Molecular and Cellular Endocrinology 380 (2013) 99–107

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

The potential role of T cell migration and chemotaxis as targets of glucocorticoids in multiple sclerosis and experimental autoimmune encephalomyelitis

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ARTICLE INFO

Article history:
Available online 8 April 2013

Keywords:
Glucocorticoids
Neuroinflammation
T cells
Migration
Chemokines

ABSTRACT

Glucocorticoids (GCs) are the most commonly prescribed drugs for the treatment of acute disease bouts in multiple sclerosis (MS) patients. While T lymphocytes were shown to be essential targets of GC therapy, at least in animal models of MS, the mechanisms by which GCs modulate T cell function are less clear. Until now, apoptosis induction and repression of pro-inflammatory cytokines in T cells have been considered the most critical mechanisms in ameliorating disease symptoms. However, this notion is being challenged by increasing evidence that the control of T cell migration and chemotaxis by GCs might be even more important for the treatment of neuroinflammatory diseases. In this review we aim to provide an overview of how GCs impact the morphological alterations that T cells undergo during activation and migration as well as the influences that GCs have on the directed movement of T cells under the influence of chemokines. A deeper understanding of these processes should not only help to advance our understanding of how GCs exert their beneficial effects in MS therapy but may reveal future strategies to intervene in the pathogenesis of neuroinflammatory diseases.

1. Introduction

Multiple sclerosis (MS) is the most prevalent neuroinflammatory autoimmune disease in the western world (Sospedra and Martin, 2005). It is characterized by severe motor deficits and impaired neurocognitive functions which arise as the result of focal demyelination and axonal loss in the central nervous system (CNS) (Hafler, 2004). To interfere with the progression of MS a plethora of treatment regimens have been developed over the years or are currently being tested in clinical trials. These include IFNβ, glatiramer acetate (GA), small molecular weight compounds such as fumarate derivatives and laquinimod and monoclonal antibodies directed against leukocyte antigens and cytokines (Barten et al., 2010; Buck and Hemmer, 2011; Hafler, 2004; Noseworthy, 2003). In the case of acute disease relapses, however, treatment with glucocorticoids (GCs) is still the measure of choice (McDonald et al., 2001). Initially established as a new therapy for rheumatoid arthritis patients in the late 1940s (Hench, 1950), GCs later became a standard regimen to treat acute relapses in MS patients (Milligan et al., 1987).

T cells are the most important targets of GCs in experimental autoimmune encephalomyelitis (EAE) and presumably MS (Wüst et al., 2008). For a long time it was assumed that the therapeutic efficacy of GCs mainly relies on induction of T cell apoptosis (Herold et al., 2006; Reichardt and Lühder, 2012), repression of pro-inflammatory cytokines (Baschant and Tuckermann, 2010) and modulation of leukocyte-endothelial interactions (Pitzalis et al., 2002). This notion, however, is now being called into question by accumulating evidence that T cell morphology and migration might also be crucial targets of GC action (Ghosh et al., 2009; Müller et al., 2013). In this review we therefore set out to summarize findings pointing towards the presumably important but underestimated role played by GCs in the modulation of T cell chemotaxis and cytoskeleton rearrangements for the treatment of EAE and MS.

2. A short history of MS and EAE

MS is a chronic neuroinflammatory disease that has significant socioeconomic relevance. Most often the disease develops during early adulthood with women being affected twice as often as men. Already in 1868 Jean Martin Charcot described inflammatory lesions in the CNS of patients suffering from neurological dysfunctions (Charcot, 1868; Hafler, 2004), and over the 20th century it became clear that MS is a highly diverse disease entity. Today, we distinguish between relapsing–remitting, primary progressive and secondary progressive MS based on the disease course (Noseworthy et al., 2000). Most patients initially present with a relapsing–remitting form but eventually the majority of them

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http://dx.doi.org/10.1016/j.mce.2013.04.001

develop a secondary progressive phase characterized by increasing deficits in the absence of further relapses. Only about 10–15% of the patients suffer from primary progressive MS with continuous aggravation of the symptoms from early onwards (McFarlin and McFarland, 1982a; McFarlin and McFarland, 1982b). In the majority of the cases, MS is believed to have an autoimmune pathogenesis, with auto-reactive myelin-specific T cells playing a dominant role. This refers to $CD4^+$ T helper (Th) 1 and Th17 cells (Lovett-Racke et al., 2011) as well as $CD8^+$ T cells (Friese and Fugger, 2005; Huseby et al., 2001), even though B cells are currently being re-considered as central players in this process (DiSanto et al., 2012). Finally, antibodies and complement deposition also seem to contribute to the progression of the disease (Sospedra and Martin, 2005).

Insight into the pathomechanism of MS and its treatment regimens is to a significant degree derived from the analysis of animal models. EAE was established as the primary model of MS already several decades ago and is based on an observation originally made in the course of rabies vaccination (Zamvil and Steinman, 1990). In rare cases patients who received the vaccine composed of the fixed pathogen grown in rabbit brain developed a severe paralytic disease. Based on these findings Rivers and colleagues later immunized rhesus monkeys with rabbit CNS homogenate which resulted in a demyelinating disease that mirrors many characteristics of the human disorder and therefore became instrumental for studies of the pathogenesis and treatment of MS (Rivers et al., 1933). This eventually led to the development of EAE in which mostly rats and mice are immunized with myelin antigens emulsified in adjuvant (Kabat et al., 1947). In general, EAE is a T cell-mediated disease highlighted by the fact that it can be transferred to naïve animals using pathogenic $CD4^+$ (Zamvil and Steinman, 1990) or $CD8^+$ T cells (Huseby et al., 2001; Sun et al., 2001). While $CD4^+$ T cells alone are sufficient to induce EAE even in the absence of $CD8^+$ T cells, many studies also speak in favor of an important role of $CD8^+$ T and B cells in EAE (Cabarrocas et al., 2003; Ford and Evavold, 2005; Mars et al., 2011; Saxena et al., 2008; Ziemssen and Ziemssen, 2005). Furthermore, application of new techniques such as intravital imaging by 2-photon microscopy has allowed insight into the different phases of EAE (Bartholomäus et al., 2009). This led to the discovery that a phenotypic change of encephalitogenic T cells into a "migratory" phenotype, subsequently directing immune cell migration into the target tissue, is crucial during EAE development (Odoardi et al., 2012).

One animal model cannot reflect all aspects of the complex human disease, but rather individual EAE models reflect different features of MS. EAE induced by immunization with myelin basic protein (MBP) in Lewis rats for example follows a monophasic disease course without significant demyelination and axonal damage, thereby mainly mimicking the inflammatory features of MS. In contrast, relapsing–remitting EAE models can be induced by immunization of DA rats with myelin oligodendrocyte glycoprotein (MOG) or SJL mice with proteolipid protein (PLP), and present with massive demyelination and axonal loss. Importantly, exploiting these different EAE models has significantly helped in developing new drugs for the treatment of MS such as GA, mitoxantrone and natalizumab (Steinman and Zamvil, 2006), and contributed to our current understanding of how high-dose GC therapy interferes with MS (Schweingruber et al., 2012).

3. T cell morphology and polarization

T lymphocytes are central players in the pathogenesis of EAE and MS, and proper activation and polarization are essential for their functioning. In active EAE, T cell activation is generally achieved by the use of Complete Freund's Adjuvant (CFA) which stimulates antigen-presenting cells (APCs) and induces a pro-inflammatory milieu (Medzhitov and Janeway, 2002). In adoptive transfer EAE, T cells also have to be activated in order to be capable of infiltrating the CNS. In this case, however, they are cultured with antigen-loaded APCs *in vitro* prior to their transfer into naïve animals (Wekerle et al., 1986). Regardless of the model, T cells have to migrate to the site of inflammation and then cross the blood–brain barrier (BBB; Engelhardt and Ransohoff, 2012). To this end, T lymphocytes must adopt a unique morphology which is crucial for migration and cell–cell-interaction (Fig. 1). In general, lamellipodiae are formed on the leading edge of the cell whereas an uropod is found at the opposing pole. Part of the cell surface receptors and lipid rafts become confined to the uropod where they form the distal pole complex (DPC). In contrast, other surface molecules like integrins and chemokine receptors are concentrated at the leading edge where they serve to sense chemokines during crawling (Smith et al., 2005). These structural features are essential to allow correct movement of T cells (Krummel and Macara, 2006) and for directing their effector mechanisms such as the release of cytokines and cytotoxic molecules to the contact zone with other cells. As the cytoskeleton is crucial for morphological alterations to occur, inhibitors of F-actin polymerization such as cytochalasin D or latrunculin A were found to interfere with T cell activation and effector functions (Grakoui et al., 1999).

The cytoskeleton is composed of F-actin filaments, microtubules and intermediate filaments. While the latter provide the mechanical force necessary for migration (Vicente-Manzanares and Sanchez-Madrid, 2004), the microtubule system regulates polarization and maintenance of F-actin-dependent structures (Sancho et al., 2002). Importantly, the cytoskeleton of T cells becomes reorganized within minutes after T cell receptor (TCR) stimulation, which involves polymerization of F-actin (Bunnell et al., 2001; Tskvitaria-Fuller et al., 2003; Valitutti et al., 1995), reorientation of the microtubule-organizing centre (MTOC) towards the immunological synapse and formation of the DPC. Consequently, cell surface receptors are redistributed and intracellular signalling complexes assembled, events that are important for the formation of the immunological synapse as well as for migration (Krummel et al., 2000). The relevance of the cytoskeletal organization for proper T cell function is underscored by several loss-of-function studies in mice, where deficiency in individual cytoskeleton regulatory proteins led to impaired T cell activation, cytokine production and proliferation (Billadeau et al., 2007).

4. T cell migration in EAE

Soluble mediators that trigger leukocyte migration are called chemokines and produced by a variety of immune cells as well as fibroblasts and endothelial cells (Jaerve and Müller, 2012; Mortier et al., 2012). Following their release chemokines can attach to extracellular matrix (ECM) components or specialized receptors and thereby form cues for migrating leukocytes. Under physiological conditions constitutively expressed chemokines establish gradients that guide leukocytes to their appropriate location within primary and secondary lymphoid organs for which reason they are prerequisite for immune surveillance and maintenance of tissue homeostasis (Holman et al., 2011). Migration of leukocytes to their target tissues and lymph nodes along chemokine gradients is then followed by interaction of cell-surface molecules on trafficking lymphocytes with their ligands on endothelial cells (Engelhardt, 2008). In the case of infection or tissue damage pro-inflammatory chemokines serve to rapidly attract leukocytes to the site of inflammation and foster their extravasation from the blood. More precisely, chemokines induce firm attachment of leukocytes such as T cells to the vessel wall at inflamed sites by