Cytokine 103 (2018) 77–82

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

IL-23/IL-17 immune axis in Guillain Barré Syndrome: Exploring newer vistas for understanding pathobiology and therapeutic implications

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ARTICLE INFO

Keywords:
Guillain Barré Syndrome
Th17 cells
IL-17
IL-23
Autoimmunity
Inflammation

ABSTRACT

Guillain Barré Syndrome (GBS) is a severe disorder of the peripheral nervous system with an inadequately known etiopathology. It is a post infectious immune mediated disorder, characterized by autoantibody production, complement activation as well as T reactivity against gangliosides. However, the precise etiopathogenesis remains poorly understood in a majority of the patients. Th17 cells, a recently identified lineage of Th cells have emerged as a predominant inducer of autoimmunity and inflammation in various immunological disorders. Pathobiological role of Th17 pathway is also becoming increasingly apparent in the nervous system disorders. Two cytokines, such as IL-23, known to determine the pathogenic potential of Th17 cells and IL-17, a prototype effector cytokine of Th17 pathway can form IL-23/IL-17 immune axis. Aberrant functioning of this immune axis has been implicated in many autoimmune diseases. Therapeutic strategies that potentially target this immune axis have shown encouraging results in diseases with immunological underpinnings. Preliminary data obtained both from animal and clinical studies indicate a possible role of this immune axis in GBS. Herein, we explore and highlight the relevance and functional implications of IL-23/IL-17 immune axis in GBS. Understanding this immune axis may shed important insights into the etiology and treatment of GBS.

1. Introduction

Guillain Barré Syndrome (GBS) is an acute immune-mediated disorder of the peripheral nervous system with an annual incidence of 1.2–2.3 per 100,000 [1,2]. Although infectious microorganisms such as *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr Virus, Mycoplasma pneumonia, Haemophilus influenzae, hepatitis E, human immunodeficiency virus (HIV) and recently associated Zika virus account substantially for the complex and multifactorial nature of this disorder, the molecular mechanism underlying its pathogenesis has remained enigmatic till date [3–6]. The most widely recognized mechanism associated with the pathogenesis of GBS so far is antibody mediated 'molecular mimicry' between infectious organisms and gangliosides of the peripheral nerves [7]. However, this phenomenon explains the pathophysiology only in a subset of patients with GBS, therefore, identification of the precise immuno-pathogenetic pathway(s) is essential to unravel the etiology and develop appropriate therapy.

Activated T cell network and its ensuing effects on the progression and severity has been identified as another important etiopathological construct of GBS in recent times. Preliminary support towards this notion was provided by a study showing increased levels of soluble interleukin-2 receptors (sIL-2R) in GBS [8]. Subsequent to this, multiple studies demonstrated significant functional implications of T-cell mediated immune response in GBS. Notably, most of the studies have reported altered counts of various subsets of T cells such as Th1, Th2, Th17, Th22, γδT, Tregs and Tfh cells, both in the peripheral blood and cerebrospinal fluid (CSF) of GBS patients [9] (Table 1). In addition, increased T cell reactivity to certain gangliosides like GM1 and GD1a in patients with GBS and its acute motor axonal neuropathy (AMAN) subtype was shown by some studies [10,11]. Besides this, damaging effects of T lymphocytes to myelin sheath and proteins (P_0, P_2 etc) were also evident in GBS [12,13]. It is noteworthy that the cytotoxic effect of activated T cells against gangliosides was mediated through the production of autoantibodies or by recruiting macrophages on the surface of myelin sheath or the nodes of Ranvier [14]. These findings unequivocally provided empirical support towards the contributory role of T cells in GBS pathogenesis.

Amongst the various subsets of T lymphocytes, Th17 cells have been characterized as a novel lineage that not only bridge innate and adaptive immunity while conferring robust antimicrobial host defense but are also crucially involved in the pathogenesis of many inflammatory and autoimmune disorders, including disorders originated

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https://doi.org/10.1016/j.cyto.2017.12.029
Received 5 October 2017; Received in revised form 1 December 2017; Accepted 27 December 2017

Table 1
Abnormalities in T cells in Guillain Barré Syndrome.

Cell type	Findings	References
T lymphocytes	Significantly increased ratio of CD8+ to CD3+ T cells in sub-acute stages of GBS.	[13]
Tregs	Significantly reduced numbers of peripheral Tregs cells in the acute-stage patients with AMAN and AIDP.	[88]
T lymphocytes	No change in the number of TCD4, CD8, γδ T cells. However, reduced proportion of circulating CD4+ CD25+ cells were reported in acute GBS.	[89]
T lymphocytes	Increased number of activated T-cells and reduced number of Treg cells in GBS.	[90]
Th17 cells	Higher numbers of Th17 in peripheral blood of patients with GBS.	[48]
Th1, Th17 and Th22 cells	Significantly higher frequency of circulating Th1, Th17 and Th22 cells in GBS patients.	[87]
Th17 cells	Significantly higher frequency of Th17 cells in the peripheral blood of acute-stage GBS patients.	[23]
Tregs	Decreased proportion regulatory T cells in GBS	[91]
Follicular Th cells	Higher absolute counts of Tfh1, Tfh2 and Tfh17 in AMAN type of GBS.	[92]

from nervous system [15,16]. However, the discovery of IL-23 cytokine has brought important changes in the fundamental understanding of immunity and immunopathology. One of the important observations was the potential interaction between IL-23 and Th17 cells. The Th17 cells are predominantly known to respond to IL-23. Further, IL-23 was shown to induce gene expression of Il17a, Il17f, Il6, Csf2 and Il23r, which are unique signatures of Th17 cell population in immuno-pathological conditions [17]. This understanding has led to the hypothesis that IL-23 and IL-17 can form an immune axis, called IL-23/IL-17 axis. The discovery, mechanistic understanding and the clinical implications of this immune axis are reviewed in details by Gaffen et al. [18]. Strikingly, this immune axis seemed to be instrumental in driving the pathogenetic pathways of many immune-mediated diseases like inflammatory arthritis, Inflammatory Bowel Disease, Crohn's disease and Ankylosing Spondylitis [19–22].

Data obtained from both the human and animal studies also suggest significant functional implications of Th17 cells, IL-23 and IL-17 cytokines in peripheral nervous system anomalies. The preliminary observations, albeit limited indicate a dysregulated Th17 pathway in GBS [23,24]. Further support came from a study on Experimental Autoimmune Neuritis (EAN), an animal model of GBS, which also points towards an important role of Th17/IL-23 pathway in GBS [25]. In this study, augmented Th17 cells and their corresponding cytokines were shown to be associated with the severity of EAN [25]. These findings provide important insights into the impact of IL-23/IL-17 immune axis in the risk and progression of GBS. A significant role of Th17 cells and their effector cytokines are also being envisaged as biomarkers and potent therapeutic target(s) in GBS [26,27]. Herein, possible molecular pathways through which IL-23/IL-17 axis might contribute to immunopathogenesis of GBS have been discussed. Further, we also highlight the emerging data both from clinical and animal model studies about the efficacy of various treatment modalities on IL-23/IL-17 axis in GBS.

2. Biology of Th17 cells and cytokines

Th17 cells confer important host protective role against a variety of extracellular bacterial and fungal pathogens in mucosal surfaces of the lungs, skin and gut [28]. However, dysregulated Th17 cells can cause autoimmune reaction and lead to inflammatory responses by producing pro-inflammatory cytokines, predominantly IL-17 family of cytokines viz IL-17A and IL-17F as well as IL-21 and IL-22. The receptors for IL-17A and IL-17F are widely expressed on various cell types including fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages [29]. These effector cytokines of Th17 cells further induce the expression of a host of other molecules such as IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), Tumor Necrosis Factor alpha (TNF-α), IL-1, chemokines such as CXC-chemokine ligand 1(CXCL1), CXCL2 and CXCL5 as well as CC-chemokine ligand 20 (CCL20), monocyte chemoattractant protein 1 (MCP-1), and antimicrobial peptides (AMPs) such as β-defensins [30,31]. Most of the effector molecules of Th17 cells can lead to stimulation and attraction of neutrophils to the site of inflammation and tissue degradation during an inflammatory response through the production of matrix metalloproteinase (MMP) [31].

The regulation of the differentiation, maturation and effector function of Th cell lineages are driven by co-ordinated actions of various cytokines as well as transcription factors, such as Signal transducer and activator of transcription (STAT) proteins and Retinoic acid receptor-related orphan receptor (RORγt or RORα). Cytokines like TGF-β, IL-6 and IL-1β mediate the differentiation of CD4+ T cells into Th17 lineage, while IL-21 and IL-23 regulate the amplification and stabilization of Th17 cells [32]. Combined effect of IL-6 and TGF-β is critical for the initial commitment of naïve T cells to the Th17 lineage [33]. Besides this, additional cytokines are also known to regulate Th17 induction and expansion. Of these, IL-23 has appeared to be a crucial player in determining the phenotype of Th17 cells. Interestingly, IL-23 does not play a role in the initial differentiation of Th17 cells, as naive CD4+ T cells lack IL-23 receptor (IL-23R), but promote its expansion and maintenance [34]. IL-21 is shown to be critically involved in this process, as IL-21 induces expression of IL-23R and rendering Th17 cells responsive to IL-23. Besides this, IL-21 also aids in sustaining an autocrine amplification loop where Th17 cells enhance their own differentiation and precursor frequency by producing IL-21 [35].

Like other Th lineages, the differentiation of Th17 cell and subsequent production of its effector cytokines also require the action of two transcriptional regulators such as STAT3 and RORγt. STAT3 initiates Th17 lineage specification at early stages of its differentiation by regulating the transcription of several target genes; some of these code for transcription factors like Batf, Irf4, Rora, Rorct, Runx1, Fosl2, Ahr and c-Maf, while others for cytokines like IL-17A, IL-17F and IL-21 [36]. It is noteworthy that the induction of RORγt is dependent on STAT3, which in turn is activated by IL-6, IL-21 and IL-23. The combined expression of STAT3 and RORγt is required for the higher production of effector cytokines of Th17 cells.

3. IL-23/IL-17 immune axis and autoimmune diseases

IL-23, a new member of the IL-12 family of regulatory cytokines was discovered in 2000 [37]. IL-23 comprises IL-23p19 and p40 cytokine subunits, of which p40 is shared with IL-12 in combination with IL-12p35. The receptor complex of IL-23, made up of IL-12Rβ1 and IL-23R, is expressed on activated/memory T cells, T cell clones, NK cells, monocytes, macrophages and dendritic cell population [38]. Recent understanding suggests IL-23 as a master regulator of innate and adaptive immunity and confers protection mainly against bacterial and fungal infections. Altered expression of IL-23 has been shown to promote autoimmune inflammation [39]. IL-23 causing autoimmune destruction in diseases like experimental allergic encephalomyelitis (EAE), collagen-induced arthritis, inflammatory bowel disease, and psoriasis is becoming increasingly evident [40]. This is explained by the ability of IL-23 in driving the pathogenicity of Th17 cells as well as up-