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ScienceDirect

Neuromuscular Disorders 24 (2014) 943–952

www.elsevier.com/locate/nmd

Review

The role of interleukin-17 in immune-mediated inflammatory myopathies and possible therapeutic implications

Ellen M. Moran [a,*], Frank L. Mastaglia [a,b]

[a] *Institute for Immunology & Infectious Diseases (IIID), Murdoch University, Murdoch, WA, Australia*

[b] *Western Australian Neuroscience Research Institute, Centre for Neuromuscular & Neurological Disorders, University of Western Australia, Australia*

Received 11 March 2014; received in revised form 3 June 2014; accepted 9 June 2014

Abstract

The idiopathic inflammatory myopathies are a heterogeneous group of autoimmune muscle disorders with distinct clinical and pathological features and underlying immunopathogenic mechanisms. Traditionally, $CD4^+$ Th1 cells or $CD8^+$ cytotoxic effector T cells and type I/II interferons have been primarily implicated in the pathogenesis of the inflammatory myopathies. The presence of IL-17A producing cells in the inflamed muscle tissue of myositis patients and the results of *in vitro* studies suggest that IL-17A and the Th17 pathway may also have a key role in these diseases. The contribution of IL-17A to other chronic inflammatory and autoimmune diseases has been well established and clinical trials of IL-17A inhibitors are now at an advanced stage. However the precise role of IL-17A in the various forms of myositis and the potential for therapeutic targeting is currently unknown and warrants further investigation.

Keywords: Inflammatory myopathies; Dermatomyositis; Polymyositis; Inclusion body myositis; IL-17A; Th17

1. Introduction

The idiopathic inflammatory myopathies (IIIMs) are a heterogeneous group of autoimmune muscle disorders that include dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and the immune-mediated necrotising myopathies (IMNM) [1]. The association with myositis-specific autoantibodies and certain HLA alleles, and the overexpression of Class I and II major histocompatibility complex molecules by muscle cells and predominance of T cells and B cells in affected muscles has implicated an autoimmune origin despite the fact that the target autoantigens in DM, PM and IBM have yet to be identified. Whilst these conditions share a number of common properties, namely muscle weakness and inflammation, they have distinct clinical and pathological features and are thought to have different underlying immunopathogenic mechanisms. These have been reviewed previously [2–4], as have the underlying cellular and molecular mechanisms that may contribute to the muscle weakness in the IIMs [5]. Dermatomyositis is usually regarded as a $CD4^+$ T-cell-driven disease in which a complement-dependent humorally mediated attack on the vascular endothelium results in skin and muscle injury [6,7]. In contrast, both PM and IBM are thought to share a $CD8^+$ T-cell-mediated autoimmune process [8,9] where muscle fibres expressing MHC-I antigens are invaded by $CD8^+$ T lymphocytes which are clonally expanded *in situ,* and drive the induction of cytotoxic necrosis through the liberation of perforins and

* Corresponding author. Address: Institute for Immunology & Infectious Diseases (IIID), Building 390, Discovery Way, Murdoch University, Murdoch, WA 6150, Australia. Tel.: +61 8 9360 1368; fax: +61 8 9360 1352.

E-mail address: e.moran@iiid.com.au (E.M. Moran).

http://dx.doi.org/10.1016/j.nmd.2014.06.432

granzymes [10]. In spite of this, it is recognised that the involvement of these T cell subsets is not necessarily exclusive and that there is a certain amount of overlap in the immunopathological phenotype in the different forms of IIM. Moreover, the demonstration of a subset of $CD28^{null}$ $CD4^+$ and $CD8^+$ cells with a natural killer cell phenotype in DM and PM tissues [11] suggests that there may be multiple mechanisms of T cell mediated cytotoxicity. In contrast to the other IIMs, IBM is distinguished by the fact that the inflammatory process is accompanied by myodegenerative changes and abnormal protein aggregation and inclusion body formation in muscle fibres [12].

The majority of research to date has implicated $CD4^+$ T-helper (Th1) cells or $CD8^+$ cytotoxic effector T cells in the pathogenesis of the inflammatory myopathies, as evidenced by the detection of a type 1 interferon profile in both DM and PM and a Th1 immune profile in IMNM [13,14]. Interleukin-17 (IL-17) and the Th17 subset of $CD4^+$ cells have been strongly implicated in the pathogenesis of a number of other autoimmune diseases including psoriasis, rheumatoid arthritis and multiple sclerosis leading to the development of IL-17 targeted monoclonal antibody therapies. In this review we summarise recent observations on IL-17 and the Th17 pathway in the inflammatory myopathies and their potential as novel therapeutic targets for the treatment of these diseases.

2. Immunopathogenic mechanisms

2.1. Polymyositis and inclusion-body myositis

In PM and IBM $CD8^+$ T cells are considered to be the primary effector cells mediating muscle-fibre injury [8,9,15]. These cytotoxic T cells target muscle fibres expressing MHC Class I molecules and co-stimulatory molecules [16–19]. The muscle fibres may therefore act as antigen presenting cells [20,21] and have been postulated to form immunological synapses with the T-cell receptors (TCRs) of the auto-invasive, clonally expanded $CD8^+$ T cells [2]. These T cells have been shown to be activated, expressing ligands specific for the co-stimulatory molecules expressed by the muscle fibres [2]. Matrix-metalloproteinases (MMPs) are thought to facilitate the transendothelial migration of T cells and their attachment to the surface of the muscle fibres [2]. The T cells also display cytotoxic properties by releasing perforin granules which are directed to the muscle fibres resulting in necrosis [10]. Cytokines such as IFN-γ, IL-1 and TNF secreted by activated $CD8^+$ T cells may also contribute to muscle damage through a direct myocytotoxic effect [1].

2.2. Dermatomyositis

The disease process in DM is thought to be initiated by antibodies directed against as yet unknown antigens expressed by the vascular endothelium activating the complement pathway [1]. However, endothelial cell specific autoantibodies have as yet not been identified. Membrane attack complexes (MAC) form on the endomysial capillaries [6,7] and are thought to cause endothelial cell necrosis leading to capillary depletion and muscle ischaemia [22–24] although the mechanisms leading to capillary loss have yet to be fully elucidated. It is postulated that deposition of immunoglobulins on intramuscular capillaries activates the complement cascade, triggering the production of pro-inflammatory cytokines and chemokines, which in turn up-regulate the expression of adhesion molecules on endothelial cells leading to further recruitment of B cells, T cells and macrophages and interferon-α producing plasmacytoid dendritic cells [1,25]. The release of other cytokines and soluble mediators such as TNF and NO by the activated T and B cells may further enhance the inflammatory processes taking place in the muscle [4]. Multiple findings indicate that upregulation of the Type 1 interferon pathway plays a prominent role in the disease pathogenesis in DM [26,27] although it is not specific to DM [28,29].

2.3. Myositis specific autoantibodies

Myositis-specific autoantibodies (MSA) that target various ubiquitous autoantigens are well documented in both DM and PM, and more recently also in IMNM and IBM, and their potential value as diagnostic biomarkers is being increasingly recognised [30–34]. The best characterised are the antisynthetase antibodies which target a group of cytoplasmic aminoacyl tRNA synthetases [35] the most prevalent of which is anti-Jo-1 (anti-histidyl tRNA synthetase) which is present in about 20% of cases of PM and DM and is associated with the antisynthetase syndrome [36,37]. Other less common antisynthetases include anti-PL-12 (alanyl-tRNA synthetase), anti-PL-7 (threonyl-tRNA synthetase), anti-EJ (glycyl-tRNA synthetase), anti-OJ (isoleucyl-tRNA synthetase), anti-KS (asparaginyl-tRNA synthetase), anti-Zo (phenylalanyl-tRNA synthetase) and anti-Ha (tyrosyl-tRNA synthetase) [38]. In DM antibodies to Mi-2, which is a component of the nucleosome remodelling deacetylase complex, has a high specificity, particularly for the adult form of the disease [39,40]. More recently, a number of newer autoantibodies associated with particular subgroups of DM cases have been characterised including anti-TIF-1α/γ, anti-MDA5 and anti-NXP-2 and these have been reviewed elsewhere [31].

There is increasing evidence that in addition to their role as biomarkers MSA may also play a part in inducing and sustaining the autoimmune process in the IIM. For example, a number of studies have shown that there is a correlation between serum levels of anti-Jo-1 antibodies and both disease activity [42] and muscle damage [41], suggesting that the antibody has a causative role. In addition, histidyl-tRNA synthetase and Mi-2 are