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Review Article

The role of vitamin D and P2X7R in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is characterized by neuroinflammatory infiltrates and central nervous system demyelination. In the neuroinflammatory foci of MS there is increased expression of a purinergic receptor, P2X7R. Although implicated in the neuroinflammation, the exact role of P2X7R in the context of MS is unclear and forms the basis of this review.

In this review, we also introduce the immunopathologies and inflammatory processes in MS, with a focus on P2X7R and the possible immunomodulatory role of vitamin D deficiency in this setting.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune, neuroinflammatory disease that is characterized by demyelination and axonal damage in the central nervous system (CNS) (Goldenberg, 2012). MS is the most common cause of neurological disability in young adults between 20-50 years old, with a peak incidence occurring at 30 years of age (Milo and Kahana, 2010). The etiology of the disease remains largely unknown but a combination of genetic (Sadovnick et al., 1993) and environmental factors (Miller et al., 1990) are implicated in its pathogenesis. Moreover, MS has a two-three fold greater incidence in women than men (Orton et al., 2006; Trojano et al., 2012) and incidence and prevalence of MS increase with increasing distance from the equator (Dean, 1967; Milo and Kahana, 2010). Currently, there is no single diagnostic test for MS. A combination of clinical assessments, typical magnetic resonance imaging (MRI) lesion findings and laboratory investigations are used to make a diagnosis for MS, which is then refined to either the relapsing or progressive forms of MS according to disease progression (Goldenberg, 2012; Koriem, 2016). Many increasingly effective therapies have been introduced into the clinic in the last 20 years, these greatly reduce relapses and disability progression. However, the cause of MS remains elusive and the disease is still incurable.

Interestingly, even though vitamin D deficiency has been associated with an increased risk of developing MS (Ascherio et al., 2012; Ascherio et al., 2010), the exact role of vitamin D and its mechanism of action in the disease remain unclear. Additionally, the expression of P2X7 receptor (P2X7R) on cells of the immune and nervous system involved in MS suggest its potential role in the pathogenesis of the disease (Sperlagh and Illes, 2014; Gu and Wiley, 2018). Hence, this review provides a summary of the current literature available on MS, focusing on the role of vitamin D deficiency and P2X7R as possible contributors to the disease state. Firstly, it will briefly elaborate on the pathophysiology of MS, including the inflammatory aspects of the disease with a focus on innate and adaptive immunity. The roles of P2X7R and vitamin D in MS are further evaluated, notably the effect of vitamin D on P2X7Rs expressed on immune cells involved in MS.

2. Multiple sclerosis

2.1. Overview

Pathologically, MS is characterized by focal destruction of the myelin sheath (Nakahara et al., 2012). According to the course of disease, MS can be categorized into two groups, the relapsing form and the progressive form (Lublin et al., 2014). The first attack of demyelination without disseminating neurological symptoms in both time and space is termed a clinically isolated syndrome (CIS), which is the onset for 85-95% of MS patients (Miller et al., 2005). Recurrent inflammation, demonstrated as either a clinical relapse or as a new MRI-visible lesion defines the onset of relapsing-remitting MS (RRMS), which is the relapsing form of MS (Lublin et al., 2014). The progressive forms of MS include secondary progressive MS (SPMS) and primary progressive MS (PPMS) (Lublin et al., 2014). These are characterized by steady, gradual and progressive neurologic deficits that can occur over months to years (Lublin et al., 2014). SPMS is diagnosed when a patient has had at least one relapse with improvement in the past, while PPMS is diagnosed in

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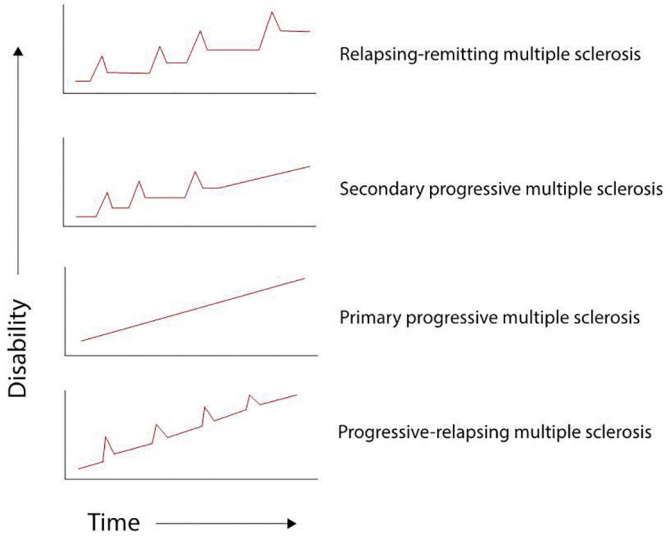

Fig. 1. Illustration of course of disease for different forms of MS. As outlined in figure 1, the relapsing form of MS, RRMS is marked by periods of relapse and remission of symptoms. Two-thirds of RRMS patients progress to SPMS where neurological deficits gradually worsen over time, without periods of remission. Patients with PPMS have persistent and gradually worsening disease from onset with no relapse-remission periods. PPMS progresses to primary-relapsing multiple sclerosis (PRMS) when patients gradually worsen with possible later super-imposed relapses.

the absence of any prior relapse but with progressive CNS disease consistent with MS (Lublin et al., 2014) (See Fig. 1).

2.2. Symptoms

The symptoms of MS are broad and can include physical, neuropsychiatric and cognitive deficits due to the multifocal nature of the lesions formed in the CNS (brain and spinal cord) (Koriem, 2016; Savransky, 2018). The variability of MS symptoms depends on the location of lesions formed. MS generally starts with focal demyelination in the CNS then followed by worsening neuronal damage, and consequently in some cases ensuing weakness, paralysis or other neurological deficits (Koriem, 2016). One of the first manifestations of MS is optic neuritis, which is an acute visual disturbance that is caused by an autoimmune attack on the optic nerves (Wilhelm and Schabet, 2015). The optic nerves are one of the most classical sites of attack in MS patients; half of all patients diagnosed with optic neuritis are found to develop MS within 15 years from the original episode (Brodsky et al., 2008). MS is a disease that evolves with relapses and remission with multifocal neurological deficits, the most common being optic neuritis and transverse myelitis (Savransky, 2018). Other possible symptoms include motor weakness, paresthesia or numbness, incoordination, problems in speech and hearing, fatigue, acute and chronic neuropathic pain, urinary urgency or retention, bowel function difficulties, sexual dysfunction, cognitive and neuropsychological deficits (Goldenberg, 2012; Koriem, 2016).

The variability of MS symptoms can lead to diagnostic uncertainty resulting in delayed diagnosis and treatment (Murphy et al., 2017). Neuropsychiatric symptoms in MS are diverse and are reported to affect 60% of MS patients (Murphy et al., 2017). They can range from mood disorders such as depression, euphoria, anxiety disorders to cognitive deficits (Murphy et al., 2017; Sommerlad et al., 2014). Major depressive disorder (MDD) is the most common neuropsychiatric symptom associated with MS, with almost a 50% lifetime prevalence following disease onset (Murphy et al., 2017; Sommerlad et al., 2014). The etiology of MDD in MS patients is complex, due to the neurological and psychosocial factors implicated in the disease (Murphy et al., 2017; Ghaffar and Feinstein, 2007). Suicide is also a significant cause of mortality in MS patients, which is found to be 7.5 times higher than the general population (Murphy et al., 2017; Sommerlad et al., 2014). The neuropathogenesis of the psychiatric conditions associated with MS remains obscure and it is still uncertain whether they are indicators of MS illness severity (Sommerlad et al., 2014). However, timely detection is essential as these disorders negatively impact quality of life and the ability of patients to adhere to recommended treatment regimens (Sommerlad et al., 2014).

2.3. Diagnosis and treatment

The diagnosis of MS is based on three criteria: (1) the space dissemination criterion (at least two different attacks), (2) the time dissemination criterion (at least two different attacks in the disease course, or evidence of simultaneous contrast enhancement and no contrast enhancement in a single MRI scan to indicate lesions of different age) and (3) the inflammatory criterion (chronic inflammation in the CNS) (McDonald et al., 2001; Garg and Smith, 2015; Thompson et al., 2018). MRI is the most common diagnostic test used to detect MS lesions in the CNS (Koriem, 2016). Currently, the pattern of MRI lesions and presence of cerebrospinal fluid (CSF) specific oligoclonal bands (OCBs) are used to confirm MS diagnosis (Fadda et al., 2018).

In 2017, there are twelve treatments approved for RRMS in Australia (Sedal et al., 2017). These include interferons beta, glatiramer acetate, monoclonal antibodies such as natalizumab and ocrelizumab, small molecule oral agents such as fingolimod, cladribine, teriflunomide and dimethyl fumarate (Reich et al., 2018; Hollingworth et al., 2014; Deeks, 2018). The interferons and glatiramer acetate are used as treatment for RRMS as both can effectively reduce MS relapses by 30% and decrease the number of active lesions on brain MRI (Tsang and Macdonell, 2011); whereas infusion therapies such as natalizumab and ocrelizumab can reduce relapse rates by up to 60-75% (Polman et al., 2006; Mulero et al., 2018). All approved treatments in general have shown beneficial effects in the reduction of relapses and accumulation of disability in MS patients (Reich et al., 2018). However, the effects of these treatments on PPMS and SPMS have not been proven and they remain largely ineffective. This is partly due to the lack of literature on the exact mechanism of action of a number of MS disease modifying agents (Koriem, 2016; Reich et al., 2018). Despite the recent development of new treatments for MS, there is still no cure with current therapies.

2.4. Glucocorticoids

Glucocorticoids such as intravenous (IV) methylprednisolone, oral prednisolone or dexamethasone are used to treat acute MS exacerbations due to their anti-inflammatory and immunosuppressive properties (Goodin, 2014; Johnson and Bhimji, 2018; Berkovich, 2013). A brief glucocorticoid treatment regimen such as IV methylprednisolone (1g daily for 3 days) is generally used to accelerate recovery from MS relapses with no significant adverse effects for most patients (Berkovich, 2013). However, the response to glucocorticoid treatment differs among patients, suggesting individual differences in sensitivity to glucocorticoid (DeRijk et al., 2004; van Winsen et al., 2005). Some studies have shown that patients with MS, particularly RRMS are less sensitive to glucocorticoids compared to healthy controls and patients with progressive forms of MS (DeRijk et al., 2004; van Winsen et al., 2005). Moreover, despite being effective in reducing relapse severity, glucocorticoids have no impact on MS disease course or the final degree of recovery (Goodin, 2014). Currently, there is no standard dose, route of administration or glucocorticoid types to treat MS relapses (Miller et al., 2000; Frohman et al., 2007). In most centers, 1g IV methylprednisolone for 3 days is utilized. More studies are required to determine the optimal glucocorticoid treatment for MS relapses, in conjunction with other MS therapeutics to optimize treatment during acute

attacks.

3. Immune system

Our present understanding of MS suggests that it is an immune-mediated disease (Yadav et al., 2015) due to the following findings: (1) T and B lymphocytes, and immune cell infiltrations are evident in lesions formed in the CNS (Lassmann, 2013); (2) immunomodulatory therapeutics affect MS disease course (Reich et al., 2018; Hartung and Kieseier, 2014); (3) genome wide association studies (GWAS) have identified numerous immune-related genetic variants (single nucleotide polymorphisms, SNPs) associated with MS (Sawcer et al., 2011; Beecham et al., 2013). Animal models and immunological studies of MS patients have also demonstrated a change in the involvement of the immune system during different phases of disease (Hemmer et al., 2015). Many studies have suggested that the peripheral immune responses targeting the CNS mediate early disease progression, whereas immune reactions within the CNS drive the progressive phase (Hemmer et al., 2015; Yadav et al., 2015; Kebir et al., 2009). The peripheral blood could also provide an accessible 'window' into the immunopathologies of MS. As suggested by Jones et al, changes in the circulating immune cells could reflect the immunological characteristics of MS lesions in the CNS and the immune dysregulation of MS patients (Jones et al., 2017).

3.1. Adaptive immune system

Neuroinflammation is the hallmark of MS, and is shown to consist of innate and adaptive immune cells such as T and B lymphocyte infiltrates as well as microglia, monocyte and macrophage accumulation (Jones et al., 2017; Yadav et al., 2015). The current central hypothesis is that myelin-reactive $CD4^+$ T-cells drive the pathogenesis of MS through the migration of autoreactive $CD4^+$ T-helper 1 (Th1) and $CD4^+$ T-helper 17 (Th17) cells into the CNS (Yadav et al., 2015). The initial activation of autoreactive $CD4^+$ T-cells is believed to take place in the systemic lymphoid organs by unknown factors; these T-cells are then subsequently activated upon encountering their target antigen (myelin components) in the CNS, resulting in demyelination, axonal damage and subsequent neurological disability (Hartung et al., 2014). For many years, MS was widely recognized as a Th1-mediated disease. These Th1 cells are differentiated in response to interleukin-12 (IL-12) and secrete the proinflammatory cytokine, interferon-γ (IFN-γ) (Renno et al., 1994; Tzartos et al., 2008). However, human in -vitro studies using peripheral blood and tissues from MS lesion and brain have later shown that along with Th1 cells, Th17 cells (i.e. $CD4^+$ T-cells that express IL-17 and IL-22) are also likely to be important co-effectors in MS (Kebir et al., 2007; Tzartos et al., 2008; Li et al., 2017). IL-17 and IL-22 secreted by Th17 cells have been identified to disrupt the blood-brain-barrier (BBB) by binding to IL-17 and IL-22 receptors expressed on BBB-endothelial cells (Kebir et al., 2007). Although current literature does not convincingly determine whether single cytokines such as IL-17 or IFN-γ can sufficiently induce MS pathology, it is likely that any combinations of factors produced by Th1 and Th17 cells will contribute to the inflammatory demyelination processes in the CNS (Kebir et al., 2009). It is also believed that defects in peripheral tolerance due to intrinsic (costimulatory signaling, transcriptional and epigenetic mechanisms) and extrinsic (regulatory T-cells) factors can lead to dysregulation in $CD4^+$ T-cell responses (Yadav et al., 2015; Gonsette, 2012). Immune responses are found to be skewed towards proinflammatory Th1/Th17 development and disrupt immune system homeostasis, subsequently leading to MS pathology (Yadav et al., 2015; Gonsette, 2012). Although $CD8^+$ T-cells are the predominant T-cells in human MS lesions, their role in MS pathology are still largely unknown (Sinha et al., 2014). Several studies have found that neuroantigen-specific $CD8^+$ T-cells exhibit immunoregulatory ability by suppressing the proliferation of self-reactive $CD4^+$ T-cells when stimulated by their cognate antigen (Correale and Villa, 2010; Baughman et al., 2011). In addition, IL-17 and IFN-γ secretion are also reduced when $CD8^+$ T-cells are added into $CD4^+$ T-cell cultures isolated from MS patients (Correale and Villa, 2010; Baughman et al., 2011). However, the immunosuppressive effects of $CD8^+$ T-cells are found to be reduced during acute exacerbations in MS, likely due to altered functionality rather than simple quantitative suppression (Cunnusamy et al., 2014; Baughman et al., 2011).

B-cells are also thought to be an important contributor to MS pathogenesis (Rahmanzadeh et al., 2018). Emerging studies have identified the following roles for B-cells in MS: (1) B-cells with hypermutated immunoglobulin (Ig) have been found to accumulate in CSF and lesions of MS patients (Colombo et al., 2000; Obermeier et al., 2008); (2) pronounced effects of B-cell therapies, in particular B-cell depleting agents (e.g. ocrelizumab and rituximab) on MS patients support the role of B-cells in MS pathogenesis (Kappos et al., 2011; Sabatino Jr. et al., 2018); (3) OCBs (produced by B cells) are detectable in 95% of MS patients (Rahmanzadeh et al., 2018) and are shown to be the second sensitive diagnostic marker after MRI (Rahmanzadeh et al., 2018; Arrambide et al., 2018). These findings suggest the potential role of B-cells in MS pathology and their use as therapeutic treatments for MS. It is also important to note that T and B lymphocytes are costimulatory. For instance, B-cell antigen presentation and co-stimulation are found to contribute to the induction of proinflammatory T-cell responses in MS pathology (Fraussen et al., 2016). Hence, it is unlikely that either T and B cell responses are independent from each other in the pathogenesis of MS.

3.2. Innate immune system

The rapid recruitment of monocytes from the periphery and activation of brain resident microglia are among the most consistent histological findings noted from MS autopsy specimens (Bruck et al., 1995; Ford et al., 1995). Despite the significant presence of innate immune cells in MS plaques, their underlying mechanisms contributing to MS pathology are not well understood (Weiner, 2009). It has been suggested that the innate immune system activates myelin-reactive T and B lymphocytes in the CNS (Hernandez-Pedro et al., 2013). The effector cells then in turn express various cytokines and activation markers that further activate the innate immune cells, creating a perpetuating cycle of neuroinflammation with ensuing neuronal damage and demyelination (Monney et al., 2002).

Due to similarities in both morphology and function, it is often difficult to distinguish microglia and monocytes using conventional immunohistochemical techniques (O'Loughlin et al., 2018). However, advancements in identifying specific molecular markers and signatures of these cells are currently being developed, allowing us to distinguish the complex roles of these cells in the neuroinflammatory and degenerative cascade in MS (Butovsky et al., 2014; Rinchai et al., 2016). Both the resident microglia and infiltrating monocytes could give rise to macrophages, but the macrophages derived are found to have different functions in the neuroinflammation of MS (Yamasaki et al., 2014). During both MS and EAE (experimental autoimmune encephalomyelitis; the murine model of MS), monocyte-derived macrophages accumulate in the inflammatory infiltrates associated with active demyelination, while CNS resident microglia-derived macrophages only participate in the later stages of disease (Yamasaki et al., 2014). Distinguishing the roles of microglia from monocytes will point towards new strategies to treat MS. Thus, more research is required to identify unique markers and signatures of these immune cells and also their specific roles in MS pathogenesis.

Microglia. Microglia cells are the most common immune cells in the CNS and are considered as CNS resident macrophages (Benveniste, 1997). They contribute to MS and EAE pathology through antigen presentation and secretion of proinflammatory cytokines (Benveniste, 1997). Persistent activation of microglia have been observed in chronic phases of relapsing-remitting (RR) EAE while increased microglial activation in white matter inflammation is more frequent in progressive

than RR patients (Kutzelnigg et al., 2005; Rasmussen et al., 2007). Microglia activate T and B lymphocytes through antigen presentation via major histocompatibility complex (MHC) class II and co-stimulatory molecules, CD83 and CD40 (Raivich and Banati, 2004; Gandhi et al., 2010). The rapid upregulation of MHC antigens is also one of the first molecular changes observed in MS patients and EAE models using immunohistochemistry techniques (Raivich and Banati, 2004). As the first-line defense in the brain, microglia express Toll-like receptors (TLRs) on their surface which contribute to neuroimmune regulation and CNS inflammation (Aravalli et al., 2007; Lee and Lee, 2002). Studies have shown an enhanced expression and upregulation of TLRs in the brain and spinal cord tissues of MS patients (Bsibsi et al., 2002; Marta et al., 2009). The role of TLRs in EAE pathology is also supported by findings that indicate the resistance of mice that lack MyD88 (the common TLR adaptor molecule) to EAE due to inhibition of monocyte and microglia activation (Marta et al., 2008; Prinz et al., 2006; Lee et al., 2018). Microglia are also involved in demyelination and phagocytosis of degraded myelin (Bauer et al., 1994), which lead to elevation in the expression of myeloperoxidases and reactive oxygen species (ROS), resulting in neuronal damage (Gray et al., 2008). Moreover, the activation patterns of microglia are distinct during different stages of MS lesions (O'Loughlin et al., 2018). Microglia in the early stages of active lesions show a more proinflammatory phenotype, with expression of inflammatory markers involved in antigen presentation, phagocytosis, generation of ROS and T-cell co-stimulation (Zrzavy et al., 2017). In later stages of active lesions, the microglial cells switch to an intermediate between pro- and anti-inflammatory phenotype (O'Loughlin et al., 2018; Zrzavy et al., 2017). In addition, microglial depletion is also shown to inhibit the development of inflammatory CNS lesions in EAE models (Heppner et al., 2005; Ponomarev et al., 2011). Thus, an understanding of the roles of microglia in MS pathology could provide a novel therapeutic target in attenuation of disease severity and demyelination for MS patients.

Monocytes. Human monocytes are derived from hematopoietic stem cells in the bone marrow and constitute around 10% of the total circulating blood leukocytes (Rinchai et al., 2016). They are released into the peripheral blood upon maturation, where they are either recruited to tissues or removed from the circulation after 1-2 days (Rinchai et al., 2016). Monocyte infiltration is evident in active MS lesions even in the early stages of disease and are associated with axonal demyelination (Baufeld et al., 2017; Bruck et al., 1995). Human monocytes are classified into three major subsets depending on the expression of cell surface markers CD14 and CD16, which also represent different inflammatory stages (Rinchai et al., 2016). The non-classical monocytes (CD14 + CD16 + +) from MS patients are found to be significantly increased in the peripheral blood, highlighting the relevance of further focus on CD16 monocyte subsets in MS (Chuluundorj et al., 2014; Gjelstrup et al., 2018). In addition, findings from EAE models also demonstrated a global monocyte profile that is biased towards the proinflammatory 'M1 phenotype' in the blood and CNS (Ajami et al., 2011; Mikita et al., 2011). Administration of ex-vivo activated 'M2 monocytes' by interleukin-10 (IL-10) and interleukin-13 (IL-13) to the peripheral blood has also been found to suppress ongoing EAE and promote immunomodulatory actions limiting the expansion of acute CNS lesions (Mikita et al., 2011). These findings open new perspectives for therapeutic applications in MS. Interesting, one study has suggested the potential pathological role of monocytes in MS disease state by demonstrating high levels of monocyte-secreted proinflammatory factors in serum of MS patients compared to healthy controls (Baufeld et al., 2017). Analysis of the cytokine production in monocytes isolated from MS patients showed a significant increase in interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα) compared to normal controls (Rudick and Ransohoff, 1992; Imamura et al., 1993; Fiedler et al., 2017). Although monocytes are thought to have primarily detrimental effects on MS lesion formation, studies have also shown that they play a dual role by promoting tissue repair and secreting anti-inflammatory factors (Vaknin et al., 2011; Denney et al., 2012). For instance, in one study, monocytes derived from MS patients were found to have increased enzyme tissue transglutaminase (TG2) levels and this increase is correlated with an anti-inflammatory and migratory profile in MS (Sestito et al., 2017).

4. P2X7 receptor

4.1. Overview

P2X7R is one of the functional members of the ionotrophic purine P2X receptor family (North, 2002). In general, all recombinant P2X subunits can assemble in vitro to form heteromeric structures, with the exception of P2X7R, which is only present as a homo-trimeric receptor (Di Virgilio et al., 2017). The main physiological agonist of P2X7R is adenosine triphosphate (ATP) but other structurally unrelated agents have been reported to activate it with unknown mechanisms (Di Virgilio et al., 2018a). Additionally, the synthetic analog, 2'-(3')-O-(4-benzoylbenzoyl)-ATP (BzATP) is found to be more potent at P2X7R activation than ATP (Jiang et al., 2013). P2X7Rs are bifunctional (Volonte et al., 2012). The binding of ATP induces a channel formation within milliseconds which is selective for small cations (Ca^{2+}, Na^{+} and K^{+}) (Di Virgilio et al., 2018b) and within seconds to minutes, a larger pore opens allowing permeation of molecules up to 900 Da (Volonte et al., 2012). In response to prolonged or repetitive stimulation, pore formation is often studied by measuring influx and intracellular accumulation of fluorescent dyes, such as YoPro-1 and ethidium (Jiang et al., 2013). The mechanism of P2X7R channel-to-pore transition remains unclear, and various intermolecular (acquisition of more P2X7R subunits) and intramolecular (dilatation of the channel opening) mechanisms have been proposed (Alves et al., 2014; Jindrichova et al., 2015; Khadra et al., 2013). A non-pore-forming mutant of P2X7R, P2X7RG345Y (where glycine 345 is changed to tyrosine) can be used to identify functional differences between the two states as this point mutation only abolishes pore conductance without altering the function and properties of the channel component (Monif et al., 2009).

4.2. P2X7R in inflammation

P2X7R has low affinity for ATP, in the millimolar range (Di Virgilio et al., 2018b). Extracellular ATP can often increase dramatically and accumulates at inflammatory sites, thus reaching the receptor activation threshold (Wilhelm et al., 2010). In addition, several factors that accumulate at inflammatory sites are shown to either act as positive allosteric modulators or support P2X7R gating mechanisms (Di Virgilio et al., 2018a; Elssner et al., 2004; Ferrari et al., 2004; Sanz et al., 2009). The binding of ATP at P2X7R alters intracellular ion homeostasis, which can result in initiation and propagation of inflammatory cascades (Di Virgilio et al., 2018b; Monif et al., 2009). In addition, the presence of P2X7Rs on virtually all cells of the innate and adaptive immunity (Di Virgilio et al., 2017) suggests they regulate immune function and inflammatory responses (Aga et al., 2002; Monif et al., 2009). P2X7R also promotes the release of proinflammatory mediators such as IL-6 (Shieh et al., 2014), interleukin-8 (IL-8) (Wei et al., 2008), monocyte-chemoattractant protein-1 (MCP-1) (Panenka et al., 2001) and ROS (Hewinson and Mackenzie, 2007).

4.3. P2X7R and IL-1β

P2X7R activation triggers a multiplicity of inflammatory responses, the most important being interleukin-1β (IL-1β) release via the activation of NLRP3 inflammasome (Munoz-Planillo et al., 2013; Savio et al., 2018; Monif et al., 2016). Initially, during innate immune responses, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) activate pattern recognition receptors (PRRs) such as TLRs expressed on immune cells (Savio et al.,

2018). TLR activation mediates the NFκB pathway, which acts as the first signal promoting the transcription of several genes that encode for inflammatory mediators such as inflammasome components and pro-IL-1β (Savio et al., 2018). P2X7R stimulation represents the second signal through triggering K^+ efflux, promoting NLRP3 inflammasome assembly and pro-IL-1β processing and IL-1 release (Quan et al., 2018). The ability of P2X7R to drive IL-1β release has clinical significance as IL-1β is involved in various immune processes such as immunogenic apoptosis (Ghiringhelli et al., 2009). IL-1β is also a key mediator in neurodegeneration, chronic inflammation and chronic pain (Volonte et al., 2012).

In addition, IL-1β is also found to be able to rescue glucocorticoid-induced apoptosis in monocytes (Schmidt et al., 1999; Achuthan et al., 2018; McColl et al., 2007). One of the apoptotic mechanisms of glucocorticoids is through inhibiting the NFκB pathways, leading to suppression of NFκB-mediated inflammatory activities and interference of immune cell survival (van der Burg and van der Saag, 1996; Ottonello et al., 2005). The transcription factor, NFκB is induced by pro-inflammatory cytokines and plays a role in inflammatory processes by directing the transcription of chemoattractants, cytokines (including NFκB-inducing cytokines), cytokine receptors and cell adhesion molecules (van der Burg and van der Saag, 1996). Even in a normal physiological setting, IL-1β is found to be able to prevent apoptosis in monocytes, highlighting its role in homeostatic control of the number of monocytes available for immune responses (Mangan et al., 1991).

4.4. P2X7R in MS

Despite the wide expression of P2X7R on immune cells (Di Virgilio and Vuerich, 2015; Yiangou et al., 2006), astrocytes (Narcisse et al., 2005), oligodendrocytes (Matute, 2008), Schwann cells (Faroni et al., 2014) and neurons (Rodrigues et al., 2015), only incomplete information is available regarding P2X7R-mediated signaling in these cells. Many immune cell types are involved in MS lesion formation, however activated monocytes are shown to be one of the first cell types to reach the brain and possibly initiate neuroinflammation (Amadio et al., 2017). Around 80% of human monocytes are found to express immunoreactive P2X7R, implicating the role of these receptors in mediating monocyte-induced inflammatory responses (Aga et al., 2002; Gudipaty et al., 2001). Moreover, human monocytes are also shown to have four to fivefold greater P2X7R expression compared to B and T lymphocytes (Gu et al., 2000). Glatiramer acetate which is an approved MS therapy has been shown to cause downregulation of P2X7R expression in peripheral blood monocytes and it is unclear if its effectiveness is simply due to this mechanism or otherwise. (Caragnano et al., 2012). In rat hippocampal cultures, we have shown that P2X7R expression drives microglia activation and proliferation (Monif et al., 2009). Another study using post-mortem spinal cord specimen of MS patients, also showed the localization of P2X7R immunoreactivity in activated microglial cells/macrophages in affected regions (Yiangou et al., 2006). These data suggest that by acquiring further knowledge about P2X7R expression and function on innate immune cells such as monocytes and microglia, we can better understand the molecular pathways of MS and possibly identify P2X7R as a potential marker for the disease.

Due to the inflammatory nature of MS, a link between P2X7R activation and MS lesion development has been proposed (Savio et al., 2018). Early post-mortem studies of MS patients have revealed high level of P2X7R expression in astrocytes and microglia in the brain and spinal cord (Narcisse et al., 2005; Yiangou et al., 2006). In studies of EAE murine models, upregulation of P2X7R in the astroglial cells has been observed during the early stages of EAE while increased expression of P2X7R in neurons and oligodendrocytes occurred in the later stages (Grygorowicz et al., 2010; Matute et al., 2007). Interestingly, the total P2X7R expression levels remained high in the brain of EAE rats even after 20 days after immunization and are found to correlate with increased levels of glial fibrillary acidic protein (GAFP), a marker of astrocyte activation (Holley et al., 2003; Grygorowicz et al., 2011). This could suggest a role for P2X7R activation in the sustained astrocytosis that is observed in the later stages of EAE and MS. A study using brain samples from MS patients has shown upregulation of P2X7R on astrocytes in the parenchyma of the frontal cortex of SPMS patients, validating the findings from EAE models (Amadio et al., 2017). Moreover, the administration of P2X7R antagonist to EAE rats has been found to decrease astrocytosis, reduce demyelination and improve neurological symptoms (Matute et al., 2007; Grygorowicz et al., 2016). These findings reinforce the role of P2X7R in EAE and possibly as a contributing factor in MS pathology.

5. Vitamin D

Vitamin D deficiency has been implicated in the onset, susceptibility, relapse frequency as well as disability and disease progression in MS (Oliveira et al., 2017; Kocovska et al., 2017; Fyfe, 2016; Breuer et al., 2018; Salzer et al., 2014). Epidemiological data supports a correlative link between an insufficiency in vitamin D and/or sunlight exposure in the early stages of life with an increased risk in developing MS during adulthood (Balbuena et al., 2016; Dobson et al., 2013). Prospective epidemiological studies have further established vitamin D as a protective factor associated with MS risk; low serum vitamin D levels have been found to correlate with an increased risk in developing MS (Munger et al., 2006; Salzer et al., 2012).

5.1. Overview

Vitamin D has two major forms: the circulating form, $25(OH)D_3$ and its active form, $1,25(OH)_2D_3$ (Jones, 2008). $25(OH)D_3$ circulates at a concentration of 25-200nmol/L in the serum and has a half-life of 15 days, whereas $1,25(OH)_2D_3$ only has a short half-life of 15 hours (Jones, 2008). The synthesis pathway for vitamin D obtained from both diet and synthesis using ultraviolet (UV) light is shown in Fig. 2.

$1,25(OH)_2D_3$ is a ligand for VDR, a member of the nuclear receptor superfamily (Carlberg, 1996). Because the binding of VDR to vitamin D response element (VDRE) leads to structural changes in the chromatin,

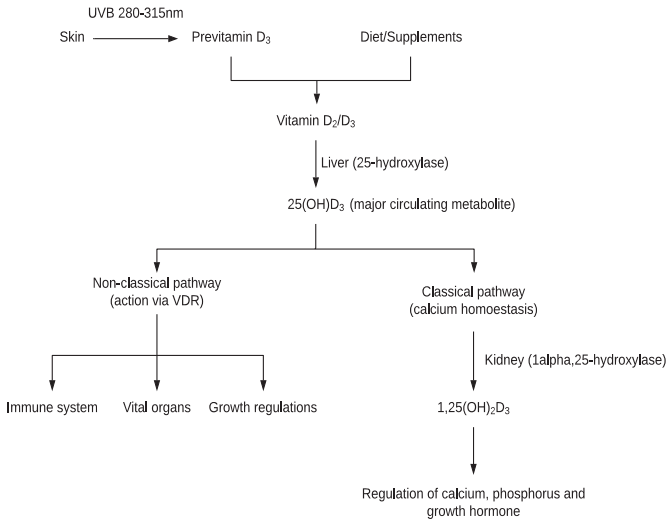

Fig. 2. Synthesis of vitamin D and its main target tissue. Vitamin D_2 and D_3 have no biological activity without a two-step hydroxylation process. The first step occurs in the liver, which requires 25-hydroxylase to convert the biological precursors, vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) to $25(OH)D_3$. The second step modifies $25(OH)D_3$ to its active metabolite, $1,25(OH)_2D_3$ via 1,25-hydroxylase in the kidneys. Physiological actions of $1,25(OH)_2D_3$ are mediated through its interactions with vitamin D receptors (VDRs) expressed in the nucleus of many different cell types.

vitamin D can regulate gene expression by facilitating gene transcription through interactions with VDR (Zhang et al., 2012). Hence, vitamin D has been found to have pleiotropic physiological functions; it not only modulates calcium and phosphorus homeostasis but is also involved in innate and adaptive immunity (Nurminen et al., 2018).

5.2. Role of vitamin D in immune function/immunity

Vitamin D is well known for its role in calcium and bone homeostasis (Gong et al., 2018; Thacher et al., 2014). However, recent studies have started to focus on the functions of vitamin D in both innate and adaptive immunity (Adams and Hewison, 2008). VDRs are expressed on most immune cell types (Provvedini et al., 1983; Brennan et al., 1987; Veldman et al., 2000) and the level of expression is found to increase with $1,25(OH)_2D_3$ treatment (Veldman et al., 2000). In addition, a study also observed that African-American individuals (known to have increased susceptibility to tuberculosis) have lower levels of $25(OH)D_3$ in their sera and were inefficient in the induction of antimicrobial peptide cathelicidin as well as the killing of intracellular Mycobacterium tuberculosis (Liu et al., 2006). These data suggest the vitamin D level variabilities might contribute to the differences in microbial infection susceptibility among human populations. This could partly be explained by the role of $1,25(OH)_2D_3$ in phenotypic differentiation of immature myeloid leukemia cells (Abe et al., 1981; Amento et al., 1984; Mangelsdorf et al., 1984; Miyaura et al., 1981). Thus, a deficiency in vitamin D could lead to ineffective development of these cells, resulting in altered antimicrobial responses to pathogens. Other than immune cell maturation, vitamin D also plays a role in maintaining immune cell responses and function during infections (Djukic et al., 2014). Vitamin D deficiency (< 15 ng/ml) has been reported to reduce the rate of microglial intracellular killing of pathogens and phagocytosis by decreasing the amount of cytokines such as TNFα and IL-6 released upon stimulation (Djukic et al., 2014). Moreover, studies in human monocytes have shown that a level of serum vitamin D above 30ng/ml (in the physiological range) is important in maintaining optimal anti-inflammatory responses (Zhang et al., 2012). Vitamin D deficiency could lead to proinflammatory states due to compromised suppression in cytokine production such as IL-6 and TNFα by monocytes (Zhang et al., 2012). The function of these inhibitory signals by $1,25(OH)_2D_3$ is further supported by their role in homeostatic control on dendritic cell development and function (Hewison et al., 2003). It has been suggested that the negative feedback mediated by $1,25(OH)_2D_3$ could potentially contribute to the maintenance of peripheral tolerance of self-antigens via VDR-dependent mechanisms (Griffin et al., 2001; Hewison et al., 2003). VDRs are expressed in lymphocytes, and vitamin D could therefore regulate adaptive immune system responses (Provvedini et al., 1983; Nunn et al., 1986). Studies have shown that the effects of vitamin D on T-cells depend on the T-cell subtype; for instance, the ability of $1,25(OH)_2D$ to suppress or enhance T-cell proliferation depends on the subtype that is being treated (Hewison, 2012). Although numerous studies have demonstrated the role of vitamin D in immunoregulation, it is important to note that many of these studies are circumstantial or association studies. Moreover, supplementation studies in humans have shown contradictory results; findings from these studies were not consistent in the demonstration of the immune-regulatory effects of vitamin D (Allen et al., 2012; Prietl et al., 2014; Sotirchos et al., 2016; Muris et al., 2016; Berlanga-Taylor et al., 2018). As suggested by Damoiseaux and Smolders, because peripheral blood are frequently used in human studies, the heterogeneity of these cell fractions under homeostatic conditions could be responsible for the discrepancies found across results from different studies (Damoiseaux and Smolders, 2018). Perhaps using a disease-specific cell or biomarker to demonstrate or measure the effects of vitamin D supplementation on immunity may yield more consistent results across different human in vivo studies.

5.3. Role of vitamin D in MS

According to current literature, vitamin D and its interaction with the immune system are implicated in the regulation of clinical disease activity in MS. This is suggested by the lower serum $25(OH)D_3$ levels during relapse than remission in MS patients (Soilu-Hanninen et al., 2005; Correale et al., 2009). Moreover, higher levels of serum $25(OH)D_3$ are also found to have a protective effect on MS risk such as a reduction in CNS lesions and relapse rate (Ascherio et al., 2014; Simpson Jr. et al., 2010). The exact mechanism of action of vitamin D in MS remains elusive, but it is likely due to its immunomodulatory effects on CNS inflammation (Lu et al., 2018). Numerous studies have documented the role of vitamin D in immune responses, in particular its association with reduced frequency in differentiation of IL-17/IL-22 producing T-cell subtypes in humans (Allen et al., 2012; Sommer and Fabri, 2015), which are implicated in MS pathology. In addition, the potential benefits of vitamin D supplementation in MS are also shown by studies in human regulatory-like T-cells (da Costa et al., 2016) and B-cells (Haas et al., 2016). The results from these studies suggest that the active form of vitamin D could reduce relapse risk by attenuating B-cell immunoreactivity and limit pathogenic T-cell responses through enhancing classical or non-classical regulatory T-cells (da Costa et al., 2016; Haas et al., 2016). Given previous research implicating vitamin D level and MS predisposition, it is likely that vitamin D deficiency plays a role in several key pathophysiological processes in MS, such as neuroinflammation, demyelination, axonal damage and remyelination (Smolders et al., 2011). Although numerous findings have demonstrated the immunomodulatory actions of vitamin D on the CNS, the exact mechanisms remain inconclusive. Inconsistency across results obtained from human studies has also shed light on the complexity and diversity of the effects of vitamin D on immune regulation. Assessment of MS-specific biomarkers or cells could be more relevant in revealing the effects of vitamin D supplementation on MS. But it is promising that a reduction in anti-Epstein-Barr virus nuclear antigen-1 (anti-EBNA-1) antibody levels in RRMS patients on vitamin D supplementation is a very consistent finding (Damoiseaux and Smolders, 2018; Rolf et al., 2018). It is also important to note that solid evidence on the effects of vitamin D status in clinical course or disability progression in MS is still lacking. There is a growing consensus on the beneficial actions of vitamin D on the inflammatory component of MS, but more studies are still required to assess its effects on the progressive degenerative component in MS pathology (Pierrot-Deseilligny and Souberbielle, 2017).

5.4. Effects of vitamin D on P2X7R

Studies on the modulation of P2X7R expression and function by vitamin D on cells of the immune and nervous systems are lacking. There are some studies on human mononuclear cells that have demonstrated the inhibitory effects of vitamin D on P2X7R expression, thus reducing P2X7R-mediated proinflammatory actions on immune cells (Lajdova et al., 2016). Moreover, because the activation of P2X7R leads to the secretion of pro-inflammatory cytokines and chemokines such as IL-1, IL-6, TNFα and C-C motif chemokine ligand 2 (CCL2) (Englezou et al., 2015; Shieh et al., 2014), the inhibitory effects of vitamin D on P2X7R reduce the inflammatory responses promoted by these inflammatory factors. Currently, the mechanism of the anti-inflammatory effects of vitamin D on P2X7R is largely undefined, but it has been shown that vitamin D prevents calcium influx through inhibiting P2X7R pore permeation (Lajdova et al., 2008). Due to the role of calcium signaling in activation and proliferation of T lymphocytes as well as innate immune cells such as microglia and monocytes (Brignall et al., 2017; Kotturi et al., 2003; Lewis, 2001; Saul et al., 2016; Tvrdik and Kalani, 2017), the inhibitory effects of vitamin D on P2X7R could reduce the activation of adaptive and innate immune cells through modulating calcium influx (Lajdova et al., 2016). Although the beneficial effects of vitamin D on MS risk have been shown in some studies,

its mechanisms on the predominant immune cells in MS such as T lymphocytes, monocytes and microglial cells remain unclear. Thus further studies are needed to explore the mechanisms and therapeutic benefits of vitamin D in MS through modulation of P2X7R expressed on immune cells.

5.5. Effects of vitamin D and dexamethasone on P2X7R

The active metabolite of vitamin D, $1,25(OH)_2D_3$ is considered as a true steroid hormone due to its origin from cholesterol (D hormone) (Cutolo et al., 2011), and therefore like glucocorticoids, it exerts immunomodulatory activities. Because of an overlap in their immunomodulatory actions, vitamin D is found to exert synergistic effects with glucocorticoids (Cutolo et al., 2014). A study has shown that $1,25(OH)_2D_3$ has additive effects on the inhibition of lymphocyte proliferation when combined with dexamethasone (Jirapongsananuruk et al., 2000), suggesting that vitamin D supplementation in conjunction with glucocorticoids during MS acute exacerbation could enhance the therapeutic benefits of the glucocorticoid treatment. In addition, $1,25(OH)_2D_3$ is also found to have additive effects on dexamethasone-mediated inhibition of Th1 cytokine production, in particular IFN-γ (Jirapongsananuruk et al., 2000), which is implicated in MS pathogenesis. While vitamin D seems to enhance the inhibitory actions of dexamethasone, high doses of dexamethasone are shown to decrease the expression of CYP27B1, which is required for local $1,25(OH)_2D_3$ production in the brain (prefrontal cortex and hippocampus) (Jiang et al., 2014). This suggests a possibility that glucocorticoids could influence the local production of $1,25(OH)_2D_3$ and disrupt vitamin D activation and signaling in the brain (Jiang et al., 2014). Thus, the effects of vitamin D and glucocorticoids on each other need to be further explored to optimize glucocorticoid treatments during MS acute exacerbation. Currently the literature on the effects of dexamethasone and vitamin D on P2X7R is scarce, but dexamethasone alone is found to inhibit P2X7R expression and function in immune cells, in particular mast cells (Yoshida et al., 2017). Taking into account the synergism between vitamin D and dexamethasone on immunity, these observations raise an intriguing possibility that vitamin D may enhance the anti-inflammatory actions of glucocorticoids on P2X7R in immune cells, providing a potential explanation for the additive effects of $1,25(OH)_2D_3$ on dexamethasone-mediated anti-inflammatory responses. In addition, because most in vitro vitamin D studies frequently use the active form of vitamin D, $1,25(OH)_2D_3$ and vitamin D supplementation is often in the form of vitamin D_2 or D_3, the exact mechanism of vitamin D supplementation on glucocorticoids remains uncertain.

6. Conclusions

MS is a chronic neuroinflammatory disease of the CNS with unknown etiology. The mechanisms of MS pathology are not well-defined, but it is known that they involve complex interactions between systems and cell types, including T lymphocytes, monocytes, microglial cells and neurons, which lead to focal lesions and neuroinflammatory demyelination in the brain and spinal cord. Interestingly, even though P2X7R is expressed on cells of both innate and adaptive immunity as well as peripheral and centrally derived cells, its exact role in MS is yet to be determined. Furthermore, the mechanisms of vitamin D on P2X7R expressed on immune cells need to be investigated as current findings suggest their possible roles in MS risk and disease activity.

Declarations of interest

None

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