expression of inhibitory receptors, such as CD22 and Fcγ receptor IIb, regulates the activation of B cells, and mice deficient in those develop autoimmunity [54]. Furthermore, an imbalance between extracellular and GC maturation may result in autoimmunity. In fact, upon initial activation in the secondary lymphoid organs, mature B cells can rapidly develop via the extracellular pathway into plasma cells that have low affinity for the antigen and are short lived or move into the GC where they will undergo affinity maturation and selection [55] to develop into memory B cells and long-lived plasma cells. Indeed, memory B cells can also represent a reservoir of self-reactive B cells [56], which can be quickly reactivated and secrete autoantibodies. Hence, on one side a functioning GC is pivotal to the maintenance of tolerance and on the other side, the extracellular response, as it misses the process of affinity maturation, carries the risk of generation of plasma cells with polyreactive or autoreactive specificities. Actually, an expansion of the extracellular response has been reported in human SLE, where it correlates with autoantibody production and disease activity [57–59] and in SARS-CoV2 infection, where it correlates with disease severity and break of B-cell tolerance [60, 61].

**T-B interaction and autoantibody formation**

Extracellular B-cell activation can be sustained by T-independent (e.g. TLR7) or T-dependent signals [58, 62]. T–B interaction drives class switch in the extracellular space [63] and is based on positive B-cell selection in the GC. In fact, T cell help is limiting in the GC, therefore higher affinity cells, collecting and processing more antigen, can receive help from cognate T follicular helper (TFH) cells in the form of CD40L and IL-21 more effectively, ensuring selection [8]. T-cell help also guides the shuffling between the dark zone, where somatic hypermutation occurs, and the light zone where B cells are selected [9, 64, 65]. In the GC, signals from both BCR ligation and interaction with TFH cells are integrated by the B cells, and both are required for positive selection [66]. How can GC selection be disrupted? How can failing of the GC reaction result in immunopathology? An increase in T-cell activation and/or availability can disrupt the delicate balance necessary to select B cells, as the help is not limiting anymore, contributing to the escape of self-reactive or poorly selected B cells. One example of this is CTLA-4 insufficiency (Fig. 1). Alternatively, a missing signal within the B cells can disrupt the selection dynamic and lead to autoimmunity, such as in - Fas deficiency (Fig. 1). In both situations, impaired cell fate decisions and GC reactions results in autoantibody production, and thereby, in immunopathology mostly in the form of cytopenia.

CTLA-4 is an inhibitory receptor, upregulated on T cells upon activation, counteracting the interaction between the costimulatory molecules CD80 and CD86 on the APCs, and CD28 on the T cells. CTLA-4 expression by T follicular regulatory cells outside of the GC contributes to B-cell differentiation, entry, and function into the GC [67]. CTLA-4-deficient mice show sponta-
neous generator -12pt of large GCs [68], which is associated with enhanced TFH cells differentiation and enhanced ICOS expression [68].

**CTLA-4 deficiency in humans**

CTLA-4-deficient patients show a quite peculiar disturbance of the B-cell compartment with progressive reduction of the B cells and an expansion of CD21low or age-associated B cells [18, 62], which are recently being re-classified as extrafollicular response B cells. Therefore, in CTLA-4-deficient patients enhanced T-cell activation results in a dysregulated GC reaction with large spontaneous GCs, as well as expansion of extrafollicular response. The defect in these immunological processes results in the generation of autoantibodies leading to immunopathology in CTLA-4-deficient patients [69]. In line with this view, in these patients the immune homeostasis can be restored by the exogenous CTLA-4 substitution using abatacept, a chimeric molecule composed by CTLA-4 fused to the constant portion of an immunoglobulin. This chimeric molecule has been developed to treat RA with the idea to induce inhibition of T-cell activation. The use of abatacept in these patients results in dramatic improvement of symptoms including autoimmunity [70–72]. Interestingly, abatacept treatment in Sjögren’s syndrome patients was shown to impact BCR signaling by restoring BTK protein expression in B cells to physiological levels [73], strongly supporting that restoration of BCR signaling may contribute as well to reverting immunopathology during treatment. Hence, the immunopathology is reverted by restoring the balance between T- and B-cell activation and the function of the GC response.

**Autoantibody-mediated autoimmunity in Fas deficiency in humans**

The selection dynamic of the GC B cells might also be disrupted by a missing signal within the B cells as it is the case in FAS deficiency. Patients with mutations in FAS that are associated with autoimmune lymphoproliferative syndrome (ALPS) [74] present with lymphoproliferation and autoantibody-mediated cytophenia (Fig. 1). In these patients, the T-cell compartment is largely dysregulated with the expansion of double negative T (DNT) cells [75, 76] that results in structural disruption in secondary lymphoid organs and a secondary defect in marginal zone B cells [77]. ALPS patients present with autoantibodies and reduced B-cell memory [17, 78]. In ALPS patients with somatic FAS mutations [79, 80], we showed that in contrast to Fas expressing memory B cells, BCRs of FAS deficient memory B cells studied in the same individual are largely polyreactive and have characteristics of self-reactivity with long CDR3s and increased frequency of positively charged amino acids [17]. These studies demonstrated that B-cell selection in the GC is impaired in absence of Fas signaling in line with the results obtained in mouse models. Indeed, conditional deletion of Fas in all B cells by using the mb1-cre promoter, or more specifically only in cells that underwent class switch by using the gamma-1 promoter, resulted in autoantibody production, T-cell proliferation, and anatomical disruption of the spleen in mice [81]. These results suggested that intrinsic defects in Fas in B cells are sufficient to disrupt GC selection and to break tolerance. Controversially, it has been also shown that Fas is dispensable for GC selection, but is essential to guard the generation of rogue B cells, which are B cells that escape selection, are prone to be self-reactive, and are mostly of IgE subclass [82]. The question remains how Fas deficiency mechanistically explains the accumulation of autoreactive B cells during the GC reaction. A simple defect in apoptosis of B cells fails to explain the extensive disruption of the B-cell compartment, including the imbalance between memory cells and plasmablasts. Further proof of Fas signaling beyond apoptosis comes from a palmitoylation defective Fas variant carrying the C194V mutation, which cannot be recruited to lipid rafts, and therefore, it cannot signal apoptosis [83]. In contrast, nonapoptotic signaling can still be transmitted by this variant. Reconstitution of autoimmune-prone MLR/lpr mice with this variant is sufficient to revert the autoimmune phenotype, even though the cells are still apoptosis resistant [83]. Hence, it is worth to consider that disruption of nonapoptotic signaling may influence the GC dynamic resulting in impaired selection and contribute to disease pathogenesis in ALPS. The PI3K pathway is an interesting candidate to mediate nonapoptotic signals by Fas. Peripheral DNT cells have been shown to have high level of PI3K activation [84]. The proliferation and survival of Fas-dependent DNT cells from ALPS patients are indeed dependent on PI3K and mTOR activation [76], and DNT numbers can be successfully controlled by the mTOR inhibitor rapamycin in these patients [85]. In addition, rapamycin reduced autoantibody-mediated autoimmunity in absence of systemic signs of immune suppression [85]. The use of rapamycin seems to re-establish the homeostasis of B-cell selection. The reactivation of disease upon ceasing of the therapy suggests a disease-specific targeting [85]. Hence, in ALPS-impaired GC, maturation results in impaired B-cell selection. Understanding the molecular mechanism underlying this phenotype can explain the therapeutic effect of rapamycin in these patients, and help identify new targets to restore Fas signaling and thereby, the physiological function in B cells.

These two models exemplify the paradox that defective GC reaction and imbalance in signaling may impact B-cell fate decisions and selection favoring the break of B-cell tolerance. Restoration and re-balancing of signaling can reestablish homeostasis.

**Autoantibodies as consequence of altered cellular distribution and interaction with the ECM**

Lymphoid organs require for their functionality an intricate compartmentalization into actively communicating heterogeneous zones [86]. For this compartmentalization, architectural support by the ECM is essential. However, the ECM is not only a passive, structural unit but is actively cell instructive and communicative [87]. Within the lymphoid ECM, there is great molecular and
Dystrophic epidermolysis bullosa

Dystrophic epidermolysis bullosa (DEB) is a rare genetic skin blistering disease caused by mutations in COL7A1, encoding the anchoring fibril-forming protein collagen VII. In the skin, anchoring fibrils enable firm cohesion of the epidermal basement membrane to the interstitial ECM [91]. Absence or formation of faulty anchoring fibrils results in extremely fragile, wound-, and blistering-prone skin [91]. Importantly for immunity, collagen VII is present in primary and secondary lymphoid organs [20, 92] (Fig. 1). DEB is a progressive disease, driven by injury and tissue inflammation [92, 93]. In severely affected individuals, a fibrotic, multi-organ, highly debilitating disease develops with time [91]. The constantly high wound burden in severe DEB patients hindered the understanding of the contribution of deficiencies in other organs to the disease. To that end, genetic mouse models proved to be useful [94]. Starting with the observation that collagen VII is present in conduits in the B-cell zone of the spleen and LN s, we disclosed a mechanism by which collagen VII, via interaction with cochlin, supports anti-bacterial innate immunity [20].

The paradox we are facing in DEB is that collagen VII deficiency in lymphoid organs results in immunodeficiency, but at the same time in pathological, disease-driving autoimmunity, both in patients and mice. Genetically evoked, as exemplified above, or virally induced destruction of the ECM and cell-ECM-associated structures of lymphoid organs such as conduits has, in the few instances this has been examined, been associated with some degree of immunodeficiency [89, 95–97]. However, disease evolution in DEB also correlates with increased activity of T and B cells [93]. Pharmacological down-modulation of this inflammatory immunity in mice effectively delayed disease progression [93]. Combined with clinical trials showing benefit of immune modulation [98, 99], these data provide strong support for DEB as a partly immune-driven disease. Interestingly, the abundance of self-reactive antibodies against various skin proteins is increased in DEB patients, with auto-antibody titers mimicking those in autoimmune skin blistering disorders [22, 100, 101]. Thus, collagen VII deficiency is linked to a breach in B-cell tolerance enhancing immunopathology in patients as demonstrated by increased autoimmune blistering disease in patients suffering from DEB (Lehr et al., manuscript in revision). Thus, autoimmunity induction is probably both a consequence and a cause of further disease progression in DEB [102, 103]. Collectively, the observations made in DEB suggest that deficiencies in the ECM of lymphoid organs may result in immune-driven disease. These data warrant further studies of ECM proteins present in the lymphoid ECM and their associated diseases.

Evidence is emerging that lymphoid ECM deficiencies may also be linked to pathological immune activation. Indeed, some remarkable facts point in this direction. For instance, tolerance induction in mice increases the abundance of collagen VI present in the T-cell zone in LNs [90, 104]. On the other side, antibody-mediated targeting of collagen VI in mouse models resulted in reduced tolerance induction and enhanced graft rejection, correlating with altered migration of alloreactive T cells and T regulatory cells to the cortical ridge ECM structure at the interphase between the T- and B-cell zone [90, 105]. The concept that a breach in B-cell tolerance may be fostered by acquired or genetic alterations of the lymphoid ECM may pave the way to the identification of new players and regulators of B-cell tolerance. Also in this setting, the reconstitution of structure, when possible, would have the potential to restore homeostasis.

Conclusions

B-cell tolerance is the result of a delicate balance between intrinsic signaling, cell–cell interaction, cell location and signals from the microenvironment. Interference with these processes may result in the escape of self-reactive B cells and the production of autoantibodies leading to immunopathology. We propose that immunopathology can be the consequence of an impaired immune reaction, in the form of altered BCR activation, enhanced T-cell help, defective intrinsic Fas signaling, or ECM deficiency in secondary lymphoid organs. While the obvious approach to autoimmunity is immunosuppression, we propose that also restoration of the missing signal can be a therapeutic avenue to reinstate homeostasis. The understanding of this paradox and its mechanisms will open new possibilities for therapy and potentially for cure of antibody-mediated diseases.

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Abbreviations: ALPS: autoimmune lymphoproliferative syndrome · CVID: common variable immunodeficiency · DEB: dystrophic epidermolysis bullosa · DNT: double negative T · RA: rheumatoid arthritis · SLE: systemic lupus erythematosus

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