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Mini review

Th1/Th2/Th17/Treg cytokines in Guillain–Barré syndrome and experimental autoimmune neuritis

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ABSTRACT

Guillain–Barré syndrome (GBS) is an immune-mediated acute inflammatory disorder in the peripheral nervous system (PNS) of humans characterized by inflammatory infiltration and damage to myelin and axon. Experimental autoimmune neuritis (EAN) is a useful animal model for GBS. Although GBS and EAN have been widely studied, the pathophysiological basis of GBS/EAN remains largely unknown. Immunocompetent cells together with cytokines produced by various cells contribute to the inflammatory process of EAN by acting as mediators or effectors. Both GBS and EAN have hitherto been attributed to T helper (Th)1 cells-mediated disorders, however, some changes in GBS and EAN could not be explained by the pathogenic role of Th1 cells and a disturbance of the Th1/Th2 balance, which has previously been considered to be important for the homeostatic maintenance of the immune responses and to explain the adaptive immunity and autoimmune diseases. The Th1/Th2 paradigm in autoimmune diseases has been greatly challenged in recent years, with the identification of a particular T cell subset Th17 cells. Studies on the associations between Th17 cells/cytokines and GBS/EAN are reviewed. But some of them occasionally yield conflicting results, indicating an intricate network of cytokines in immune response.

Human's Guillain–Barré syndrome (GBS) is an acute inflammatory disorder in the peripheral nervous system (PNS) characterized by inflammatory infiltration and myelin and axon damage [1]. Experimental autoimmune neuritis (EAN) mediated by $CD4^+$ T cell is a useful animal model for GBS. Although GBS and EAN have been widely studied, the pathophysiological basis of GBS/EAN has been incompletely known. Both GBS and EAN have hitherto been attributed to T helper (Th)1 cells-mediated autoimmune responses; however, some changes in GBS and EAN could not be explained by the pathogenic role of Th1 cells and a disturbance of the Th1/Th2 balance, which has previously been considered to be important for the homeostatic maintenance of immune responses. Specifically, mice deficient in $CD4^+$ T cells were still susceptible to EAN induction [2]. A number of previous studies have shown that deficiencies in proinflammatory or anti-inflammatory cytokines may alter the susceptibility of animals to EAN induction [3]. Of note is that interleukin (IL)-6, IL-12 or tumor necrosis factor alpha (TNF-α), alone, is sufficient to induce demyelination in peripheral nerves. These findings suggested that cytokines may directly mediate the immunopathogenesis in GBS/EAN.

1. Generic features of GBS and classification of GBS

GBS was firstly documented as early as 1916, when three French neurologists, Drs Guillain, Barré, and Strohl described two soldiers who developed acute flaccid paralysis with spontaneous recovery [4]. As a clinical syndrome, GBS was initially a descriptive diagnosis of a combination of rapidly progressive symmetric weakness in the limbs usually with sensory disturbance, hyporeflexia or areflexia, and albuminocytologic dissociation, i.e. increased protein concentration with a normal cell count in the cerebrospinal fluid (CSF) [5]. Although the pathogenesis of GBS remains largely unclear, GBS is generally defined as an immune-mediated disorder in the PNS.

GBS consists of several subtypes of acute peripheral neuropathy. Classification of GBS into subtypes depends on an understanding of the involved nerve fiber types (sensory, motor, and autonomic) and the predominant nature of nerve or nerve root injury, e.g. demyelination versus axonal degeneration [6]. The prototype of GBS, which accounts for 90% of all GBS cases in Europe and North America, is acute inflammatory demyelinating polyneuropathy (AIDP) [6]. Acute motor axonal neuropathy (AMAN) [7] and acute motor-sensory axonal neuropathy (AMSAN) [8] are more

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Table 1
The rare GBS subtypes.

Acute sensory neuronopathy [153]
Acute pandysautonomia [154,155]
Miller-Fisher syndrome (MFS) [11]
MFS–GBS overlapping syndrome [156]
The pharyngeal–cervical–brachial variant [157]

prevalent in Asia, South and Central America [9]. Other relatively rare subtypes are summarized in Table 1. The different patterns of GBS are probably due to the diverse interplay between antibodies and T cells of divergent specificities [10]. The axonal variants of GBS (AMAN and AMSAN) and Miller-Fisher syndrome (MFS) [11] are more related to autoantibodies against ganglioside GQ1b [12], while AIDP mainly involves $CD4^+$ Th cell-induced macrophage- and complement-associated demyelination [10]. Anti-GQ1b antibodies are present in approximately 95% of patients with MFS [13].

2. EAN

EAN is an immune-mediated inflammatory disorder of the PNS that serves as an animal model for AIDP. EAN can be induced in susceptible animal strains, including mouse, rat, chicken, and monkey, etc. [14] by active immunization with whole peripheral nerve homogenates, myelin proteins P0 or P2, or their neuritogenic peptides plus Freund's complete adjuvant [15,16], or by passive transfer of P0, P2, or their peptide-specific $CD4^+$ T cell lines [17].

Pathophysiologically, EAN is characterized by breakdown of the blood–nerve barrier (BNB), robust accumulation of autoreactive T cells and macrophages in the PNS, and demyelination [1]. An alteration in BNB permeability occurs early in EAN, coincident with inflammatory cell infiltration [18]. The migration of blood-derived inflammatory cells across the BNB or the transduction of chemotactic signals for migration is a critical step in the initiation of immune responses in EAN. Cytokines, chemokines, adhesion molecules, nitric oxide (NO), and matrix metalloproteinases (MMPs) contribute to this process [19]. Autoreactive immune cells penetrate the compromised BNB, accumulate in the PNS, and give rise to the effector phase of the immune response in EAN [20]. Locally, macrophages serve as the main antigen presenting cells (APCs), thereby promoting the Th1 polarization [19]. Polarized Th1 cells in turn activate macrophages to express a proinflammatory phenotype (M1) [21]. M1 macrophages are key effector cells in EAN [22]. The pivotal detrimental role of macrophages in the acute phase of immune-mediated nerve damage consists of a direct phagocytotic attack on myelin, as well as release of proinflammatory cytokines including TNF-α, IL-1 and IL-6 and other noxious molecules [1,22]. Proinflammatory cytokines and other toxic mediators (NO, MMPs, etc.) released by activated macrophages further promote T cell activation and induce inflammation [22]. Schwann cells (SCs) can function as facultative APCs in certain conditions by expressing major histocompatibility complex (MHC) class II (MHC II) molecules and costimulatory molecules [23]. Anti-myelin autoantibodies, crossing the BNB [24] or locally produced by B cells, can also mediate demyelination by antibody-dependent cellular cytotoxicity (ADCC) or activating the complement system, and can block functionally relevant epitopes for nerve conduction [22]. Although the role of IL-17 in the pathogenesis of EAN remains largely unclear, it presumably acts as a proinflammatory effector that directly stimulates endothelial cells and fibroblasts to produce proinflammatory cytokines and chemokines, further aiding in the recruitment of neutrophils and macrophages [25], and enhances inflammation in the PNS. During the recovery phase, Fas ligand (FasL, CD95) expressed by SCs and macrophages is important for inducing the apoptosis of effector T cells and for terminating the local immune responses [22]. Macrophages can phagocytose myelin debris by Fc/complement receptors through ADCC or complement mediated mechanism [26]. Yet macrophages may also contribute to tissue repair and promotion of SCs proliferation and remyelination, through secretion of antiinflammatory cytokines, such as IL-10 and transforming growth factor beta (TGF-β) [22]. The role of cytokines in the pathogenesis of EAN is presented in Fig. 1.

3. Th cells, Regulatory T cells (Tregs) and cytokines in GBS and EAN

A variety of immune cell subsets and a complex network of cytokines are involved in the pathogenesis of GBS and EAN. Th1, Th2, Th17 and Treg cells, the four common subsets of $CD4^+$ T cells (Table 2), antagonize or restrict each other by releasing their effector cytokines. The net effects of Th cytokines determine the direction of immune responses (either a Th1, or Th2 or Th17 direction), and the consequence of EAN and GBS (Fig. 2).

3.1. The Th1/Th2 paradigm and M1/M2 unbalance in GBS and EAN

The Th1/Th2 paradigm of Th cell differentiation, which was initially introduced by Mosmann and Coffman [27,28], has helpfully explained some observed phenomena in immune responses and autoimmune diseases. The classic Th1/Th2 paradigm in autoimmune response provided the basis for understanding the mechanisms of autoimmune diseases for the past two decades. A Th1-oriented response is related to an acute-phase reaction to pathogens, while a Th2 response is related to the elimination of antigens and recovery of diseases [29]. This paradigm has also been utilized to explain the adaptive immunity and autoimmune response.

Th0 cells can differentiate into Th1 or Th2 cells depending on the exogenously or endogenously provided cytokines in their milieu. Th1 differentiation is regulated by Interferon gamma (IFN-γ) produced mainly by natural killer (NK) cells and Th1 cells per se [30] and by IL-12 produced by dendritic cells (DCs) after Toll-like receptor (TLR) activation [31]. IL-4 is essential for Th2 cell differentiation [32]. IFN-γ and IL-4, respectively, can act as autocrine growth factors for themselves as well as inhibitory factors for the opposite cell subset. Th1 cells promote B cells to potentiate immunoglobulin (Ig)G2a synthesis through IFN-γ, whereas Th2 cells induce B cell to produce IgE and IgG1 production through IL-4 [33]. Th1 cytokines include IL-12, IFN-γ, TNF-α and IL-1β. These cytokines can activate macrophages to produce reactive oxygen intermediates and NO, stimulate their phagocytotic functions and enhance their antigen presenting capacity by upregulating the expression of MHC II [34]. Th2 cytokines including IL-4, IL-5, IL-10 and IL-13, provide potent help for B cell activation, Ig class switching to IgE and IgG1, and down-regulate proinflammatory macrophage activation [34].

The unbalance of Th1 and Th2 cells has a direct relevance to autoimmune responses, which has been observed in several autoimmune diseases, such as GBS and multiple sclerosis (MS), an autoimmune inflammatory demyelinating disease affecting the central nervous systems (CNS) in humans. Nyati and colleagues

Table 2
Th cell subsets implicated in GBS/EAN, and their signature cytokines and transcription factors.

Th cell subsets	Signature cytokines	Key transcription factors
Th1	IFN-γ	T-bet
Th2	IL-4	GATA-3
Th17	IL-17A	RORγt
Treg	TGF-β	FoxP3