REVIEW

Emerging role of semaphorin-3A in autoimmune diseases

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Abstract

Autoimmune diseases (ADs) are featured by the body's immune responses being directed against its own tissues, resulting in prolonged inflammation and subsequent tissue damage. Currently, the exact pathogenesis of ADs remains not fully elucidated. Semaphorin-3A (Sema3A), a secreted member of semaphorin family, is a potent immunoregulator during all immune response stages. Sema3A has wide expression, such as in bone, connective tissue, kidney, neurons, and cartilage. Sema3A can downregulate ADs by suppressing the over-activity of both T-cell and B-cell autoimmunity. Moreover, Sema3A shows the ability to enhance T-cell and B-cell regulatory properties that control ADs, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and systemic sclerosis. However, it can also induce ADs when overexpressed. Together, these data strongly suggest that Sema3A plays a pivotal role in ADs, and it may be a promising treatment target for these diseases. In the present review, we focus on the immunological functions of Sema3A and summarize recent studies on the involvement of Sema3A in the pathogenesis of ADs; the discoveries obtained from recent findings may translate into novel therapeutic agent for ADs.

Keywords Semaphorin-3A · Therapeutic agent · Autoimmune diseases

Abbreviations

ADs	Autoimmune diseases
αB-crystallin	Alpha B-crystallin
BAFF	B-cell activating factor
Bregs	B regulatory cells
CIA	Collagen-induced arthritis
CNS	Central nervous system
CpG-ODN	Cytosine-phosphodiester-guanine oligodeoxynucleotides
DAS28-CRP	Disease Activity Score 28-joint count C reactive protein
DCs	Dendritic cells
dSSc	Diffuse systemic sclerosis
EAE	Experimental autoimmune encephalomyelitis
FoxP3	Forkhead box P3
IL-2	Interleukin 2
IL-10	Interleukin 10
IL-17	Interleukin 17
IFNs	Interferons
ISSc	Limited systemic sclerosis
LGN	Lupus glomerulonephritis
MAG	Myelin binding glycoprotein
MAPK	Ras/mitogen-activated protein kinase
MOG	Oligodendrocyte glycoprotein
MS	Multiple sclerosis
NRP-1	Neuropilin-1
OA	Osteoarthritis
OPC	Oligodendrocyte precursor cell
PBMCs	Peripheral blood mononuclear cells
PSI	Plexin–semaphorin–integrin
RA	Rheumatoid arthritis
ROC	Receiver operating characteristic
RRMS	Relapsing–remitting multiple sclerosis
Sema3A	Semaphorin-3A
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
TGF-β	Transforming growth factor beta
Th1	Helper T-cell type 1
Th17	Helper T-cell type 17

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TNF	Tumor necrosis factor
Tregs	Regulatory T cells
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Introduction

Autoimmune diseases (ADs) are a pathophysiological state wherein immune responses are directed against, and damage, the body's own tissues (Guan et al. 2017). ADs contain a broad spectrum of disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic sclerosis (SSc). ADs, being able to activate complement and deposit in many sites, induce multi-organ inflammation and subsequent irreversible organ injuries such as in skin, joint, and kidney (Vadasz and Toubi 2012). Although significant progresses have been achieved in the treatment strategies of ADs, the exact cause and pathogenesis of ADs are still unclear. Unraveling the complex pro-inflammatory mechanisms in the pathogenesis of ADs was the focus in a large number of studies for several decades. These mechanisms include cellular and humoral immune responses followed by the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interferons (IFNs), and interleukin 17 (IL-17), as well as the overexpression of co-stimulatory molecules such as CD86 and CD40 on effector T cells, and the elevated production of B-cell activating factor (BAFF) (Kim 2015; Vadasz et al. 2015b). In the last decade, the involvement of regulatory immune responses in ADs has drawn much attention, the normal function of which was proven to maintain immune-mediated homeostasis. The early identified immunoregulators include regulatory T cells (Tregs) and the inhibitory cytokines, such as interleukin 10 (IL-10) and transforming growth factor beta (TGF-β) (Yuan et al. 2014). Nevertheless, more recently, other regulatory responses were emerging, such as the involvement of B regulatory cells (Bregs) and the regulatory semaphorins in suppressing autoimmunity.

In recent years, emerging data indicate that semaphorins, which were identified originally as guidance cues for developing axons, play regulatory roles in the immune system (Kumanogoh et al. 2005; Vadasz and Toubi 2013). The semaphorins are implicated in most stages of both normal and pathological immune responses and have been revealed to participate in autoimmune pathologies (Mizui et al. 2009; Vadasz et al. 2010; Vadasz and Toubi 2013). Semaphorins comprise a large family of proteins that are either secreted or membrane bound. Semaphorin-3A (Sema3A), a secreted member of semaphorin family, is identified as a potent immunoregulator in all stages of immune response, including both the early initiation and the late phase of inflammatory processes (Suzuki et al. 2008; Vadasz and Toubi 2013). Sema3A was also demonstrated to enhance T-cell and B-cell regulatory properties. It could inhibit the responsiveness of human monocytes and T cells to chemokine gradients (Ji et al. 2009; Delaire et al. 2001; Takamatsu et al. 2010a). Therefore, Sema3A has been recently considered as a new paradigm in the pathogenesis of ADs, such as SLE (Vadasz et al. 2011, 2012, 2015a; Vadasz and Toubi 2012), RA (Perez et al. 2016; Yoshida et al. 2014), MS (Costa et al. 2015; Kremer et al. 2015; Eixarch et al. 2013a; Gutiérrez-Franco et al. 2016; Okuno et al. 2011; Rezaeepoor et al. 2017; Williams et al. 2007), and SSc (Rimar et al. 2014; Olewicz-Gawlik and Samborski 2016; Vadasz et al. 2015d). Sema3A exerts an effective immunosuppressive role in these diseases through inhibiting the over-activity of both T-cell and B-cell autoimmunity. In addition, Sema3A could upregulate the expression of forkhead box P3 (FoxP3) in Tregs (Cozacov et al. 2017), further suggesting the potential of Sema3A as an immune regulator of inflammation in ADs.

In the present review, we focus on the immunological functions of Sema3A and summarize recent evidences on the involvement of Sema3A in the pathogenesis of ADs; the discoveries obtained from recent findings may translate into novel therapeutic agent for ADs.

Literature search method

"All relevant studies regarding the association of Sema3A with autoimmune diseases (SLE, RA, MS and SSc) were searched in Pubmed, Embase and the Cochrane Library databases. The following keywords and subject terms were used in the literature search: 'Systemic lupus erythematosus' OR 'SLE' AND 'Semaphorin-3A' OR 'Sema3A'; 'Rheumatoid arthritis' OR 'RA' AND 'Semaphorin-3A' OR 'Sema3A'; 'Multiple sclerosis' OR 'MS' AND 'Semaphorin-3A' OR 'Sema3A'; 'Systemic sclerosis' OR 'SSc' AND 'Semaphorin-3A' OR 'Sema3A'. Variants for all keywords were used to increase the number of studies returned by the search. All resulting articles were then screened and carefully reviewed."

Sema3A and its receptors

Currently, the semaphorin family contains 20 members in mice and humans, and 5 members in Drosophila; they are classified into 8 classes, namely 1–7 and V (Committee 1999; Yazdani and Terman 2006). The 8 classes of semaphorins have different overall structural and sequence characteristics, but all members of this family possess a conserved

extracellular domain that consists of approximately 500 amino acids, which is termed semaphorin domain (Yazdani and Terman 2006). Sema3A, originally named collapsin, is a member of class 3 semaphorins (Piaton et al. 2011); semaphorin domain, plexin–semaphorin–integrin (PSI) domain, immunoglobulin-like domain, and basic domain were constitute of Sema3A (Püschel et al. 1995; Elizabeth et al. 1995; Kolodkin et al. 1993; Fiore and Püschel 2003) (Fig. 1). It was found in the parallel experiments that a neuronal growth cone collapsing factor associated with chicken brain membranes was biochemically purified (Committee 1999; Luo et al. 1993). Sema3A is secreted by a variety of cell types such as neurocyte and several immune cells (Schlahsa et al. 2009).

Comparing with other semaphorins, Sema3A has wide expression, such as in bone (Wright et al. 1995), cancer cells (Rieger et al. 2003), connective tissue (Püschel et al. 1995), heart (Wright et al. 1995), kidney (Villegas and Tufro 2002), neurons (Wright et al. 1995), cartilage (Wright et al. 1995), and teeth (Loes et al. 2001). The expression patterns of the Sema3A are the best characterized in the nervous system, particularly during development (Fiore and Püschel 2003). Sema3A also has many functions, for instance, Sema3A participates in the process of cell death (Gagliardini and Fankhauser 1999), cell adhesion and aggregation (Kashiwagi 2005), and cell migration and patterning (Miao et al. 1999). Sema3A repulses peripheral axons and contributes to proper wiring of peripheral nervous system (Kawasaki et al. 2002; Taniguchi et al. 1997). Sema3A also can positively contribute to the observed partial regeneration of peripheral nerves (Scarlato 2003).

Plexin and neuropilin families are two major receptors for semaphorins. Plexin 1 and neuropilin-1 (NRP-1) form a stable complex. Plexin 1 alone does not bind Sema3A, but the NRP-1/plexin 1 complex has a higher affinity for Sema3A than does NRP-1 alone. While Sema3A binding to NRP-1 does not alter non-neuronal cell morphology, Sema3A interaction with NRP-1/plexin 1 complexes induces adherent cells to round up. Expression of a dominant-negative plexin 1 in sensory neurons blocks Sema3A-induced growth cone collapse. Sema3A treatment leads to the redistribution of growth cone NRP-1 and plexin 1 into clusters. Therefore, physiologic Sema3A receptors consist of NRP-1/plexin 1 complexes (Takahashi et al. 1999). Sema3A binds to NRP-1 with a high affinity and signals through plexin 1; however, Sema3A can also signal through plexin-A4 in different pathways (Eixarch et al. 2013b).

Immunological functions of Sema3A

In recent years, there has been increasing evidence regarding the involvement of the semaphorins in the regulation of the immune system. Roth et al. proposed a viewpoint that one of the major discoveries in the field of immunity is probably the identification of a potentially crucial role of semaphorin
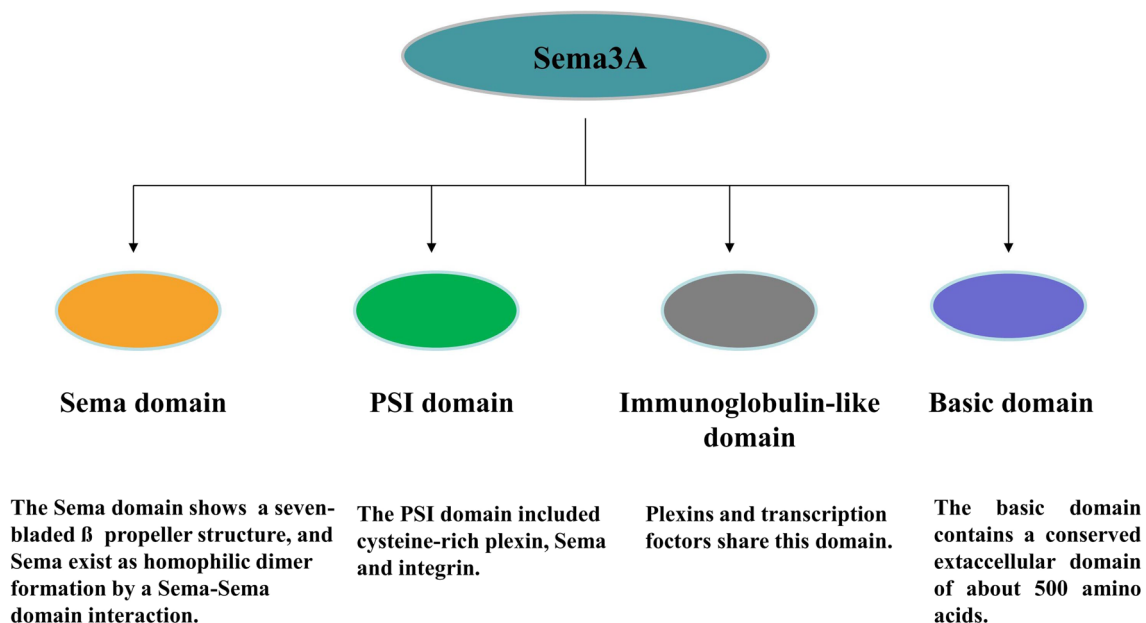
Fig. 1 The structure of semaphorin-3A (Sema3A). Sema3A consists of semaphorin domain, plexin–semaphorin–integrin (PSI) domain, immunoglobulin-like domain, and basic domain. The sema domain is expressed as a seven-bladed ß propeller structure. The PSI domain included cysteine-rich plexin, sema, and integrin. Plexins and transcription factors share the immunoglobulin-like domain. The basic domain contains a conserved extracellular domain of about 500 amino acids

functions in the immune system (Roth et al. 2008). Suzuki et al. reported that Sema3A is a potent immunoregulator during all immune response stages. Sema3A is involved in lymphocyte migration to the thymus and from the bloodstream to inflamed tissues. It is expressed on many types of immune cells such as B cells, T cells, and dendritic cells (DCs), but mainly on Tregs, leading to the inhibition of T effector cell proliferation and production of pro-inflammatory cytokines (Roth et al. 2008; Vadasz et al. 2010, 2012).

Sema3A normally binds to B cells (including memory/autoreactive B cells); it downregulates the expression of CD100 (a stimulatory molecule) and upregulates the expression of CD72 (inhibitory molecule) on B cells. When cocultured with Sema3A, IL-10 and TGF-β expressions were enhanced in CD19$^+$CD25^{high} Breg cells; Breg cell properties were enhanced by Sema3A through upregulating CD72 expression on B cells (Vadasz et al. 2014). Bregs are a subgroup of activated B cells, which play a crucial role in maintaining self-tolerance and preventing autoimmunity, demonstrating the immune-regulatory role of Sema3A.

When Sema3A binds Hepler T-cell type 1 (Th1) and Hepler T-cell type 17 (Th17) cells, it decreases their proliferation and the production of tumor necrosis factor (TNF), interferons (IFNs), and IL-17 (Vadasz and Toubi 2012). Rimar et al. and Suzuki et al. reported that Sema3A plays a regulatory role in immune responses, mainly serves as a negative regulatory for T cells in physiological and pathological immune responses (Rimar et al. 2015a). The inhibitory effect of Sema3A on T cells is mediated by the blockade of Ras/mitogen-activated protein kinase (MAPK) signaling pathway (Catalano 2006; Vadasz and Toubi 2013). The addition of Sema3A to DC/T-cell co-cultures significantly inhibited allogeneic T-cell proliferation. Sema3A acted directly on T cells as it could block the anti-CD3/CD28-stimulated T-cell proliferation. Sema3A exerts its immunomodulatory functions through the blockage of actin cytoskeleton reorganization, affecting TCR polarization and interfering with early TCR signal transduction events such as ZAP-70 or focal adhesion kinase phosphorylation (Lepelletier et al. 2006). The other immunoregulatory mechanisms of Sema3A may be maintaining self-tolerance; it was shown that Sema3A triggers a proapoptotic program that sensitizes activated T cells to Fas (CD95)-mediated apoptosis (Moretti et al. 2008). The NRP-1-plexin-A4 receptor complex transduces Sema3A-mediated immune suppressive signaling. Plexin-A4 is expressed in various cells, including T cells, DCs, and macrophages. Both *NRP-1*-mutant T cells, in which the Sema3A binding site is specifically disrupted, and plexin-A4$^{-/-}$ T cells exhibit enhanced in vitro proliferation after TCR stimulation. Moreover, plexin-A4$^{-/-}$ mice have enhanced T-cell priming and exacerbated T-cell-mediated immune responses (Yamamoto et al. 2008), suggesting that plexin-A4 negatively regulates T-cell-mediated immune

responses. In viral infection, Sema3A is also involved in virus-induced immune suppression. Measles virus-infected DCs, which fail to promote T-cell expansion, have greater early Sema3A secretion, resulting in a loss of actin-based protrusion on T cells (Tran-Van et al. 2011). A very recent study by Cozacov et al. showed that the co-culture of condition medium with 2 mcg/ml of recombinant human sema3A with CD4 + T cells increased the expression of FoxP3 in Tregs, which play a critical role in preventing autoimmunity (Cvetanovich and Hafler 2010), strongly suggesting its potential as an immune regulator of inflammation (Cozacov et al. 2017) (Figure 2).

In addition, it has been shown that plexin-A1, a critical receptor component for Sema3A, was crucially involved in the entry of DCs into the lymphatics. In addition, Sema3A was essential for DC transmigration and that Sema3A produced by the lymphatics promoted actomyosin contraction at the trailing edge of migrating DCs. These findings indicate that Sema3A plays an essential role in the migration of DCs, and identify a previously unknown mechanism that induces actomyosin contraction as these cells pass through narrow gaps (Takamatsu et al. 2010b).

Becoming a frontier player in the regulation of immune responses and the maintenance of self-tolerance, Sema3A is thus implicated in the pathogenesis of ADs, including SLE (Vadasz et al. 2011, 2012, 2015a; Vadasz and Toubi 2012), RA (Perez et al. 2016; Takagawa et al. 2013; Yoshida et al. 2014), MS (Costa et al. 2015; Kremer et al. 2015;
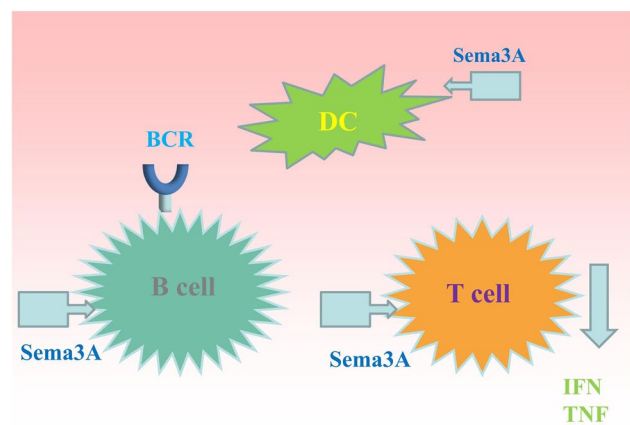
Fig. 2 Immunological function of Sema3A. Sema3A suppressed B-cell proliferations through increasing the expression of CD72 (inhibitory molecule), and the signaling of BCR. Sema3A decreases the production of IFN and TNF by macrophages and reduces the production of pro-inflammatory cytokines by T cell. Due to the blockage of actin cytoskeleton reorganization, immunomodulatory functions of Sema3A pushing TCR polarization and interfering with early TCR signal transduction events. When increasing it to DC cell and T-cell co-cultures, Sema3A significantly inhibited allogeneic T-cell proliferation. Sema3A also guides the entry of DC cell into the afferent lymphatics by promoting actomyosin contraction

Eixarch et al. 2013a; Gutiérrez-Franco et al. 2016; Okuno et al. 2011; Rezaeepoor et al. 2017; Williams et al. 2007), and SSc (Rimar et al. 2014; Olewicz-Gawlik and Samborski 2016; Vadasz et al. 2015d).

Semaphorin-3A in autoimmune diseases

ADs arise an inappropriate immune response against self-components, including macromolecules, cells, tissues, and organs.(Pan et al. 2013a). These groups of diseases involve a variety of molecules, cells, and tissues, which are targeted by the autoimmune responses (Pan et al. 2013b). Although the exact etiologies of ADs remain to be further elucidated and the clinical characteristics of these diseases are diverse, current findings have revealed that Sema3A is involved in the pathogenesis of ADs, including SLE (Gao 2017; Vadasz 2012), RA (Takagawa et al. 2013; Yoshida et al. 2014), MS (Rezaeepoor et al. 2017), and SSc (Olewicz-Gawlik and Samborski 2016; Rimar et al. 2015a; Vadasz et al. 2015c) (Table 1).

Semaphorin-3A in systemic lupus erythematosus

SLE is a prototypical ADs, characterized by the production of autoantibodies to components of the cell nucleus in association with a variety of clinical manifestations. The exact etiology of SLE is unknown; it has been confirmed that genetic factors play an important role in the predisposition of SLE, but multiple environmental or yet unclear factors may also be responsible (Mok and Lau 2003; Li et al. 2016). In the interaction of various factors such as genetic factors, environmental factors, and estrogen levels, it leads to a decrease in T lymphocytes, a reduction in T-suppression cell function, an excessive hyperplasia of B cells, a large amount of autoantibodies, and a combination with corresponding autoantigen in vivo (Mok and Lau 2003; Yu et al. 2014). The corresponding immune complexes are deposited on the skin, joints, small blood vessels, and glomeruli

(Rua-Figueroa Fernandez de Larrinoa 2015). Antimalarials, steroids, and immunosuppressive drugs have been used in the treatment of SLE for many years. Although these drugs are efficient in improving quality of life, survival rate and well being, and maintaining long remissions, they are associated with several severe side effects. Thus, novel and better focused treatments are urgently needed (Lerang et al. 2012; Ruiz-Irastorza et al. 2010; Vadasz and Toubi 2012). For example, the monoclonal antibody against BAFF and the discovery of many regulatory molecules, some of these are protective and of therapeutic potential (Navarra et al. 2011).

Recently, Vadasz et al. reported that Sema3A was expressed strongly in the tubuli in lupus glomerulonephritis (LGN), suggesting that it can serve as a histological marker for tubular damage (Vadasz et al. 2011). Later, they observed significantly lower serum Sema3A levels in SLE patients compared with RA patients and normal controls. In addition, serum Sema3A levels were inversely correlated with SLE disease activity and renal damage. The expression of both Sema3A and NRP-1 was found to be significantly lower on Bregs of SLE patients in comparison with healthy controls. Furthermore, upon the co-culture of Sema3A with cytosine-phosphodiester-guanine oligodeoxynucleotides (CpG-ODN)-stimulated B cells of SLE patients, their TLR-9 expression was markedly decreased (Vadasz et al. 2012). Bregs have an important position in the immunomodulatory, specifically in preventing SLE with a role in the maintenance of self-tolerance (Lund and Randall 2010). Sema3A enhances Breg properties by upregulating CD72 expression on B cells. The immunomodulatory effect of Sema3A was demonstrated (Vadasz et al. 2014). T-cell dysfunction is evident in SLE patients. The total number of T cells in the peripheral blood usually decreases (Bakke et al. 1983). The expression of Sema3A and its receptor NRP-1 as binding receptors and plexin A protein as signal transducers have been found to increase and activate T cells on differentiated macrophages, showing that they can regulate inflammation situation (Lepelletier et al. 2006). Therefore, Sema3A may be a promising therapeutic agent for SLE, such focused

Table 1 Sema3A expression in autoimmune diseases

Author (study year)	Disease	Parameter	Increase/decrease compared with controls
Gao et al. (2017)	SLE	Serum level of Sema3A	Decrease
Vadasz et al. (2012)	SLE	Serum level of Sema3A	Decrease
Takagawa et al. (2013)	RA	Serum level of Sema3A	Decrease
Yoshida et al. (2014)	RA	Serum concentrations of Sema3A	Increase
Rezaeepoor et al. (2017)	MS	Serum level of Sema3A	Decrease
Rimar et al. (2015a)	SSc	Serum level of Sema3A	Decrease
Vadasz et al. (2015a)	SSc	Serum level of Sema3A	Decrease
Olewicz-Gawlik and Samborski (2016)	SSc	Serum level of Sema3A	Increase

therapies will contribute to the maintenance of self-tolerance and attenuate pro-inflammatory status in this disease (Vadasz et al. 2015a).

A very recent study by Gao et al. also demonstrated similar results; Sema3A and NRP-1 were both significantly decreased in serum and PBMC of SLE patients, suggesting that the circulating expression of Sema3A and NRP-1 was seriously defected in SLE. In addition, circulating Sema3A was significantly correlated with disease activity and blood damage in patients with SLE. Furthermore, the result of receiver operating characteristic (ROC) curve showed that Sema3A had the potential to be a new diagnostic biomarker in SLE (Gao et al. 2017). All these findings above strongly indicate the therapeutic and diagnostic potential of Sema3A in SLE.

Semaphorin-3A in rheumatoid arthritis

RA is a chronic inflammatory disease characterized by the destruction of peripheral joint in which the articular cartilage and bones are destroyed by the proliferative synovitis. The synovial lesion is formed by inflammatory cell infiltration, marked proliferation of the synovial lining cells, and enhanced angiogenesis. Angiogenesis occurs in the synovia from the early stage of RA, which is considered to be one of the key processes for progression of the arthritic lesions in this disease (AE 1998; Vadasz et al. 2010). Although both basic scientific researches and clinical researches have attempted to determine the factors involved in the pathogenesis of RA, the exact cause of this disease is still unclear.

In RA patients, serum vascular endothelial growth factor (VEGF) levels are significantly related to joint destruction and disease activity score (Clavel et al. 2007; Kurosaka et al. 2010). Sema3A is also a receptor for $VEGF_{165}$ (Miao et al. 1999). Studies have shown that the expression levels of Sema3A and VEGF are correlated with disease activity in several tumors (Barresi and Tuccari 2010; Osada et al. 2006). Takagawa et al. showed that Sema3A expression in synovial lining cells was reduced in RA tissues compared with osteoarthritis (OA) samples. There was also a significant reduction of Sema3A mRNA levels in RA synovial tissue samples than in OA and a significantly negative correlation of the ratio of Sema3A/VEGF-A mRNA expression levels with Disease Activity Score 28-joint count C reactive protein (DAS28-CRP), but there was no significant correlation between Sema3A and $VEGF_{165}$ (Takagawa et al. 2013).

The RA synovium contains activated T and B cells, all of which are recruited through a vigorous neovascularization process with lymphangiogenesis (Brennan and McInnes 2008). The immunogenetics of RA suggests that the abnormal pathway of T-cell activation plays a key role in the occurrence and/or continuation of the disease (André et al. 2009). Catalano et al. reported on the defective expression of Sema3A on CD4 T cells derived from patients with RA. Sema3A increases the $CD4^+NP-1^+T$ cell ability to suppress alloresponses, that its transient expression is altered in rheumatoid inflammation and that the reintroduction of Sema3A is sufficient to attenuate collagen-induced arthritis (CIA), an experimental model of human RA, supporting its therapeutic potential in the treatment of this disease (Catalano 2010). Sema3A inhibits osteoclast function and increases osteoblast function (Negishi-Koga and Takayanagi 2012). It may be a key mediator of bone immunity in RA and has immune activation-related bone destruction. However, Yoshida et al. showed that serum concentration of Sema3A was elevated in RA patients, but serum Sema3A level did not associate with disease activity and marker of bone metabolism (Yoshida et al. 2014). These findings suggest that Sema3A might play an important role in RA pathogenesis.

Semaphorin-3A in multiple sclerosis

MS, one of the most prevalent autoimmune diseases, is a chronic and disabling neurological disease characterized by a disturbance in myelination, which mainly occurs in people aged 15–40 years (Arizmendi-Vargas et al. 2011). Its clinical features are focal disturbances of the paroxysmal optic nerve, spinal cord, and brain. These neurological disorders can have varying degrees of remission and recurrence. The most common form of this disease is relapsing–remitting MS (Dendrou et al. 2015). MS tissue damage and neurological symptoms are thought to be caused by an immune response directed against myelin antigens (Huseby et al. 2001). Viral infections or other stimulatory factors may cause T cells and antibodies to enter the central nervous system (CNS) by destroying the blood–brain barrier, resulting in increased expression of cell adhesion molecules, matrix metalloproteinases, and pro-inflammatory cytokines that together act to attract other immune cells and breakdown cells (Ransohoff and Brown 2012; Tubridy et al. 1999). In particular, Th1 cytokines such as IL-2 and IFN-γ may be associated with the incidence of MS (Arizmendi-Vargas et al. 2011). Due to immune attack, the myelin sheath can be exfoliated, which slows nerve conduction and leads to neurological symptoms (Chang et al. 2002; Huseby et al. 2001). At present, the etiology of MS remains incompletely elucidated.

Sema3A is a secreted molecule that inhibits regenerating axons sprouting into glial scars of astrocytes and an axon guidance molecule in the CNS (De Winter et al. 2002). Sema3A is involved not only in MS pathogenesis but also in the nervous systems. Sema3A may have a positive effect in the immune system since it aborts the immune response. In the context experimental autoimmune encephalomyelitis (EAE) model of MS, this may be due to the over-activation of MOG-specific T cells, and plexin-A4-deficient mice exhibit a worse clinical course of disease, suggesting

that the Sema3A/NRP-1/plexin-A4 pathway is involved in the pathogenesis of EAE (Yamamoto et al. 2008). Rezaeepoor et al. revealed that the serum level of Sema3A and its expression in peripheral blood mononuclear cells (PBMCs) of relapsing–remitting multiple sclerosis (RRMS) patients were significantly lower than in normal subjects. It suggested that Sema3A could be involved in pathogenesis of MS and might be a potential diagnostic biomarker for the disease (Rezaeepoor et al. 2017). Since a higher expression of Sema3A and its receptors, especially in astrocytes but also in microglia/macrophages, was found in MS lesions compared to progressive multifocal leucoencephalopathy and acute cerebral infarct lesions (Costa et al. 2015). In addition, Sema3A has been shown to be aberrantly expressed in brains with MS (Williams et al. 2007), suggesting that Sema3A is involved in the regeneration of oligodendrocytes or axons (Okuno et al. 2011). Inhibition of Sema3A during remyelination showed reversible blockade of oligodendrocyte precursor cell (OPC) differentiation in the presence of Sema3A. Although some remyelination has occurred in MS, this reinforces the deregulation of sema3A expression in the CNS that may be an important factor in impaired OPC recruitment and/or differentiation during MS injury, which ultimately limits myelin repair (Majed et al. 2006; Piaton et al. 2011; Syed et al. 2011). Nevertheless, further studies are still required to precisely evaluate its potential utility as a circulating biomarker and a novel therapeutic target for MS.

Semaphorin-3A in systemic sclerosis

SSc is a multisystem disease with varied course from being a relatively benign condition involving the skin and peripheral vasculature to a rapidly progressive disease affecting internal organs with a consequent high mortality risk, and represents one of the systemic autoimmune diseases with worse prognosis (Bryan et al. 1996; Rubio-Rivas et al. 2014). SSc can be identified as two subsets: a stable, limited cutaneous group (limited systemic sclerosis, lSSc), representing the majority of patients, and a more rapidly advancing smaller group with diffuse cutaneous (diffuse systemic sclerosis, dSSc) involvement (LeRoy et al. 1998). The etiology of SSc remains not fully understood. It may be due to genetic, environmental factors (viral infections, chemical substances such as silicon, etc.), cellular and humoral immune abnormalities, and other factors; fibroblasts synthesis and secretion of collagen increased, leading to skin and visceral fibrosis (LeRoy 1988; Steen and Medsger 2007).

Sema3A as an immunomodulatory molecule mainly affects the activation of Tregs. Most recent studies demonstrated lower serum Sema3A expression levels in SSc patients compared to normal controls (Rimar et al. 2014; Vadasz et al. 2015d). Rimar et al. reported that the expression of Sema3A on Tregs was also lower in SSc patients

compared to normal control. In addition, serum Sema3A level was negatively correlated with the disease duration and low C4 level. A lower serum Sema3A level was associated with SCL-70 antibody positivity (Rimar et al. 2015b). The decreased expression of sema3A on Tregs in SSc patients may be associated with impaired regulation. The lower expression level of Sema3A both in serum and Tregs in SSc patients may help explain the attenuated activation of Tregs in SSc. However, there are also studies showing no significant change in serum level of Sema3A (Romano et al. 2016) or even higher level of Sema3A (Olewicz-Gawlik and Samborski 2016) in SSc patients when compared with normal controls. The expression level of VEGF in the dermis of SSc patients is significantly increased (Distler et al. 2004; Mackiewicz et al. 2002). VEGF exerts its biological function by binding to NRP-1 of Sema3A receptor and VEGFR-1, VEGFR-2 of tyrosine kinase receptor, both of which are upregulated in dermal endothelial cells in SSc-infected skin (Distler et al. 2002; Mackiewicz et al. 2002). Therefore, the role of Sema3A in SSc still needs further research.

Semaphorin-3A as a promising therapeutic agent for autoimmune diseases

Because of its immunosuppressive role in systemic autoimmunity, targeting Sema3A or its receptors may have promise as a potential therapeutic strategy for ADs. With known of the specific mechanisms of Sema3A in ADs, together with the knowledge on the capacity of current treatment strategy to target, this process may open a door to novel therapeutic options for ADs. In fact, studies in animal models of several ADs have demonstrated encouraging results. Overexpression of Sema3A partially prevents and attenuates the progression of CIA, the animal model of RA (Catalano 2010). In EAE, the animal model of MS, mice deficient in plexin-A4 demonstrate a worse clinical course Dendrou et al. 2015. Furthermore, NRP-1-deficient CD4 + T cells result in increased EAE severity; the conditional knockout mice exhibit preferential Th17 lineage commitment and decreased Tregs functionality. Conversely, CD4 + T cells expressing NRP-1 inhibit effector T-cell proliferation and cytokine production independent of Tregs (Solomon et al. 2011). Serum Sema3A levels were inversely correlated with SLE disease activity and renal damage (Vadasz et al. 2011), and the expansion of Bregs in SLE patients was enhanced when stimulated with Sema3A, suggesting that this regulatory molecule may be considered as a potential therapy for SLE (Vadasz et al. 2012). Collectively, these evidence illustrated that Sema3A may serve as a promising therapeutic agent for ADs.

The prospective and the limitation of Semaphorin-3A in clinical application

Since its suppressive activity in ADs has been appeared in many reports, both in vitro and in vivo, Sema3A may act as a therapeutic agent for these diseases in clinical application. Recently, there were several studies about Sema3A and ADs. Gao et al. suggested that Sema3A was significantly correlated with disease activity and blood damage in SLE patients; it had the potential to be a new diagnostic biomarker in SLE (Gao et al. 2017). Perez et al. demonstrated that class 3 semaphorins are differentially expressed in the synovium of early patients depending on the severity and the progression of the disease, and that Sema3A plays an important role in the invasive capacity of RA (Perez et al. 2016). Rezaeepoor et al. found that the serum level of Sema3A was significantly lower in MS patients; it could be involved in pathogenesis of MS (Rezaeepoor et al. 2017). Vadasz et al. demonstrated that Sema3A levels were significantly decreased in both serum and Tregs in SSc patients (Rimar et al. 2015b). These results suggest that overexpressing Sema3A provides a useful approach for basic research on treatment of ADs.

Despite emerging evidence that Sema3A has therapeutic potential in several ADs studies, it is still too early to ensure the efficacy of Sema3A in clinical application. Researches into the involvement of Sema3A in pathogenesis and treatment of ADs are relatively limited and with contradictory results. In addition, the clinical features of ADs are diverse, and the causes of these diseases are complicated. Furthermore, the pathogenesis of MS includes both the immune and the nervous systems. Sema3A appears to play a protective role in the immune system, but it also has a damaging effect in the CNS due to its inhibitory effect on OPC migration toward the site of lesion, or the repulsive activity that impedes the outgrowth of injured neurons. Therefore, the effect of manipulating expression of sema3A on MS outcome remains inconclusive.

Conclusions

Although Sema3A has confirmed roles in immune responses or immune cell differentiation. The Sema3A expressed in the vast majority of immune cells remains ill defined. The challenge going forward will be to identify the Sema3A-based mechanisms that regulate immune responses, and to dissect the specific functional sequences and domains that execute the biological functions of Sema3A. New technologies are being developed and applied to study the biochemistry of Sema3A, its structures, and receptor, which will advance research in this field.

The available evidence clearly supports the involvement of Sema3A in the pathogenesis in human diseases; however, Sema3A research in ADs is a nascent field. Future studies will undoubtedly uncover additional and novel insights into the functions of Sema3A in immunomodulatory and ADs. Studying Sema3A that is differentially expressed in immune cell subtypes or damaged tissues between patients and healthy individuals should provide further insights into the pathogenesis of ADs and further elucidate the molecular mechanisms of Sema3A in the regulation of immune responses and inflammation. SNPs within Sema3A-encoding genes may affect the expression or function of Sema3A in ADs.

Further investigation is also needed to unveil how Sema3A-related loci contribute to pathogenesis, and will enhance our understanding of ADs. Advances in genome-editing technologies such as CRISPR/Cas9 should enable researchers to determine the involvement of a given Sema3A-related SNP in pathogenesis. We believe that Sema3A has potential as disease biomarkers and therapeutic targets, and that researches in this area should help the development of novel diagnostic and therapeutic approaches to treat ADs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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