Autoimmunity Reviews 9 (2010) 825–829

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Neuropilins and semaphorins — from angiogenesis to autoimmunity

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ARTICLE INFO

Article history:
Received 18 July 2010
Accepted 23 July 2010
Available online 1 August 2010

Keywords:
Neuropilin
Semaphorin
Angiogenesis
Immune system
Autoimmunity

ABSTRACT

Angiogenesis, the growth of new blood vessels from preexisting ones, is an important process in health and disease. The persistence of neovascularization in inflammatory diseases, such as rheumatoid arthritis (RA), might facilitate the entrance of inflammatory cells into the synovium and stimulate pannus formation. Several potent pro-angiogenic cytokines have been implicated in inflammatory angiogenesis. Of these, vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) have been demonstrated to play a central role in RA, systemic lupus erythematosus (SLE) and multiple sclerosis (MS). Increased serum levels of VEGF were found to correlate with disease activity and severity of these diseases whereas, remission was associated with decreased levels.

In the last few years, other molecules, initially found in neurodevelopment, were found to be involved in angiogenesis and recently also in the immune system and autoimmunity. Neuropilins (NPs) are VEGF receptors, while some of the semaphorins (SEMAs) are neuropilins' ligands. Their involvement in the development of autoimmune diseases and the various mechanisms by which they may induce autoimmunity will be discussed in this review.

Contents

1. Introduction

Angiogenesis is a physiological process with a well coordinated progression of events: endothelial cell proliferation, selective degradation of vascular basement membranes and surrounding extracellular matrix, and migration of endothelial cells leading to tube formation and finally resulting in capillary growth from preexisting vessels [1]. This process is mandatory during embryogenesis, but was also found to be a pivotal process in tumorigenesis and metastasis, in cardiovascular and inflammatory diseases [2]. Vascular endothelial growth factor (VEGF) was reported to be the most pro-angiogenic as well as a vascular permeability promoting factor and therefore is involved in the development of inflammation [3]. The involvement of VEGF in autoimmune diseases was reviewed in recent years. Its role in the development of RA, SLE and several vasculitides [4–6], and its titers in the sera of these patients were found to be in correlation with disease activity and treatment response [7]. VEGF isoforms, and their receptors VEGFR-1, VEGFR-2, and neuropilin-1 receptor were found to be increased in RA synovial tissue compared to normal controls [8]. Thus anti-angiogenic therapy in RA and lupus (such as bevacizumab), could be promising [9].

Due to the growing interest in the angiogenic process and its role in many immune mediated diseases, other molecules were recently described. These are: the neuropilins (NP-1 and NP-2), also known as

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doi:10.1016/j.autrev.2010.07.014

VEGF receptors and the semaphorins (SEMAs), recognized as neuropilin's ligands, both involved in immune mediated responses. Accumulating evidence indicates that semaphorins and neuropilins have distinct biological activities in various phases of immune responses, from immune initiation to terminal inflammatory immune responses. This review will put some light on the recent development in this field, namely on the precise mechanisms by which these molecules contribute to the development of autoimmune diseases.

1.1. NP-1 and the normal immune system

Neuropilin-1 (Np-1) was initially characterized as a neuronal receptor for specific secreted members of the semaphorin family involved in axon repulsion [10]. Few years later it was found that Np-1 also serves as a receptor for the VEGF family, expressed by endothelial cells (such as in the heart and placenta) and by tumor cells [11,12]. Neuropilin-2 (Np2) was identified as an alternative neuronal receptor for some class 3 semaphorins involved in axon guidance and also identified as a functional VEGF-165 receptor [13,14].

NPs have a short cytoplasmic domain that lacks signaling activities, therefore they bind other transmembrane proteins such as VEGFRs, acting as coreceptors to transduce the effects of VEGF. Np-1 was shown to enhance VEGF activity and binding to its receptors by forming a bridge between Np-1 and VEGF-R1/R2, bringing these receptors into closer proximity [15].

In the human thymus, NP-1 is expressed at low levels on all CD4/CD8-defined thymocyte subsets and at high levels on microenvironmental cells. However, 88% of mouse thymocytes express NP-1, mainly the double positive (DP) and CD8 subpopulations [16].

Recently NP-1 was reported to play an important role in the healthy immune system. It was demonstrated that Np-1 mediates interactions between activated DCs and resting T cells that are essential for initiation of the primary immune response [17]. Moreover, preincubation of DCs or resting T cells with blocking neuropilin-1 antibodies inhibited DC-induced proliferation of resting T cells. Np-1 was also shown to regulate the activation and cytotoxic activity of T cells in response to tumor cells. This regulation is made by decreasing the MEK\ERK signal transduction [18,19]. It was also found that murine Treg cells express high levels of NP-1 on their surface, suggesting that a high expression of Np-1 on Treg cells promoted their prolonged interaction with immature DC [19]. This may contribute to the development of peripheral tolerance by providing an advantage to Treg to interact with immature DCs that present autoantigens, thereby preventing activation of naive autoreactive T cells (Fig. 1).

Recently, it was described, that metastatic tumor draining lymph nodes were enriched in Np-1+ Treg when compared with metastasis-free tumor draining lymph nodes [20]. A tolerogenic cytokine milieu in these metastatic draining lymph nodes may increase the amount of regulatory phenotype Np-1+ T cells. It has been reported that T cells could acquire Np-1 expression after contact with Np-1-expressing DC or activated monocytes by an intercellular cell transfer mechanism called trogocytosis [21], or by *in-vitro* activation.

In addition, Np-1 was shown to be a receptor for TGF-β1, and as such activates its latent form, and therefore is relevant to Treg activity and tumor biology [22,23]. Treg cells frequently bear latency-associated peptide (LAP)-TGF-β1, and this appears to contribute to their suppressive activity in some settings. Lately, it was found that Np-1-Fc (but not Fc alone) bound LAP-TGF-β1 and active TGF-β1 at high affinity. Moreover, it was shown that LAP-TGF-β competed with VEGF for binding to Np-1-Fc and appeared to bind at the same site [24,25].

Further work has to be done in order to explore the precise biological properties of NP-1 in the human immune system.

1.2. Neuropilins and autoimmunity

Rheumatoid arthritis (RA) is characterized by the destruction of peripheral joints in which the articular cartilage and the surrounding bones are destroyed by proliferative synovitis. The synovial lesion in RA is formed by infiltration of inflammatory cells, proliferation of the lining cells, and increased angiogenesis. Angiogenesis occurs in the synovia from the early stage of the disease, and is thought to be one of the pivotal processes for progression of the arthritic lesions in RA [26]. It was found in synovial RA that there is a selective up-regulation of the VEGF165 isoform and its receptors and signalling via VEGFR1 and neuropilin-1 [27]. These results were in correlation with the extent of angiogenesis in the diseased synovium, suggesting that these molecules are crucial for synovial angiogenesis in RA .Rheumatoid arthritis synoviocytes are resistant to apoptosis and exhibit a transformed phenotype, which might be caused by chronic exposure to toxic stimuli including reactive oxygen species and growth factors. Recently, it was demonstrated that the ligation of recombinant VEGF165 to its receptor NP-1, prevented the apoptosis of synoviocytes, by triggered phospho-Akt and phospho-ERK signal transduction activity and by inducing Bcl-2 (apoptosis inhibitor) expression in the rheumatoid synoviocytes. Thus the interaction of VEGF165 with neuropilin-1 is crucial to the increased survival of rheumatoid synoviocytes and their damaging proliferation [28]. Moreover, it was found recently that *in-vitro* and *in-vivo* treatment with anti-NP-1 peptide suppressed VEGF165-induced increases in synoviocyte survival, adhesion, migration and angiogenesis, and thereby blocked

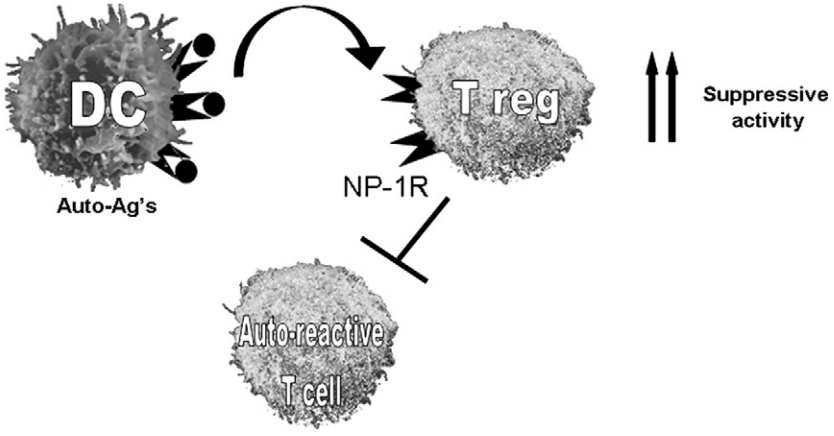

Fig. 1. The continuous presentation of auto-Ag by DCs to NP-1^{+} Treg cells increases the suppressive ability of these cells, thus down regulating auto-reactive T cells. This phenomenon may suggest a role in the maintenance of peripheral tolerance.