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HIGHLY-CONSERVED MECHANISMS OF CELL MIGRATION AND CONTACT IN IMMUNE AND NERVOUS SYSTEMS

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REVIEW

ABSTRACT. DESPITE THEIR VERY DISTINCT TISSUE ARCHITECTURES and also very different biological mandates, the immune and nervous systems of the body resemble each other in many unique ways and also exert somewhat comparable tasks. Prominent in this regard is the similar repertoire of functional macromolecules, including SDF-1/CXCR4, Slit/Robo, integrins, semaphorins and neuropilins, which play a crucial role in the development and normal functioning of both systems. In this article, we discuss the emerging recent evidence which supports the notion that leukocytes and neurons are both controlled by highly-conserved similar molecular mechanisms for their structural development as well as functional regulations.

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INTRODUCTION

The immune system of the body combats a vast array of pathogens originating in the environment while it also effectively maintains self-tolerance and limits autoimmune-mediated pathological processes. In order to accomplish all these diverse tasks, it is crucial that the recruitment, activation and functioning of specific leukocyte populations are organized and regulated in precise and collaborative manners. The microenvironment-selective homing of leukocytes serves as an excellent example in this regard. During the homing process, complex leukocyte trafficking is precisely guided and determined by the temporal and spatial expression of cell adhesion molecules and chemokines, which provide a combinatorial diversity of traffic signals [1,2]. For instance, selectins (CD62) may interact with the cognate carbohydrate ligands for leukocyte rolling [3,4]; integrins may interact with the immunoglobulin (Ig) superfamily cell-adhesion molecules for leukocytes to form firm adhesion [5]; and chemokines may interact with chemokine receptors for the migration and activation of leukocytes [6-9]. In addition, many immune cells, like T or B lymphocytes, must also be in contact with the antigen-presenting cells (APCs) in order to acquire maturation as well as functional properties. For example, naïve T cells need to be in contact with dentritic cells (DCs) in the secondary lymphoid organs, which triggers the proliferation and differentiation of the T cells to effector T cells. They contribute to antigen elimination only when the effector T cells encounter APCs again in the periphery.

On the other hand, the nervous system functions to store, compute, integrate, and transmit numerous external and internal signals in wide varieties. During the course of development, a majority of the neuronal precursors, if not all, need to migrate to their final residence as a result. Radial migration and tangential migration are two well-documented models as to how neuronal precursor cells migrate to other locations in the central nervous system [10,11]. Radial migration is usually defined as the migration of neurons in a direction perpendicular to the surface of the brain, whereas tangential migration refers to the migration of neuorns in a direction parallel to the surface of the brain [12]. Biochemical and genetic studies have thus far uncovered a variety of crucial molecules that are involved in the migration of neurons and the formation of synapses, which included mitogenic factors, guidance cues, extracellular matrix substrates, transcriptional regulators, and others.

The immune and nervous systems each have evolved highly sophisticated structures and functions, such as antigen recognition and synapse patterning. Each system also utilizes specific molecular events for the internal and external communications in order to precisely realize their specified functionalities. Cell migration and cell-cell/cell-matrix contact are the basic biological events for both systems (FIG. 1) [13,14]. Although different cell populations may use different migration pathways controlled by different molecular mechanisms, there is emerging evidence from recent studies also suggesting a convergent molecular repertoire that may control cell migration and contact in diverse biological systems [15-17], such as the cytoskeleton rearrangement, dynamic changes of adhesiveness to the surroundings, and microenvironmental guidance signals. In this article, we present a brief review and discussion of the recent literature concerning several highly-conserved mechanisms that govern the regulation of migration and adhesion of leukocytes (or lymphocytes) and neurons (or axons).

SDF-1/CXCR4

Stromal cell-derived factor-1 (SDF-1, CXCL12), a product of bone marrow stromal cells, was originally thought to be a stimulatory factor for pre-B cells. In mice lacking SDF-1 or CXCR4, B cell lymphopoiesis and myelopoiesis are decreased in fetal liver and virtually absent in bone marrow [18-20]. In wild-type mice, B cells emigrated from bone marrow to peripheral circulation, while in mutant mice, their responsiveness to SDF-1 was decreased. In addition to preventing precursor cell emigration, SDF-1 might also direct close interactions between hematopoietic progenitor cells and stromal cells in hematopoietic organs. During the maturation process that produces functional T cells in the thymus, thymocytes usually migrate from the cortical regions of the thymus to the medullary areas before they enter the circulation. However,

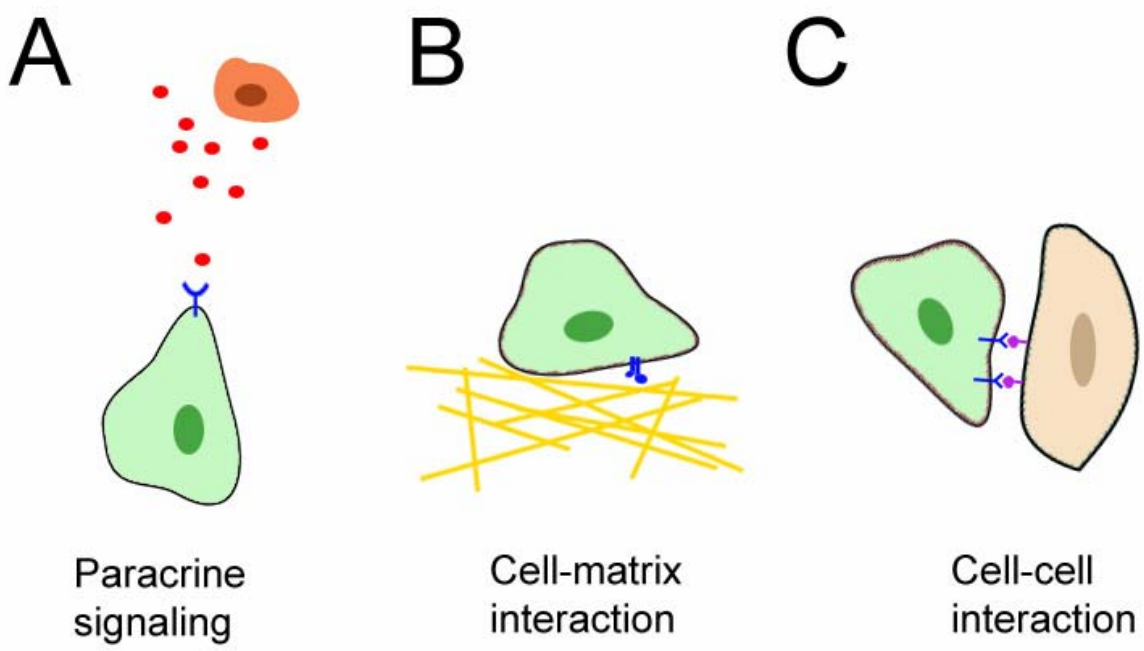

FIGURE 1. THREE HIGHLY-CONSERVED PATTERNS OF CELL MIGRATION AND CONTACT COMMONLY SEEN IN THE IMMUNE AND NERVOUS SYSTEMS. A: Paracrine interactions. Some of the factors (such as Slit or SDF-1) are released from remote sources and then bind to the receptors (Robo or CXCR4) in the plasma membrane of the targeted cells, causing enhanced or attenuated cell migration. B: Cell-matrix interactions. Integrin-mediated adhesion process is a critical step required for migration of leukocytes and neurons. C: Cell-cell interactions. Semaphorin/neuropilin pair is essential for the repulsion of axons and maturation of lymphocytes.

thymocytes appeared to develop normally in SDF-1 or CXCR4-null mice, which might be explained on the basis of redundancy of various chemokines and chemokine receptors in the thymus.

In the CNS, SDF-1 is expressed in the cerebellar pia and its sole receptor CXCR4 is expressed on the granule cell precursors [21]. SDF-1 is found to trigger migration of human neuronal cell lines and neuronal progenitors *in vitro*. The significance of SDF-1/CXCR4 in neuronal development was initially discovered in mouse genetic studies. Deletion of either CXCR4 or SDF markedly affected the cerebellar development of the fetus, displaying an aberrant laminar structure [18-22]. In these mice, the external granular layer (EGL) cells in the cerebella migrate prematurely to the internal granular layer (IGL) at E17, which normally occurs after birth. The SDF-1/CXCR4 interaction is also reportedly required for the migration of interneurons [23] in the developing neocortex and embryonic cerebellar neurons [24]. It is thus evident that the abnormal inward migration of external granule cells is possibly due to the absence of the SDF-1/CXCR4-mediated signaling mechanism.

Slit/Robo

Slit is a family of secreted neuronal migratory cues that signal through Roundabout (Robo) receptors [25,26]. The best-understood functions of Slit proteins are in midline guidance in *Drosophila* and in the formation of the optic chiasm in vertebrates. In *Drosophila*, Slit is expressed at the ventral midline where it signals through Robo and acts as a short-range repellent to prevent ipsilateral axons from crossing the midline and commissural axons from re-crossing [27,28]. Two other Slit receptors, Robo2 and Robo3, specify the lateral positions of axons that run parallel to the midline, presumably in response to a long-range gradient of

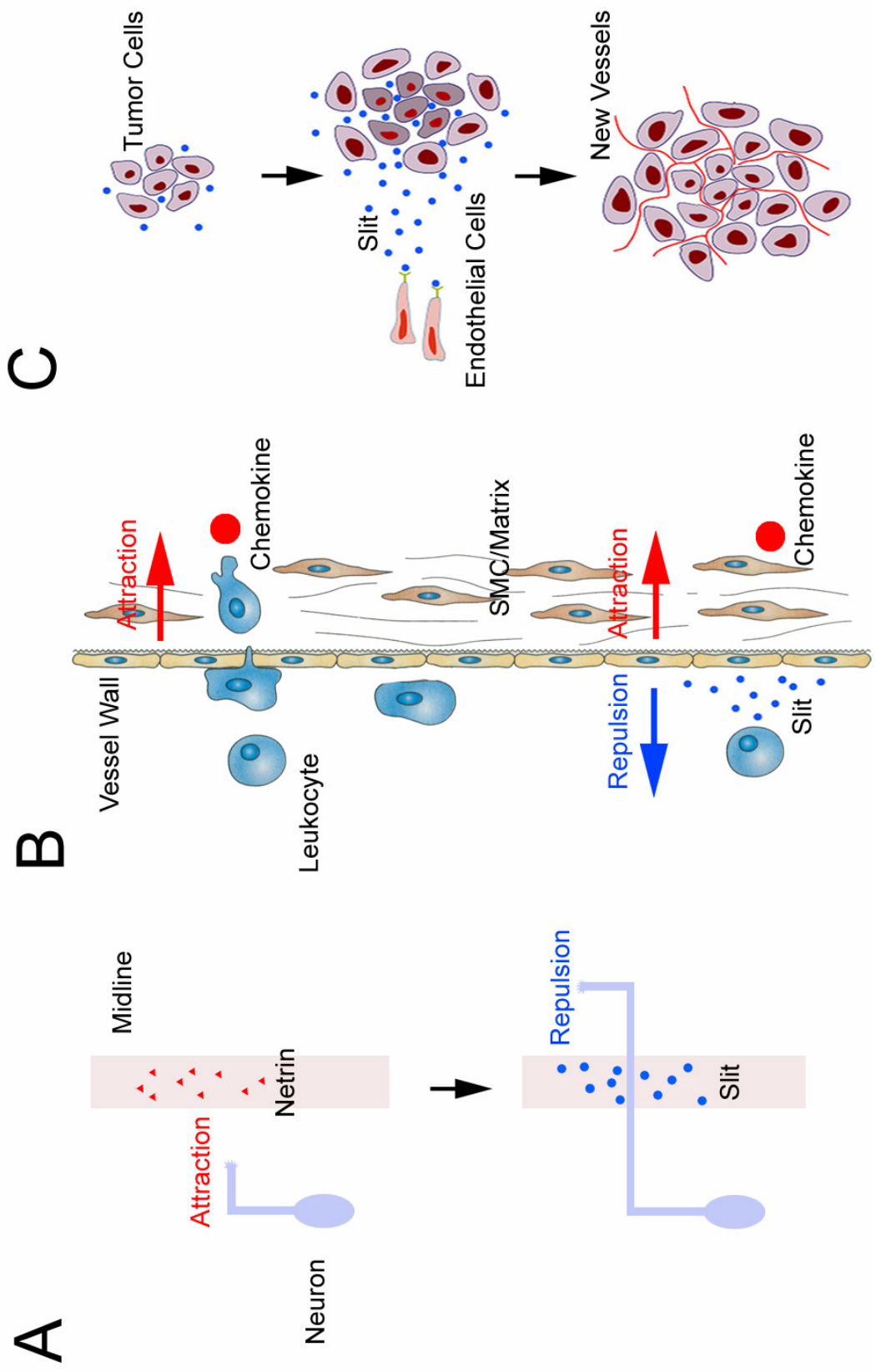

FIGURE 2. FUNCTIONS OF THE SLIT/ROBO. A: In *Drosophila*, the axons are attracted by Netrin from the midline first, after crossing the midline, the axons are switched to be repelled away from the midline by Slit. B: In veterbrate immune system, Slit, can inhibit the leukocytes chemotaxis induced by the chemokine, SDF-1. C: Tumor cells express Slit, which attracts endothelial cells migration and promotes tumor angiogenesis.

the Slit activity diffusing away from the midline [29,30]. Slit1/2-deficient mice manifest striking defects in their ability to form optic chiasm [31,32], thus suggesting that they may cooperate in a unique fashion to channel retinal axons along appropriate pathways and define precise positioning along the neuronal axis at which this important commissure develops. Slit also repels the migration of neuronal precursor cells from the anterior subventricular zone (SVZa) into the olfactory bulb to form interneurons in the developing mammalian forebrain [33]. Further studies show that Slit can repel the cortical GABAergic neurons to migrate out of the ganglionic eminences (GEs) [34].

Slit also inhibits leukocyte chemotaxis induced by chemotactic factors (such as SDF-1). Reconstitution of CXCR4 and Robo renders the Slit-induced inhibition of the SDF-1-mediated chemotaxis, likely suggesting the presence of a functional crosstalk between the single (Robo) and seven (CXCR4) transmembrane receptors [35]. Further along this line of studies, recent results showed that Slit and Robo are co-expressed in some cancer cells and vascular endothelial cells, respectively. Interestingly, Slit attracted endothelial cells and promoted tube formation *in vitro*, and specific neutralization of Slit/Robo interaction reduced the size of the human malignant melanoma A375 cell xenografts and the density of microvessels [36,37]. These observations are in line with the suggestion that a conserved mechanism also guided the migration of metazoan cells (FIG. 2) [38].

As also mentioned above, the SDF-1/CXCR4 interaction is involved in the migration of neuronal precursor cells during cerebellar development. Thus, it will be of considerable interest to also determine weather the functional crosstalk between Robo and CXCR4 would affect neuronal migration. Similarly, it would also be exciting to determine how Slit repulses neurons and inhibits SDF-1-induced chemotaxis of leukocytes, while it attracts endothelial cells in the same time?

INTEGRINS

Integrins are a large family of transmembrane heterodimeric adhesion molecules expressed in the cell-surface of almost all eukaryotic cells, which are essential for cell-cell and cell-matrix interactions and communications [39,40]. Upon activation by various agonists, they undergo a conformational change to increase their affinities and form the cell-surface clustering from either the cell surface pool or the intracellular pool to increase their avidity, which mediates firm adhesion (arrest) of leukocytes upon endothelial cells. For example, recruitment of lymphocytes to lymph nodes and Peyer's patches depends on α_4-integrins including $\alpha_4\beta_1$ (very late antigen 4, VLA-4) and $\alpha_4\beta_7$, $\alpha_L\beta_2$ (lymphocyte function-associated antigen 1, LFA-1) and L-selectin (CD62L) for lymphocyte rolling and firm adhesion to vascular endothelium in specialized post-capillary high endothelial venules (HEVs) [41]. In the gut-associated lymphoid tissues, such as mesenteric lymph nodes and Peryer's patches, the $\alpha_4\beta_7$ integrin and its endothelial ligand, mucosal addressin cellular adhesion molecule-1 (MAdCAM-1), play critical roles, both in lymphocyte rolling and firm adhesion [42,43].

In addition, cell-matrix adhesion mediated by integrins and extracellular matrix components is essential for cell migration. *In vitro* studies have shown that blockade of $\alpha_3\beta_1$ functions with highly-specific antibodies leads to de-adhesion of migrating neurons from the radial glial fibers. Deficiency in $\alpha_3\beta_1$ integrin switches embryonic cortical neurons from gliophilic to neurophilic adhesive preference [44]. Notably, biochemical studies have revealed that the integrin behaved like the Reelin receptor, since it participated in the formation of a supermolecular complex containing Reelin and lipoprotein receptors. A more recent study provided further evidence that Reelin regulates neuronal migration and layer formation through modulation of $\alpha_3\beta_1$ integrin-mediated neuronal adhesion and migration [45].

Tenascin-C, a hexameric protein member of the tenascin family of extracellular matrix (ECM) proteins that is largely absent in normal adult tissues except in brain, bone marrow and T cell-dependent areas of lymphoid organs, inhibits monocyte adhesion to fibronectin and CD3-mediated T cell activation [46,47]. Blockade of $\alpha_v\beta_1$ integrin reverses the inhibitory effect of tenascin on chemotaxis of monocytes and leukocytes [48], which is dependent on the interaction of $\alpha_v\beta_1$ and tenascin-C via its fibronection III domains [49]. In the nervous system, Tenascin-C can regulate the

entry of crest cells into the rostral half, neuronal migration and axon path-finding *in vitro* [50,51]. Analysis of the Tenascin-C$^{-/-}$ mice also confirmed that tenascin-C is important for the fine-tuning of neuronal connections and/or synaptogenesis [52]. However, it is currently not known whether, in analogy to leukocytes, adhesion of neuronal cells to ECMs will induce a partial activation of integrins [53], which allows them to transit either to a non-adhesive or firmly adhesive phenotype, depending on additional chemical and biophysical signals within the surrounding microenvironment [54].

SEMAPHORIN/NEUROPILIN

Semaphorins are a large family of cell-surface and secreted guidance cues [55], which are defined by the presence of the so-called "Sema" domain, a stretch of ~500 amino acid residues containing 17 highly-conserved cysteines at the amino-terminus. Semaphorins signal through multimeric receptor complexes, including plexins [56,57] and neuropilins [58]. Neuropilins do not appear to have a signaling function, but rather they may contribute to ligand specificity. Other essential components of the semaphorin receptor complexes include the neural cell adhesion molecule L1 (for Sema3A), the receptor tyrosine kinase Met (for Sema4D), and the catalytically inactive receptor tyrosine kinase OTK (for *Drosophila* Sema1A). Genetic analysis of semaphorin function in flies and in mice suggests that they primarily function as short-range inhibitory cues, which deflect axons away from inappropriate regions, or guide them through repulsive corridors [59-60].

Although semaphorins were identified originally as guidance cues for developing neuronal axons, mounting evidence indicates that several of the semaphorins are also expressed in the immune system and exert critical functions. The first semaphorin found to be expressed in hematopoietic cells was CD100 [61], which was identical with Sema4D, a member of the semaphorin family. Subsequent studies indicated an even broader expression pattern of Sema4D, which included the primary T and B lymphocytes, natural killer cells, and myeloid cells [62]. In Sema4D-deficient mice, T cells develop normally, but after immunization with protein antigens, the CD4$^+$ T cells obtained from peripheral lymph nodes of these animals have a markedly impaired proliferative response and cytokine production [63]. It was thus hypothesized that Sema4D (CD100), which is constitutively expressed in T cells, may enhance the activation of B cells and DCs through CD72, a cell-surface receptor [64,65].

Another member of the semaphorin family, Sema4A, which is expressed in DCs, is also believed to be involved in the activation of T cells through interactions with Tim2 [66]. Sema4A acts as a co-stimulatory signal for T cells and is involved in the activation of T cells by professional APCs. Administration of Sema4A following immunization enhanced the proliferative response of CD4$^+$ T cells and produces more interferon and IL-4 when these cells were stimulated *in vitro*, suggesting that Sema4A plays a role in the antigen-specific T-cell activation *in vivo*.

Neuropilin-1 is a receptor for some members of the Class III semaphorins [58]. It forms the functional receptor complex with plexin-A1 [67]. It also acts as an important player in establishing cellular contacts (commonly called "immunological synapse") between naïve T cells and DCs [68]. Expressed in both naïve T cells and mature DCs, neuropilin-1 mediates a homotypic interaction that is essential to the initial exploratory adhesion events between naïve T cells and DCs, because neutralization of neuropilin-1 in either naïve T cells or allogeneic DCs interferes with naïve T cell-DC clustering and naïve T cell proliferation. Whether neuropilin-1 can bind to an uncharacterized semaphorin-like ligand expressed on both naïve T cells and DCs remains unclear. Furthermore, neuropilin-1 co-localizes with CD3 at the interface of naïve T cells and DCs, which facilitates the formation/maintenance of the immunological synapse. Thus, neuropilin-1 is crucial for the formation of both neurological and immunological synapses, although it acts differently — receiving guidance cues in the former while mediating cell-cell adhesion in the latter. These data emphasize that the similar molecular mechanisms may underlie the seemingly different forms of cell-cell contacts in axonal guidance and immune response.

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