Potential Roles of Prostaglandin E$_2$ and Interleukin-1β in Experimental Autoimmune Encephalomyelitis

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Abstract

Multiple sclerosis (MS) is a progressive disease that is characterized by multifocal inflammation and demyelination in a central nervous system. Experimental autoimmune encephalomyelitis (EAE) is an animal model of MS that shows ascending flaccid paralysis with inflammation of spinal cord. We focus on the potential roles of inducible prostaglandin E$_2$ (PGE$_2$) and interleukin-1β (IL-1β) in EAE after myelin oligodendrocyte glycoprotein 35-55 peptide immunization in this review. PGE$_2$ synthesized by cyclooxygenase (COX)-2 and microsomal prostaglandin E synthase-1 (mPGES-1) in vascular endothelial cells (VECs) or macrophages/microglia aggravates inflammation, demyelination and paralysis and facilitates the activation and differentiation of CD4-positive (CD4$^+$) T cells into interleukin-17 (IL-17)-producing helper T cells to promote neuronal dysfunction and blood-spinal cord barrier disruption in the EAE model. PGE$_2$ also causes vasculature and increases IL-1β production in VECs and CD4$^+$ T cells, and IL-1β plays a crucial role in facilitating EAE progression and stimulates the synthesis of COX-2 and mPGES-1 to produce PGE$_2$. Thus, the local PGE$_2$-IL-1β signaling pathway facilitates IL-17 production in inflammatory lesions in the spinal cord of EAE animals. This pathway represents a possible mechanism by which PGE$_2$ participates in EAE pathology. Taken together, this evidence highlights the intercellular PGE$_2$ signaling pathway in the spinal cord as a therapeutic target for ameliorating MS severity after disease onset.

Keywords: Prostaglandin E$_2$; Interleukin-1β; Microsomal prostaglandin synthetase-1; Multiple sclerosis; Experimental autoimmune encephalomyelitis; CD4-positive (CD4$^+$) T cells; Vascular endothelial cells

Abbreviations: MS: Multiple Sclerosis; PGE$_2$: Prostaglandin E$_2$; COX: Cyclooxygenase; mPGES-1: Microsomal Prostaglandin E Synthetase-1; mac/mic: Macrophages/microglia; VECs: Vascular Endothelial Cells; EAE: Experimental Autoimmune Encephalomyelitis; MOG35–55: Myelin Oligodendrocyte Glycoprotein35–55 Peptide; IL-1β: Interleukin-1β; IL-1RN: Interleukin-1 Receptor Antagonist; IL-1R1: Interleukin-1 Receptor 1; mPGES-2: Microsomal Prostaglandin E Synthetase-2; cPGES: Cytosolic PGE$_2$ Synthase; EP: E-prostanoid; mPGES-1-/-: Microsomal Prostaglandin Synthetase-1-deficient; WT: Wild Type; IL-17: Interleukin-17; BBB: Blood-Brain Barrier; CD4$^+$ T cell: CD4-positive T cell; Th1: Type 1 helper T cell; IFN-γ: Interferon-γ; VEGF: Vascular Endothelial Growth Factor; IL-17R: Receptor for IL-17; ASC: Apoptosis-associated Speck-like Protein Containing a Caspase Recruitment Domain.

Introduction

Multiple sclerosis (MS) is a progressive disease showing multifocal inflammation and demyelination. Inducible prostaglandin E$_2$ (PGE$_2$) is an inflammatory mediator synthesized by cyclooxygenase (COX)-2 and microsomal prostaglandin E synthase-1 (mPGES-1), also known as PTGES. COX-2 is increased in macrophages/microglia (mac/mic) in the brains of MS patients and in vascular endothelial cells (VECs) in animals with experimental autoimmune encephalomyelitis (EAE), an animal model of MS [1,2]. In addition, mPGES-1 expression is induced in brain VECs in fever and neuronal injury after kainic acid injection [3-4]. Rodents with EAE induced by the myelin oligodendrocyte glycoprotein 35-55 peptide (MOG35–55) exhibit typical perivascular infiltration of mononuclear cells and inflammatory foci in the spinal cord and brain. MOG35–55-induced EAE also results in infiltration of the cerebral meninges at the third and lateral ventricles, as well as severe parenchymal infiltration in the spinal cord [5,6]. The symptomatic course of EAE involves progressive flaccid paralysis with inflammation which targets the spinal cord but accordingly, we mainly focus on spinal inflammation in EAE and its association with PGE$_2$ in this review [7,8].

PGE$_2$ is increased after EAE induction in spinal cord and treatment with selective COX-2 inhibitors prevent the development of EAE-associated paralysis. Similarly, the induction of mPGES-1 expression in infiltrating macrophages stimulates the clinical EAE progression in mice. Moreover, mPGES-1 expression is also induced in VECs located around inflammatory foci and accelerates inflammation, demyelination, and paralysis in EAE models. Thus, PGE$_2$ produced by mPGES-1 promotes disease progression in the spinal cord of animals with EAE [9-15].

Interleukin-1β (IL-1β) is also an important inflammatory and pathological mediator of EAE mice. The administration of a recombinant interleukin-1 receptor antagonist (IL-1RN) delays disease onset and decreases EAE severity [16]. Additionally, the expression of a defective interleukin-1 receptor 1 (IL-1R1) gene in mice show complete resistance to EAE [17]. IL-1β is generally known to stimulate PGE$_2$ production; whereas, evidence showing that PGE$_2$ stimulates IL-1β production is unavailable. However, we recently find that IL-1β is a mediator or component of the mechanism by which PGE$_2$ promotes the progression of EAE [18].

In this review article, we summarize the roles of PGE$_2$ and IL-1β in EAE and their relations with inflammatory molecules related to spinal cord inflammation. Furthermore, we discuss intercellular interactions among VECs, CD4$^+$ T cells, and monocytes mediated by PGE$_2$ and autocrine IL-1β signaling in EAE mice.

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Received February 01, 2019; Accepted March 28, 2019; Published April 05, 2019

Citation: Takemiya T (2019) Potential Roles of Prostaglandin E$_2$ and Interleukin-1β in Experimental Autoimmune Encephalomyelitis. J Mult Scler (Foster City) 8: 225. doi: 10.4172/2376-0389.1000225

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PGE\textsubscript{2} Induction in EAE Models

Patients with definite MS have higher baseline PGE\textsubscript{2} expression in leukocyte cultures than healthy control subjects and PGE\textsubscript{2} expression is similarly elevated in peripheral blood monocytes from chronic MS patients [19-20]. Based on these reports, peripheral PGE\textsubscript{2} expression might be related to MS progression. PGE\textsubscript{2} is synthesized from arachidonic acid by COX and PGES, and COX exists as constitutively active (COX-1) and inducible (COX-2) isoforms. MS patients show COX-2 induction in chronic, active lesions in the brain [1]. COX-2 expression also appears in mac/mic in the spinal cord 16 days after EAE induction [21]. In EAE models, COX-2 is localized to ECs in the spinal cord, particularly 14-25 days after immunization [2]. Thus, COX-2 in central nervous system (CNS) is a crucial mediator of MS and EAE pathology. PGE\textsubscript{2} concentration is elevated in the spinal cord after EAE induction (Figure 1A) [12].

Three isoforms of PGES have been identified: mPGES-1, microsomal prostaglandin E synthase-2 (mPGE\textsubscript{S}-2) and cytosolic PGE\textsubscript{S}, synthase (cPGE\textsubscript{S}). Notably, mPGE\textsubscript{S}-2 and cPGE\textsubscript{S} are constitutively appeared, while mPGE\textsubscript{S}-1 expression is induced in a manner functionally coupled to COX-2 in macrophages or osteoblasts following pro-inflammatory stimulation [22-25]. In the brain, mPGE\textsubscript{S}-1 expression is induced by COX-2 in VECs during fever, kainic acid-induced neuronal injury, and cerebral ischemia [3,4,26]. In EAE models, mPGE\textsubscript{S}-1 is expressed in ECs macrophages and mac/mic (Figure 2) but not in CD\textsuperscript{4} \ T cells in the spinal cord [11,12,18]. COX-2 expression is also induced in ECs, but conflicting information about the induction of COX-2 expression in mac/mic has been reported [2,21]. Therefore, VECs in CNS are undoubtedly important sources of PGE\textsubscript{S}, synthesized by COX-2 and mPGE\textsubscript{S}-1 in response to pro-inflammatory changes in the spinal cord of EAE animals.

Effects of PGE\textsubscript{2} on Neuro Inflammation and EAE Models

In the brain and spinal cord, mPGE\textsubscript{S}-1 activates several neuroinflammatory processes in neurodegenerative disease states and under physiological conditions. For example, mPGE\textsubscript{S}-1 exacerbates hippocampal neuron injury induced by seizure and cerebral ischemia after transient occlusion of the hemilateral middle cerebral artery [4,26-29]. Moreover, mPGE\textsubscript{S}-1 expression is associated with the β-amyloid plaque density, microglial accumulation, and learning impairment in subjects with Alzheimer’s disease [30]. The expression of mPGE\textsubscript{S}-1 is also induced by lipopolysaccharide treatment and plays a crucial role in amyotrophic lateral sclerosis [3,31-34]. Finally, mPGE\textsubscript{S}-1 stimulates macrophage activation in the spinal cord and is related with anoxia and the maintenance of wakefulness. According to these reports, PGE\textsubscript{2}, synthesized by mPGE\textsubscript{S}-1 is a pathological mediator of and therapeutic target for neurodegenerative diseases and CNS injury [35-37].

Several studies have investigated the effects of PGE\textsubscript{2} inhibition on EAE. COX-2 inhibitors limit the extent of EAE severity and T cell responses [13-15]. The administration of COX-2 inhibitors starting on the day of immunization are more effective at reducing EAE severity than administration starting 8 days or 14 days after immunization. Four subtypes of PGE\textsubscript{2}, receptors have been identified (E-prostanoid (EP) receptors EP\textsubscript{1-4}), and EP\textsubscript{4}-deficient mice show a significant attenuation of EAE symptoms. Moreover, the treatment of EP\textsubscript{2}-deficient mice with an EP\textsubscript{4} antagonist from days 3 to 7 after
immunization completely blocks the onset of EAE [13,15,38]. In addition, mPGES-1-deficient (mPGES-1-/-) mice show a delayed, brief period of symptomatic disease followed by recovery rather than progression, and exhibit the impairment for 26 days or 28 days after immunization (Figure 1B). Compared to wild-type (wt) mice, mPGES-1-/- mice exhibit a delayed EAE onset [11,12,18]. Moreover, mPGES-1 aggravates the inflammation and demyelination associated with EAE (Table 1 and Figure 3). Thus, PGE, synthesized by COX-2 and mPGES-1 plays important roles in early disease onset and later during disease maintenance. Because PGE, is a generalized production, the source of PGE, is not limited in spinal cord and brain in acute inflammation of EAE.

However, researchers have not clearly determined the source of PGE; VECs in CNS and mac/mic in the spinal cord or peripheral blood monocytes. Interestingly, based on the findings from bone marrow transplantation models, which enable EP expression or PGE, synthesis to be blocked in peripheral immune cells, EP4 or COX-2 deletion in bone marrow-derived cells causes a significant delay in the EAE onset, but the animals ultimately experience serious pathology, similar to the controls. Moreover, the deletion reduces the number of T cells and levels of IL-6 and interleukin-17 (IL-17) in the blood [39]. Therefore, the peripheral PGE, /EP4 pathway is very important during EAE onset but does not control the severity of EAE. Researchers have hypothesized that inducible PGE, synthesized by COX-2 and mPGES-1 in VECs in CNS and mac/mic facilitates pathological changes in the spinal cord of EAE models that lead to symptom manifestation.

**Effects of IL-1β on EAE and IL-1β Production**

In a clinical study, MS patients presented significantly higher levels of IL-1β in the serum and cerebrospinal fluid than healthy control subjects [40]. IL-1β has consistently been shown to play an important role in EAE. The administration of recombinant IL-1RN to EAE animals delays the onset of the disease and decreases its severity. Moreover, a mutation in the IL-1RN gene in mice show complete resistance to EAE [16,17]. IL-1β also regulates blood-brain barrier (BBB) permeability through endothelial IL-1R1 and induces BBB disruption. IL-1β also excites neuronal inflammation and is showed at high levels in infiltrating macrophages [41-48]. The expression of the IL-1β mRNA is induced in peritoneal leukocytes right after the initial induction of EAE [49]. In addition, macrophages have a minor contribution to the total IL-1β production during EAE pathogenesis and CD4-positive (CD4+) T cells are thought to be a major source of IL-1β in EAE pathogenesis [44,48-50]. IL-1β levels are increased in activated CD4+ T cells in inflammatory lesion in the spinal cord of EAE animals, and the increased IL-1β levels are mediated by mPGES-1 (Figure 4). Moreover, IL-1R1 expression in CD4+ T cells in EAE models is also controlled by mPGES-1. IL-1R1 is expressed on IL-17-producing helper T cells (Th17), but not type 1 helper T cells (Th1), in EAE mice and early Th17 differentiation is regulated by IL-1β signaling through IL-1R1 [18,50-52].

IL-1β also stimulates IL-1R1 expressed on ECs and induces the production of IL-6 and chemokine ligand 2 in inflammatory lesions in EAE models whereas, no studies have evaluated the IL-1β production in ECs. Recently, we investigated whether IL-1β expression was increased in ECs by PGE, synthesized from mPGES-1. When we compared IL-1β levels in ECs from wt and mPGES-1-/- mice, IL-1β levels were significantly elevated in wt EAE mice than in mPGES-1-/- EAE mice. Therefore, IL-1β also plays an important role in ECs, and IL-1β expression is regulated by PGE, during EAE [44,53].

**Relationship between IL-1β and COX-2/mPGES-1**

COX-2 expression is facilitated by IL-1β. IL-1β induces COX-2 expression in synovial fibroblasts and an intraperitoneal IL-1β injection induces the COX-2 mRNA expression in VECs in the brain [54-55]. The main protein that upregulates the COX-2 expression in the spinal cord is IL-1β, which promotes PGE, production, and contributes to pain hypersensitivity. IL-1β also plays a role on mediating the activity of nuclear factor kappa B and the COX-2 transcription in cells of the BBB in response to inflammation. COX-2 inhibitors prevent IL-1β-induced increases in PGE, production in the brain. It suggests that IL-1β controls PGE, production by modulating the synthesis of COX-2. Moreover, crosstalk between microvascular ECs and tumor cells increases COX-2 and mPGES-1, which are strongly inhibited by an IL-1R antagonist [54-59]. Thus, IL-1β plays an important role in the induction of COX-2 and mPGES-1 to produce the pathophysiological protein PGE,.

In contrast, IL-1β levels in CD4+ T cells were elevated by PGE, derived from mPGES-1 in EAE spinal cords (Figure 4) [18]. Moreover, IL-1β was also increased in ECs present in inflammatory lesions in EAE models therefore, IL-1β expression in CD4+ T cells and ECs is stimulated by PGE, in the spinal cord of EAE animals [53].
T cell Activation by PGE₂ and IL-1β in EAE Models

PGE₂ also regulates T cell activation and differentiation, depending on the cellular environment. PGE₂ enhances the Th17 responses of CD4⁺ T cells via EP4 and EP2 promotes Th17 differentiation and function through EP4 and EP2 and works with IL-23 and IL-1β to enhance IL-17A expression through EP4 [60-63].

In wt EAE mice, CD4⁺ T cells form perivascular clusters and infiltrate the spinal cord parenchyma, whereas they are scattered around vessels in the spinal cord of mPGES-1⁻/⁻ EAE mice and no T cells are detected in the spinal cords of both control mice (Figure 5). Researchers have postulated that CD4⁺ T cells infiltrate the spinal cord of animals with EAE through the disrupted blood-spinal cord barrier, and the infiltration and/or the activation of CD4⁺ T cells is regulated by PGE₂. Because CD4⁺ T cells almost completely colocalize with IL-1β in wt EAE mice, whereas IL-1β is expressed at very low levels in the spinal cord of mPGES-1⁻/⁻ EAE mice, this pathway may represent the mechanism by which PGE₂ directly activates CD4⁺ T cells to increase IL-1β production in EAE models [12,18] (Figure 4).

An analysis of Th17 and Th1 cells in culture supernatants revealed high IL-17 expression in Th17 cells and high interferon-γ (IFN-γ) expression in Th1 cells in EAE models [64]. IL-17 staining is colocalized with CD4⁺ T cells in wt EAE mice, whereas morphological changes are restricted and IL-17 staining is weak in mPGES-1⁻/⁻ EAE mice. In contrast, IFN-γ is co-expressed in few CD4⁺ T cells in either wt or mPGES-1⁻/⁻ EAE mice [18]. Thus, mPGES-1 stimulates the production of IL-17 in CD4⁺ T cells. In contrast, IFN-γ staining is partially colocalized with CD4⁺ T cells in both wt and mPGES-1⁻/⁻ EAE mice, suggesting that PGE₂ does not regulate the production of IFN-γ, which means an activity of Th1. The EAE incidence and scores are reduced when EAE mice are mediated with anti-IL-17 antibodies prior to the observed increase in CD4⁺ IL-17⁺ T cells, suggesting that CD4⁺ T cells control tissue inflammation by inducing IL-17 production [65]. Because PGE₂ regulates IL-17 expression in EAE models, we postulate that this mechanism is a potential explanation for the participation of PGE₂ in EAE pathology.

Vascularity Induced by PGE₂ and IL-1β in EAE Models

Inflammation induces the vasodilation of small blood vessels, subsequent more perfusion and resulting in an obvious increase in vessel density, which is known as vascularity. After EAE induction, vascularity is caused by vasodilation and angiogenesis. Angiogenesis is facilitated by vascular endothelial growth factor (VEGF), which leads to the degeneration of the vascular basement membrane and BBB breakdown [66,67]. In MS patients, BBB dysregulation and the trans-endothelial migration of activated leukocytes are the earliest signs of cerebrovascular dysfunction. VEGF is involved in EAE process during the acute phase [66,68,69]. In addition, inhibition of VEGF receptor 2 reduces clinical signs of EAE in the acute phase of the EAE progression. Furthermore, the number of blood vessels increases...
during the relapse phase of EAE animals [66,69]. Thus, angiogenesis aggravates inflammation in the spinal cord of EAE animal [70,71]. Vascularity is triggered upon EAE induction, regardless of the presence of mPGES-1. In addition, the PGE2 produced by mPGES-1 stimulates vascularity in the spinal cord of animal models of EAE, and aggravates inflammation, demyelination, and paralysis. Therefore, vascularity is one mechanism by which PGE2 aggravates EAE. In contrast, vascularity is one mechanism by which PGE2 aggravates inflammation, demyelination, and paralysis. Therefore, stimulation of angiogenesis after inflammation promotes neural remodeling through the production of prostaglandin I2 during the EAE chronic phase [70,71].

**IL-17 and Th17 in EAE**

IL-17 is a proinflammatory cytokine produced by activated memory T cells, and the IL-17s are secreted proteins of 150–180 amino acids. There are at least six members of the IL-17 family (IL-17A, IL-17B, IL-17C, IL-17D, IL-25 (IL-17E) and IL-17F) in mice and humans [72,73]. The receptor for IL-17 (IL-17R) is a transmembrane protein of approximately 130 kDa. The IL-17 is expressed only by T-cells, whereas its receptor is expressed in all tissues. Moreover, four receptors are identified which share partial sequence homology to IL-17R. EAE development is suppressed in IL-17 knockout mice. The severity of EAE in mice immunized by PLP is reduced when IL-17 is neutralized [74-76]. In addition, T cell-intrinsic apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) is required for the effector stage of EAE, and ASC deficiency in T cells impaired Th17 but not Th1-mediated EAE. Moreover, IL-17 is produced by a Th17 cell-intrinsic ASC-NOD-like receptor 3-Caspase-8 inflammasome during CNS inflammation. There is an autocrine action of Th17-derived IL-1β through IL-1R [50]. We found that PGE2 facilitates this autocrine function of IL-1β [18]. It is clear that IL-17 produced in Th17 cells has an important role on EAE. In contrast, IL-17 is also produced in CD8+ positive T cell, yot cells, neutrophil or monocyte, therefore in the future we need to investigate the role and the regulatory mechanisms of IL-17 produced by other cells [77].

Next, I discuss other cytokines concerning with EAE and Th17. IL-12p40 knockout mice show no clinical symptoms with no inflammation, whereas IL-12p35 knockout mice show more severe symptoms with severe inflammation. It suggests that p40-containing cytokine distinct from IL-12 is essential for the development of EAE. Moreover, IL-23 is a heterodimeric cytokine composed of a p19 subunit and the p40 subunit of IL-12, and IL-23p19 knockout mice are resistant to EAE. IL-23 also promotes an activation of distinct CD4 T cell producing IL-17. In addition, mice whose T cells cannot respond to signalling of TGF-β lack Th17 cells and do not develop EAE. Local administration of antibody to block TGF-β prevents the differentiation of Th17 cell and the onset of EAE [78-82]. On the contrary, mice whose T cells overexpress TGF-β develop more severe EAE and the T cells produce massive amounts of IL-17. These reports suggest that TGF-β regulates the differentiation of Th17 cell. Furthermore, IL-6 knockout mice do not develop a Th17 response. The orphan nuclear receptor RORyt expression is induced by IL-6 and TGF-β and RORyt induces transcription of the genes encoding IL-17 [83-85]. Moreover, IL-21 potently induces Th17 differentiation. IL-21 knockout mice impair the generation of Th17 cells and protect against EAE. IL-9 knockout mice are resistant to the induction of EAE and exhibit fewer inflammatory infiltrates in the CNS, with lower levels of IL-17 and IFN-λ expression. Th17 cells express IL-22, an IL-10 family member, at substantially higher amounts than Th1 or Th2 cells. Similar to IL-17, IL-22 expression is regulated by TGF-β in the context of IL-6 and other proinflammatory cytokines [86-88]. In addition, IL-27 suppresses the development of Th17 cells mediated by IL-6 and TGF-β, and IL-27 suppresses IL-6-mediated T cell proliferation. IFN-β-treated animals show a decrease of IL-17 expression and IFN-β knockout mice exhibit earlier onset and more rapid progression in EAE. Furthermore, CD4 T cells in Tyk2 knockout mice reduce the IL-17A level in response to MOG35–55 [89-93]. Many cytokines including IL-17 are related

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>EAE mice (transgenic or general)</th>
<th>Antigen type PLP/ MOG/ MBP</th>
<th>Findings</th>
</tr>
</thead>
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<tr>
<td>Becher B</td>
<td>2002</td>
<td>IL-12p40 (-/-) mice IL-12p35 (-/-) mice</td>
<td>MOG 35-55</td>
<td>IL-12p40 (-/-) mice does not show any clinical symptoms with no inflammation, and IL-12p35 (-/-) mice shows more severe symptoms and severe inflammation.</td>
</tr>
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<td>Gran B</td>
<td>2002</td>
<td>IL-12p40 (-/-) mice IL-12p35 (-/-) mice</td>
<td>MOG 35-55</td>
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<td>Cua DJ</td>
<td>2003</td>
<td>IL-12p40 (-/-) mice IL-12p35 (-/-) mice IL-23p19 (-/-) mice</td>
<td>MOG 35-55</td>
<td>IL-23 p19 (-/-) and IL-12 p40 (-/-) mice are resistant to EAE. IL-12p35 (-/-) mice is susceptible to EAE.</td>
</tr>
<tr>
<td>Komiya Y</td>
<td>2006</td>
<td>IL-17 (-/-) mice</td>
<td>MOG 35-55</td>
<td>EAE development is suppressed in IL-17 (-/-) mice with ameliorated histological changes.</td>
</tr>
<tr>
<td>Veldhoen M</td>
<td>2006</td>
<td>C57BL/6 mice</td>
<td>MOG 35-55</td>
<td>Mice whose T cells cannot respond to TGF-β signaling lack Th17 cells and do not develop EAE.</td>
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<tr>
<td>Betelli E</td>
<td>2006</td>
<td>2D2 x TgTGF-β-β mice</td>
<td>MOG 35-55</td>
<td>Mice whose T cells overexpress TGF-β develop more severe EAE and the T cells produce massive amounts of IL-17.</td>
</tr>
<tr>
<td>Nuriev R</td>
<td>2007</td>
<td>IL-21 (-/-) mice</td>
<td>MOG 35-55</td>
<td>IL-21 potently induces Th17 differentiation. IL-21 (-/-) mice impair the Th17 cells generation and protect against EAE.</td>
</tr>
<tr>
<td>Korn T</td>
<td>2007</td>
<td>IL-6 (-/-) mice</td>
<td>MOG 35-55</td>
<td>IL-6 (-/-) mice does not develop a Th17 response.</td>
</tr>
<tr>
<td>Martin-Saavedra FM</td>
<td>2008</td>
<td>SJL mice</td>
<td>MBP</td>
<td>IFN-β treated animals show a decrease of IL-17 expression.</td>
</tr>
<tr>
<td>Korn T</td>
<td>2008</td>
<td>T cell-conditional gp130 (-/-) mice</td>
<td>MOG35-55</td>
<td>T cell-conditional gp130 (-/-) mice, which fail to induce IL-6, show no clinical EAE development with lower levels of IL-17.</td>
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<td>Tigno-Aranjuez JT</td>
<td>2009</td>
<td>SJL/J mice</td>
<td>PLP 139-151</td>
<td>The severity of EAE in PLP in CFA-immunized mice is reduced when IL-17 is neutralized in vivo.</td>
</tr>
<tr>
<td>Du C</td>
<td>2009</td>
<td>C57BL/6 mice</td>
<td>MOG 35-55</td>
<td>miR-326 result in fewer Th17 cells and mild EAE, and its overexpression led to more Th17 cells and severe EAE.</td>
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with Th17 differentiation; therefore Th17 is potent T cell to effect on inflammation and CNS injury in EAE and MS (Table 2).

**Intercellular Interactions in the EAE Spinal Cord**

In the EAE spinal cord, PGE$_2$ derived from mPGES-1 promotes CD4$^+$ T cell invasion and facilitates IL-1$\beta$ production by CD4$^+$ T cells via EP receptors; IL-1$\beta$ in turn participates in autocrine signaling through IL-1R1 expressed on CD4$^+$ EP receptors; IL-1$\beta$ in turn participates in autocrine signaling through PGE$_2$ synthesis, which may directly or indirectly influence cell migration and proliferation (26). IL-1$\beta$ produced in nearby CD4$^+$ T cells can activate EP receptors expressed on the surface of ECs, VECs, and other cells, leading to the production of pro-inflammatory cytokines and chemokines, as well as the induction of adhesion molecules and cell activation (27). IL-1$\beta$ produced in nearby CD4$^+$ T cells can activate EP receptors expressed on the surface of ECs, leading to the production of pro-inflammatory cytokines and chemokines, as well as the induction of adhesion molecules and cell activation (27).

Finally, we must consider whether peripheral monocytes are a source of PGE$_2$. Peripheral PGE$_2$ produced by monocytes induces IL-6 release through EP4 expressed on monocytes, which in turn induces IL-17 secretion from T cells. Moreover, PGE$_2$ induces matrix metalloproteinase-9 expression in T cells through EP4, leading to a disruption of the blood-spinal cord barrier. Furthermore, COX-2/PGE$_2$/EP4 signaling in peripheral immune cells facilitates the development of EAE, particularly during disease onset; however, EAE severity and maintenance/progression are not affected by peripheral immune cells but instead appear to be regulated by mPGES-1/PGE$_2$/IL-1$\beta$ signalling between ECs and CD4$^+$ T cells in the spinal cord. Accordingly, CNS and peripheral PGE$_2$ participate in different aspects of EAE pathology [39].

**Conclusions**

PGE$_2$ induces the EAE progression by regulating IL-1$\beta$ production and subsequently promoting neuronal dysfunction and disruption of the BBB in the spinal cord of subjects with EAE, leading to serious EAE symptoms. Furthermore, intercellular signalling pathways including PGE$_2$ and IL-1$\beta$ in the spinal cord may be an important therapeutic target in MS.

**Acknowledgments**

This work was supported by a grant from KAKENHI (17K10064). The author would like to thank the staff of the Medical Research Institute at Tokyo Women’s Medical University for their assistance with my research.
References


