Recent Insights in Primary Immunodeficiency Diseases: The Role of T-Lymphocytes and Innate Immunity

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Abstract. In recent years, the field of primary immunodeficiency diseases (PID) has experienced remarkable progress with the identification of a number of new genes associated with specific diseases. Yet the diagnosis of PID remains difficult. In fact, this field requires continuous updating because once a novel molecule related to the immune function is discovered, the corresponding PID will soon be described. Since comprehensive reviews on the classification of PID are available, we concentrate here on reviewing some controversial and new issues, mainly those related to the role of T-cells and innate immunity. We will consider common variable immunodeficiency as an example of a PID where several immune pathways are impaired. We will also discuss the restricted usage of the T-cell receptor repertoire in PID. Innate immunity and Toll-like receptors (TLR) are new major players in this field. We will therefore discuss the association of TLR with the function of Bruton tyrosine kinase (Btk) that is essential in the development of B-cells and in the pathogenesis of X-linked agammaglobulinemia. Finally, we will discuss the role of mast-cells. These cells were once thought to be relevant almost exclusively to the pathogenesis of allergy. Now we know that mast cells are involved in initiating the adaptive response and may contribute to ineffective immune responses.

Keywords: immunodeficiency diseases, T-lymphocytes, Toll-like receptors, mast cells, innate immunity

Introduction

Over the last two decades, the field of primary immunodeficiency diseases (PID) has experienced remarkable advances, with the identification of mutations of genes that encode components of the immune system, thus enabling the possibility of gene therapy [1]. These mutations result in more than 90 known defects, with an overall prevalence estimated at 1:10,000. Yet despite improvements in understanding of the molecular pathogenesis of PID, many cases remain undiagnosed [2]. Moreover, several findings related to pathogenetic mechanisms are controversial. The field of PID requires constant updating because, as soon as new molecules relevant to the immune response are identified, the hunt for the corresponding immune deficiency begins, contributing to the complexity of the field. Comprehensive reviews of the classification of PID by immunological societies are updated regularly [3] and, therefore, will not be the aim of this paper. Rather, we will focus on some of the more controversial and/or new issues, mainly those related to the role of T-cells and innate immunity.
Common Variable Immunodeficiency (CVID)

CVID is a defect of Ig production diagnosed in adults and must be differentiated from the agammaglobulinemias observed in children such as X-linked agammaglobulinemia (XLA) and transient hypogammaglobulinemia of infancy [4]. In contrast to XLA, B-cells are present in CVID. Because B-cells from CVID patients can produce Ig in vitro in the presence of normal T-cells, CVID was traditionally thought to be related to an impairment of some T-cell subpopulation in providing helper signals. Despite decades of intense investigation, the pathogenesis of CVID remains elusive and, because of the number of affected immune pathways, this disease has been referred to as “the immune system in chaos” [5]. Its related disease, the selective immunoglobulin A deficiency (IGAD) [OMIM 137100], is the most common primary immunodeficiency, with a prevalence of 1/600 in Caucasians. It is associated with CVID as well as other diseases including celiac disease [6]. The affected individuals lack IgA in serum and mucosal secretions; as a result they may suffer from frequent respiratory and gastrointestinal infections.

The pathogenesis of CVID and IGAD is still poorly understood, but recent pieces of new evidence have elucidated some of the mechanisms underlying both diseases [7]. New TNFR family members have been discovered such as the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI or TNFR13B). B-cells from individuals with TACI mutations do not transduce signals, resulting in isotype switch and consequent IgG and IgA production [8,9]. TACI mutants do not respond to two ligands referred to as a proliferation-inducing ligand (APRIL) [10] and B-cell activating factor (BAFF) [11,12]. Thus, mutations in several B-cell activating factors of the receptor ligand system may be associated with both Ig defects [11,13]. In addition to defects in B-cell signalling, CVID may be the result of a T-cell defect through mutations of T-cell restricted molecules such as the inducible costimulator of activated T-cells (ICOS) [14].

In studying IGAD pathogenesis, more insight has been provided by a better understanding of the switch of IgM+, IgD+ naive B cells to IgA. This switch appears to be complex and involves a deletional recombination of switch regions upstream of C mu and the constant genes of gamma, alpha, and, eventually, epsilon regions. This class switch recombination is under the control of several factors including regulatory genes, cytokines, and a second signal delivered by members of the tumor necrosis factor receptor (TNFR) family on B-cells. The most important of these receptors is CD40. Engagement of CD40 (on B-cells) by its ligand (CD40L) expressed on T-cells induces the switch. Mutation of CD40 or its ligand results in failure to undergo isotype switch and hyper IgM syndrome [15].

In summary, mounting evidence suggests heterogeneous genetic involvement in the pathogenesis of CVID: several molecules on B and T-cells, such as TACI, its ligands, or ICOS, can be mutated in these patients [16]. In addition to its role as a survival factor for B-cells, the BAFF/BAFF-receptor interaction is also important for B-cell development and maturation through the regulation of CD21 and CD23 B-cell surface antigens [17]. Chemokines and chemokine receptors may also be involved in the pathogenesis [18].

Skewed T-cell Receptor Repertoire in PID

Peripheral blood lymphocytes from normal donors show a polyclonal TCR usage and this diversity is an important feature of the competent immune system. We have reported biased repertoires in several diseases, typically those where the immune response is thought to be addressed against well defined epitopes, such as occur in cancers [19,20] or rheumatoid arthritis [21]. Recently, a biased TCR repertoire has been reported in some forms of PID, namely CVID [22] and DiGeorge syndrome [23]. The significance of such observations is obscure, but may be attributed to oligoclonal proliferation in response to recurrent infection, as well as to reduced thymic output, which has been seen in DiGeorge syndrome [23] and CVID [24].

Innate Immunity

The traditional view of a sharp separation between innate and adaptive immune responses has been
profoundly challenged by the discovery of Toll-like receptors (TLR). In 1996, a remarkable sequence similarity between Toll, a transmembrane protein involved in Drosophila embryogenesis and human interleukin-1 (IL-1) was described and the human gene was mapped. This breakthrough subsequently permitted the discovery of a new group of human receptors commonly referred to as Toll-like receptors (TLR). Today, 10 mammalian TLR have been described [25,26]. TLR constitute an archetypal pattern recognition system that allows innate immunity to discriminate between highly diverse microbial pathogens and self.

TLR are expressed in various tissues [27] and may be expressed on the surface membrane or in the cytoplasm of several immune cells including lymphocytes, monocytes, dendritic cells, mast cells, and monocytes, thus recognizing bacterial and viral ligands. TLR were originally considered as characteristic of innate immunity [28]. Later, it became clear that TLR also play a role in initiating adaptive responses [29,30]. For instance, TLR4 signaling in small intestinal epithelium promotes B-cell recruitment and IgA production in the lamina propria [31]. Viral double-stranded RNA triggers Ig class switching in B-cells through the TLR3 pathway. Interestingly, this process occurs via BAFF [32], thus providing additional evidence of the presence of an interacting network in the immune responses.

Complement Defects

The complement pathway has a central role in innate immunity, and primary complement deficiencies (OMIM 217000, 120810, 216950) may result in severe immunodeficiencies. Recently, a defect of Ficollin-dependent complement activation resulting in increased susceptibility to infections has been described [33].

Primitive Defects of TLR

The description of new molecules of the immune system often leads to discovery of disorders caused by genetic mutations of those molecules [34]. In the case of TLR, three diseases have been so far described resulting from TLR mutations [35,36]:

1. X-linked hypohydrotic ectodermal dysplasia with immunodeficiency [37] was the first recognized example of a human disease affecting TLR function. Hypomorphic mutations within the IKKBKG (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase of gamma), a gene involved in NF-KB signaling, accounts for this X-linked recessive PID, characterized by defective specific antibody production (particularly against polysaccharide antigens) with increased susceptibility to pyogenic bacterial infections.

2. Autosomal dominant hypohydrotic ectodermal dysplasia with immunodeficiency: a single case with a missense mutation in the NFKBIA gene encoding the IkB alpha protein [38].

3. Interleukin-1 receptor associated kinase 4 (IRAK4) deficiency is a novel PID that specifically affects TLR function. IRAK4 deficiency, affecting a key signaling intermediate in the TLR pathway, abrogates signaling through all known TLR (except TLR3). IRAK4-deficient patients predominantly suffer from recurrent infections caused by pyogenic Gram-positive bacteria [39].

Several polymorphisms of TLR have also been reported [36]. More important, TLR polymorphism has been linked to altered susceptibility to infectious diseases [40,41].

Bruton’s Tyrosine Kinase and TLR

Bruton’s tyrosine kinase (Brk) mutation is responsible for X-linked agammaglobulinemia (XLA), the first PID described by Bruton in the 1950s. Brk is essential for B-cell development [42]; many lines of evidence have shown that Brk is important in several TLR-related activation pathways. For instance, Brk regulates IL-10/IL-12 production in TLR9-stimulated B-cells [43,44]. Moreover, it is required for TLR2 and TLR4-induced TNF production [45]. Brk is also required for TLR8 and TLR9 signaling [46]. Since XLA patients benefit from regular iv immunoglobulin treatment, the defect in TLR may explain the susceptibility of these patients to viral infection. In fact, enteroviral infections are the most common cause of mortality in XLA [47]. TLR8 is impaired in XLA and this contributes to entroviral infections in these patients [48]. TLR are also involved in the
pathogenesis of CVID. In fact, a recent report shows that TLR9 is defective in CVID [49]. On the other hand, Btk is required for TLR signaling in dendritic cells, thus contributing to the severity of infections in XLA patients [50]. These data shed some light on the complex interactions between innate and adaptive immunity. On the other hand, augmented TLR-9 induces Btk and provokes autoimmunity [51].

Mast cells

Mast cells are long lived CD34+ -derived cells that migrate to sites of inflammation and regulate immune responses through the production of cytokines and other inflammatory mediators. Btk is involved in regulation of mast cell growth and survival [52]. Mast cells express TLR1, TLR2, and TLR4 depending on the particular site and species [53]. The role of mast cells in immune responses was originally thought to be limited to allergic reactions [54]. However, we now know that they participate in initiating adaptive immune responses by production of chemokines [55] and in the recruitment of CD4 T-cells by IL-16 [56]. With the discovery that TLR are abundantly expressed on mast cells, it has become clear that these cells are more generally involved in immune responses. In fact, TLR3-induced activation of mast cells modulates CD8+ recruitment [57]. Finally, mast cells, through TLR, are also direct effectors of antimicrobial responses. Mast cells can participate in the recognition of viruses through TLR via production of type I interferon [58]. Mast cells can respond to enterobacterial infection through TLR4 [59]. Mast cells stimulate activated T-cells through direct contact and TNF [60]. Mast cells can counteract regulatory T-cell suppression through cytokines and enhance Th17 differentiation [61].

In recent years, evidence has pointed to a pivotal role of mast cells in the immune pathogenesis of a broad spectrum of diseases, including autoimmune diseases [62], cancer [63,64], multiple sclerosis [65], and autism [66]. No PID characterized by primary defects of mast cells have been reported so far, although it is known that acquired immunodeficiency induced by HIV may induce a mast cell defect [67]. These divergent actions of mast cells could only be made possible through their ability to secrete and respond to distinct mediators selectively [68,69].

Conclusions

The complex network highlighted in this review between adaptive and innate immunity, taking place through TLR, Btk, and mast cells, suggests the need for a new integrated approach to the study of PID. The evaluation of immunodeficiencies is currently based on quantification of Ig, lymphoid cells, and other cells that characterize the immune response. In the future, such studies should also include evaluations of TLR and their relations to mast cells and lymphocytes.

References


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