A new avenue in the pathogenesis of systemic sclerosis: the molecular interface between the endothelial and the nervous systems

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ABSTRACT
Systemic sclerosis (SSc) is a connective tissue disorder characterised by immune dysregulation, endothelial cell dysfunction followed by defective vascular repair and neovascularisation and progressive tissue fibrosis of the skin and internal organs, whose pathophysiology remains to be fully elucidated. Perturbed neuroendothelial control mechanisms comprising either endothelial cell or peripheral nerve fibre impairment are supposed to play an important role in the onset of Raynaud’s phenomenon and development of microvascular abnormalities which are the earliest events and key features of SSc. Such pathogenic neuroendothelial mechanisms may trigger both the early endothelial cell damage and the subsequent loss of peripheral microvascular integrity characterised by the lack of compensatory angiogenesis. Of note, the vascular and nervous systems have several anatomical similarities that extend to molecular level, and the molecular mechanisms of nerve regulation are shared by the vascular system. In this context, increasing evidence demonstrated that endothelial cells express receptors for axon guidance molecules, including Ephrin family receptor tyrosine kinases, Neuropilins, Plexins, Robos, and UNC5B that are able to respond to their soluble neuroendothelial trophic ligands, such as Semaphorins and Slits, to guide the sprouting of endothelial tip cells. Here, we first provide a historical view of neuroendothelial control mechanism alterations in the pathogenesis of SSc, and then discuss the emerging role of a class of molecules sharing neurogenic and angiogenic properties, such as members of Semaphorin/Plexin/Neuropilin and Slit/Roundabout families, in SSc-related peripheral microvasculopathy.

Introduction
Systemic sclerosis (SSc, scleroderma) is a multisystem connective tissue disorder characterised by immune dysregulation, widespread endothelial cell dysfunction followed by defective vascular repair and neovascularisation and progressive tissue fibrosis of the skin and internal organs (1-3). Despite recent progresses in the understanding of the etiology of SSc, the primary causes or the molecular mechanisms underlying disease clinical onset, progression, and outcomes remain to be fully elucidated (1-3). Dysregulation of neuroendothelial control of vascular tone has historically been considered a leading pathogenic feature of SSc. Starting from this historical background, the present review will provide an overview of recent findings pointing toward the emerging role of a class of molecules sharing neurogenic and angiogenic properties (i.e. members of Semaphorin/Plexin/Neuropilin and Slit/Roundabout (Robo) families) in SSc-related disturbed neuroendothelial control mechanisms and peripheral microvasculopathy. For this purpose, we performed a Medline search of English language articles published in the PubMed database up to 30th November 2018. The following key words: systemic sclerosis, scleroderma, peripheral nervous system, Raynaud’s phenomenon, vascular tone, endothelial cell, angiogenesis, peripheral vasculopathy, Semaphorin, Plexin, Neuropilin, Slit, Roundabout formed the data sources.

Dysregulated neuroendothelial control of vascular tone as a cardinal feature of peripheral microvascular disease in systemic sclerosis: the historical view
A substantial body of evidence indicates that the microcirculation is the primary
target in both the initiation and spreading of SSc. In fact, Raynaud’s phenomenon (RP), a recurrent and reversible cutaneous vasospastic response to cold or emotional stress affecting peripheral small vessels, and the presence of swollen and edematous fingers (commonly referred to as puffy fingers) are the most frequent early clinical manifestations being even considered as “red flags” to suspect the presence of the disease (4). Moreover, when RP and puffy fingers are present, nailfold capillary abnormalities and specific autoantibodies can be frequently detected (4). In definite SSc, the prolonged ischaemia-reperfusion injury effects due to recurrent RP attacks and an uncontrolled vascular regeneration (i.e. defective angiogenesis and vasculogenesis) and subsequent loss of peripheral microvessels may eventually lead to necrotic lesions, such as digital ulcers (DU) and gangrene (1-5). It has been suggested that a dysregulation in multiple neuroendothelial control mechanisms comprising either endothelial cell or peripheral nerve fibre impairment may play a key role in RP onset and evolution toward SSc (3, 5). Interestingly, such pathogenic neuroendothelial mechanisms may trigger both the early endothelial cell damage and the subsequent loss of peripheral microvascular integrity characterised by the lack of compensatory angiogenesis. It is well accepted that the delicate control of vascular tone depends mainly on a complex interplay between three cardinal groups of vascular mediators, namely neuropeptides/neurotransmitters, products of the vascular endothelium (vasoactive factors, either vasoconstrictors or vasodilators) and platelet release products (6-11). In this context, a pivotal role of peripheral nervous system (PNS) in the dysregulation of vascular tone has been well recognised and characterised throughout the last decades. A large body of evidence indicates that PNS is often affected in SSc, especially in the earliest disease phase, though it is not clear whether PNS involvement represents a primary or a secondary pathogenic event (10). Hyper-reactivity of sympathetic nervous system has been described as a prominent feature of RP and up-regulation of vascular smooth muscle α2C-adrenoreceptors that enhance vasoconstrictive responses to stress or cold stimuli is implicated in the dysfunction of the thermoregulatory vessels leading to RP. Morphological and functional changes in PNS, such as reduction in sensory and parasympathetic nerves and an increase in α2-receptor activity, have been described in SSc (12). Ultrastructural modifications to the cutaneous PNS have been linked to the progression and severity of SSc skin involvement (13). A decrease in the levels of a number of neuropeptides released from nerve endings was suggested to contribute to the abnormal vasospastic response seen in RP and SSc (14, 15). In particular, a generalised reduction in calcitonin gene-related peptide and vasoactive intestinal polypeptide, present in sensory and parasympathetic fibres, respectively, as well as a decrease in the pan-neuronal marker protein gene product 9.5 and neuronal nitric oxide synthase-immunoreactive nerve fibres was reported in the skin of SSc patients (16). Moreover, patients with RP and SSc showed an abnormal response to the infusion of substance P, a neuropeptide found in sensory fibres able to modulate neurogenic inflammation, smooth muscle contraction, and vasodilatation (17-18). A role of neuropeptide Y in RP/SSc is also suggested by an increase in the density of neuropeptide Y-ergic fibres in the skin of SSc patients compared with healthy subjects (19) as well as by raised circulating levels of this neuropeptide (20). Collectively, it was suggested that neuropeptide containing nerves may contribute to the pathologic processes of SSc digital skin and to vasomotor dysfunction. In addition, in SSc the imbalance between vascular vasoconstrictor and vasodilator signals, such as overproduction of the vasoconstrictor endothelin-1 and underproduction of the vasodilators nitric oxide and prostacyclin, leaves the endothelium vulnerable to apoptotic signals and promotes an environment of chronic ischaemia, hypoxia and tissue fibrosis through the release of cytokines and profibrotic growth factors (14, 21). Recent experimental data have also shown that platelets and platelet-derived molecules, such as platelet factor 4 (also known as CXCL4) and serotonin, are implicated in RP and may participate in SSc pathogenesis. Indeed, early endothelial dysfunction may lead to platelet activation and the release of several proinflammatory and profibrotic mediators (11). These factors secreted by platelets are also able to inhibit angiogenesis and may contribute to the progression of SSc-related peripheral microvascular damage, defective vascular repair, and fibrosis (22).

A new perspective: fresh insights into the role of neurovascular guidance molecules in systemic sclerosis peripheral microvasculopathy

It is broadly recognised that the vascular and nervous systems share several anatomical and structural similarities, as both systems comprise a complex and branched network, reaching the most distant cells in the organism and requiring precise control over their guidance and growth. In peripheral tissues such as the skin, nerve fibres and blood vessels align into two parallel structures (23, 24); this spatial distribution facilitates access to oxygen and nutrients for the cells of the PNS and facilitates vessel innervation by postganglionic sympathetic fibres, which control vascular tone and participate to blood pressure regulation (25). During the formation of their extensive networks, vessels produce signals that attract axons to track alongside the pioneer vessels, conversely, nerves may also produce signals to guide blood vessel growth. In this context, increasing evidence demonstrated that endothelial cells express receptors for axon guidance molecules, including Ephrin family receptor tyrosine kinases, Neuropilins (Nrp), Plexins, Robos, and UNC5B that are able to respond to their soluble neuroendothelial trophic ligands, such as Semaphorins and Slits, to guide the sprouting of endothelial tip cells (25). Gene knockouts for these receptors have been demonstrated to lead to defective blood or lymphatic vessel sprouting, suggesting a functional role of such receptors in vascular development. Although some of these receptors can directly guide the sprouting of en-
endothelial tip cells, others, such as Nrps and Robos, seem to have evolved novel functions in the vasculature, especially modulation of the activity of vascular endothelial growth factor (VEGF) signalling pathway, thus affecting guided vascular patterning by rendering vessels more or less responsive to VEGF. In addition to the vascular patterning in response to nerve-derived signals, vessels can also produce guidance cues for axonal growth. For instance, arterial smooth muscle cells secrete endothelins, which are involved in the control of blood pressure and are able to attract sympathetic nerve fibres expressing the endothelin receptor type A (26, 27).

Following the identification of the major regulatory roles played by the aforementioned neuroendothelial molecules in the development and maintenance of the vascular and neuronal networks, recently emerging evidence suggests that these factors may be critically involved in several pathological processes including tumour growth and metastasis, development of diabetic retinopathy and nephropathy, as well as autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (28). As far as SSc is concerned, besides the possible involvement of axonal guidance molecules in the perturbation of immunoregulatory mechanisms, recent works from our group have highlighted that they may be crucial in the development and progression of peripheral microvasculopathy.

Semaphorins, plexins and neuropilins

Semaphorins are a large family of cell-associated and secreted proteins grouped into eight classes based on their structural domains, and are characterised by an amino-terminal Sema domain that is essential for signalling and can play a repulsive or attractive role depending on the cell types and biological context (29-31). Membrane-associated Semaphorins bind to Plexins, whereas secreted class III Semaphorins (Sema3s) bind to Neuropilins (Nrps), which do not signal themselves but function as coreceptors for Plexin signalling (32). As an exception, Sema3E does not interact with Nrps but directly binds PlexinD1 (31), a receptor prominently expressed in angiogenic endothelial cells (33). Sema3s have been shown to regulate endothelial cell angiogenesis (34, 35). In particular, both Sema3A and Sema3E have antiangiogenic properties: the former inhibits endothelial cell adhesion and migration promoting cell apoptosis (36-38), the latter activate an antiangiogenic signalling cascade leading to the inhibition of endothelial cell adhesion to the extracellular matrix and retraction of filopodia in endothelial cells of growing blood vessels.

In a recent study from our group, serum Sema3E levels were found increased both in subjects with primary RP and in SSc patients in respect to healthy individuals, and a correlation between high Sema3E levels and early nailfold videocapillaroscopic (NVC) pattern and the absence of DU was found in SSc patients (39). These results suggested that Sema3E might participate in the vascular tone disturbances characteristic of RP and might also have a role as a biomarker of early vascular involvement during SSc. The expression of Sema3E in SSc-affected dermis was also strongly increased respect to controls, particularly in the microvascular endothelium, while no difference was found in the expression of its receptor PlexinD1. Additional in vitro experiments demonstrated that although total PlexinD1 expression was not different in microvascular endothelial cells (MVECs) obtained from healthy individuals (H-MVECs) and SSc patients (SSc-MVECs), these latter showed a significant increase in the expression of the activated (phosphorylated) form of PlexinD1 (39). Moreover, treatment with SSc sera was able to increase phosphorylated PlexinD1 and Sema3E expression also in H-MVECs, promoting an antiangiogenic effect. The addition of a Sema3E-binding PlexinD1 soluble peptide attenuated the antiangiogenic effect of SSc sera on H-MVECs. Collectively, these data support the hypothesis that aberrant Sema3E expression and activation of the PlexinD1/Sema3E pathway in the endothelium may have a role in the defective angiogenesis and neurovascular alterations of SSc, which is particularly evident in the early phases of the disease (28, 39). Nrps (Nrp1 and Nrp2) are single-pass transmembrane, non-tyrosine kinase glycoprotein receptors (32) expressed in all vertebrates, with an important role in a wide range of physiological processes including development, axonal guidance, angiogenesis, immunity, and in pathological conditions such as cancer (32, 40-47). Nrp2 is the predominant neuropilin expressed in lymphatic vessels, whereas Nrp1 is expressed in blood vessels (48). Nrps may regulate cell motility in both the nervous and the vascular system. In particular, in the nervous system, Nrps respond to Semaphorins and have a repulsive effect that mediate growth cone collapse (49), while in the vascular system these glycoproteins have an attractive effect mediating tip cell extension and guiding vessel sprouting in response to VEGF family growth factors.

Originally identified as an axon guidance molecule (50-52), Nrp1 may function as a receptor for both VEGF-A165 and Sema3s suggesting that the latter also play a role in the modulation of angiogenesis. In particular, it has been reported that Sema3A acts as an antiangiogenic molecule impairing endothelial cell adhesion (36, 37, 53). The absence of functional Nrp1 results in embryonic mouse lethality because of dysregulated heart development and severe vascular defects due to impaired angiogenic sprouting and branching very much resembling the disturbed vessel morphology seen in patients with SSc (53-55). Moreover, endothelial specific Nrpl knockout is associated with important cardiac and vascular defects, suggesting a crucial role of this receptor in endothelial functions (56). In this context, it has been widely demonstrated that Nrp1 is implicated in important angiogenic mechanisms such as vessel sprouting and branching and that it is able to potentiate the VEGF-A165/VEGF receptor (VEGFR)-2 signalling pathways leading to enhanced migration and survival of endothelial cells in vitro (57-62).

The possible implication of Nrp1 in SSc pathogenesis was investigated in two studies performed by our group...
In the first study, we found that circulating levels of Nr1p were significantly decreased in SSc patients respect to controls, and that patients with active/late NVC patterns and DU had serum soluble Nr1p levels significantly lower than healthy controls. Moreover, circulating Nr1p progressively decreased in SSc patients reaching the lowest values in patients having the active and late NVC patterns, which are characterised by severe architectural changes of microvessels and progressive capillary loss with formation of avascular areas. Thus, it was speculated that the levels of soluble Nr1p could even serve as a biomarker reflecting the severity and progression of SSc microvasculopathy (63). As far as Sema3A is concerned, no difference in its expression was observed between SSc and controls either in the circulation or in the cutaneous tissue. Nr1p protein expression was strongly reduced also in SSc-MVECs. Moreover, treatment with SSc sera could significantly reduce Nr1p expression in H-MVECs, an effect which is in line with the reported antiangiogenic properties of SSc sera. Conversely, no difference was found in Nr1p protein levels between peripheral blood late-outgrowth endothelial progenitor cell-derived endothelial cells from SSc patients and controls, suggesting that the dysregulated expression of this receptor is restricted to locally injured microvasculature in an overt disease without affecting bone marrow-derived circulating endothelial progenitors (63). Interestingly, NRPI gene silencing in H-MVECs resulted in a strong impaired angiogenic response comparable to that of SSc serum-treated cells, further supporting the involvement of Nr1p deficiency in SSc-disturbed angiogenesis. In line with previous reports, challenging of H-MVECs with recombinant proangiogenic VEGF-A165 strongly increased Nr1p expression indicating that this angiogenic factor can further contribute to angiogenesis by a mechanism that involves upregulation of its homologous receptor Nr1p. In this context, the downregulation of Nr1p in H-MVECs stimulated with SSc sera is in line with the evidence that the majority of VEGF-A detected in SSc circulation is not the proangiogenic VEGF-A165, but rather the antiangiogenic VEGF-A16b, an isoform which is unable to bind Nr1p. Further experiments underlined that both the proangiogenic VEGF-A165 and the antiangiogenic VEGF-A16b isoform slightly influenced the angiogenic performance of Nr1p-silenced H-MVECs, further corroborating the notion that the angiostatic effect of VEGF-A16b is mainly dependent on its inability to recruit the VEGFR-2/Nr1p co-receptor complex and activate downstream signalling. Since it has been demonstrated that, in the absence of Nr1p, VEGF-A16b may induce differential intracellular vascular trafficking of VEGFR-2 towards the degradative pathway, it is conceivable that both a switch from the proangiogenic to the antiangiogenic VEGF-A isoform and the concomitant Nr1p co-receptor downregulation may have a crucial role in the insufficient angiogenic response found in SSc. Finally, it could be demonstrated that Flt1 transcription factor deficiency, which is believed to have an important role in the development of peripheral microvasculopathy during SSc, may be largely responsible for the insufficient endothelial Nr1p expression (63).

In the second study from our group (64), circulating levels of Nr1p were measured in definite SSc patients as well as in patients not fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc (i.e. total score <9) (1) and enrolled in the very early diagnosis of SSc (VEDOSS) project (65). In this study, both SSc patients and patients defined as VEDOSS had lower circulating soluble Nr1p compared with healthy controls. Interestingly, soluble Nr1p levels were not statistically different in VEDOSS and SSc patients suggesting that the VEDOSS “environment” already presents characteristics of the established disease, rather than being a “pre-disease”. In agreement with the findings of the former study (63), Nr1p protein expression was significantly decreased in H-MVECs treated with VEDOSS sera compared with healthy sera. Further experiments highlighted that the ability of H-MVECs to proliferate, migrate and form tube-like structures in vitro was compromised after challenge with VEDOSS sera. Collectively, these findings corroborated the hypothesis that VEDOSS patients already present circulating biomarkers of defective angiogenesis and that the involvement of the microvascular system and endothelial cell injury occur in very early SSc, even when only a few clinical signs and symptoms are present (64). Nr1p deficiency has therefore been suggested as a novel key factor contributing to peripheral microvasculopathy not only in definite SSc but also in the very early phases of the disease.

**Slits and roundabouts**

The Slit family consists of three secreted glycoproteins, namely Slit1, Slit2, and Slit3, acting as cognate ligands for transmembrane Robo receptors, which regulate the repulsive cues on axons and growth cones during central nervous system development. The Robo receptor family consists of the following four members: Robo1, Robo2, Robo3, and Robo4. Robo1 is expressed both in the nervous and the vascular systems, while Robo2 and Robo3 are predominantly expressed in the nervous system (66-69). The latest discovered member of this family, Robo4, also called “magic roundabout”, is a novel endothelial cell protein which was recently identified by using bioinformatic data mining (70). In the last decade, the Slit/Robo signalling has been implicated in physiological and pathological angiogenesis. Indeed, Slit2 may act as a proangiogenic factor by promoting endothelial cell migration and tube formation in a Robo1-dependent manner (68, 71-73), and Robo1 has been demonstrated to be necessary for VEGF-induced phosphorylation of VEGFR-2 in endothelial cells, especially in the presence of Slit2 (72, 73). Conversely, Slit2 may behave as an antiangiogenic factor by interacting with Robo4, thus inhibiting VEGF-induced endothelial cell migration, tube formation and vessel permeability in vitro and vascular leak in vivo (68, 74-78), possibly by blocking Src family kinase activation (74). Furthermore, it has been demon-
strated that Robo4 is required to maintain endothelial cells in a quiescent state by counteracting VEGF signalling and behaving as a negative regulator of angiogenesis (74, 77). In fact, in vivo experiments on Robo4 knockout mice showed that these mice are viable, suggesting that this receptor is not necessary for murine developmental angiogenesis, but exhibit increased basal and VEGF-induced vascular permeability and pathological angiogenesis during experimentally induced ocular neovascularisation (68, 79).

The possible contribution of neurovascular guidance molecules belonging to the Slit/Robo family (Slit2, Robo1 and Robo4) to SSc endothelial cell dysfunction was investigated in a very recent report published by our group (80). In this study, Slit2 levels were measured in sera from SSc and VEDOSS patients and correlated with the NVC pattern and the presence/absence of DU in SSc, as measures of peripheral microvascular involvement severity. Circulating Slit2 was found significantly increased in both SSc and VEDOSS patients with DU, as patients with normal NVC had Slit2 levels comparable to healthy controls. Thus, it has been hypothesised that an increase in circulating Slit2 could reflect the presence of microvascular abnormalities since the very early phase of SSc (80). Moreover, the lack of difference between Slit2 levels in VEDOSS and definite SSc patients strengthened the evidence that VEDOSS patients may already exhibit overt disease-related circulating biomarkers of defective angiogenesis (64). An increase in the protein levels of Slit2 and of its cognate receptor Robo4, but not of Robo1, was further found both in the skin and dermal MVECs of SSc patients. To further clarify the possible functional effects of Slit2/Robo4 axis activation, in vitro experiments resembling the main angiogenic steps necessary for the formation of developing capillaries, such as proliferation and migration of endothelial cells, as well as formation of tubular structures, were performed both in H-MVECs and...
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SSc-MVECs. It was possible to show that the administration of exogenous Slit2 had an antiangiogenic effect on H-MVECs similar to that elicited by Slit2-enriched SSc sera, an effect that was significantly reduced after preincubation of SSc sera with an anti-Slit2 blocking antibody (80). The effective antiangiogenic role of Slit2/Robo4 in SSc-MVECs was corroborated by targeting this axis through the blockade of autocrine Slit2 with a specific neutralising antibody or Robo4 gene silencing. In fact, interfering with Slit2/Robo4 signalling resulted in a higher ability of SSc-MVECs to proliferate, migrate and perform capillary morphogenesis. Mechanistically, Slit2/Robo4 axis was found to interfere with angiogenesis through the inhibition of Src kinase phosphorylation (80). Collectively, these data add Slit2 to the considerable list of angiogenesis mediators which are dysregulated in SSc circulation and appear to be largely responsible for MVEC dysfunction in this disorder (63, 80-84). Taken together, it was proven that Slit2/Robo4 antiangiogenic signalling is triggered in SSc microvascular endothelium and may contribute to peripheral microangiopathy since the very early phase of the disease.

Conclusions
Perturbed neuroendothelial control mechanisms are supposed to play an important role in the onset of RP and development of microvascular abnormalities which are the earliest events and key features of SSc. Indeed, in SSc, pathogenic neuroendothelial mechanisms may drive the early endothelial cell injury followed by loss of peripheral microvascular integrity and lack of compensatory angiogenesis. In this context, recent works shed light on the implication of a recently discovered class of molecules sharing neurogenic and angiogenic properties (referred to as neurovascular guidance molecules) in SSc-related peripheral microvascularopathy (Fig. 1). These molecules include members of both Semaphorin/ Plexin/Neurupulin and Slit/Robo families that have been shown to be altered in the circulation and skin endothelial cells of SSc patients and clinically correlate with disturbed nailfold capillary architecture and the occurrence of ischaemic DU. The evidence that dysregulation of these molecules can be detected even in VEDOSS patients further suggests their possible active role in disease pathogenesis, namely at its onset. Functional studies also revealed that a dysregulation of these neuroendothelial pathways is critically involved in SSc-related antiangiogenic defects, which highlights that these molecules may be clinically extremely relevant as they could become targets for novel specific therapies aiming at preventing further vascular injury and stimulating vascular repair. Prospective follow-up studies on circulating levels of neuroendothelial factors are warranted to verify their possible predictive value in the development and progression of microvascular complications, as well as in reflecting the shift from VEDOSS to definite SSc. Unveiling the validity of these molecules as potential biomarkers for risk stratification and severity of peripheral microvascularopathy might allow an earlier therapeutic intervention in the next future.

References
25. LARRIVEE B, FREITAS C, SUCHTING S, BRUNET I, EICHMANN A: Guidance of vas- cular development: lessons from the nervous...
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57. KAWAMURA H, LI X, GOISHI K et al.: Neuropilin-1 in regulation of VEGF-induced activation of p38MAPK and endothelial cell organization. Blood 2008; 112: 3638-49.


66. HUMINIECKI L, GORN M, SUCHTING S, POULSOM R, BICKNELL R: Magic roundabout is a new member of the roundabout receptor family that is endothelial specific and expressed at sites of active angiogenesis. Genomics 2002; 79: 547-52.


70. JONES CA, LONDON NR, CHEN H et al.: Robo4 stabilizes the vascular network by inhibiting pathologic angiogenesis and en-
Neuroendothelial pathways in SSc / E. Romano et al.