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Research update

Non-canonical actions of Nogo-A and its receptors

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ABSTRACT

Nogo-A is a myelin associated protein and one of the most potent neurite growth inhibitors in the central nervous system. Interference with Nogo-A signaling has thus been investigated as therapeutic target to promote functional recovery in CNS injuries. Still, the finding that Nogo-A presents a fairly ubiquitous expression in many types of neurons in different brain regions, in the eye and even in the inner ear suggests for further functions besides the neurite growth repression. Indeed, a growing number of studies identified a variety of functions including regulation of neuronal stem cells, modulation of microglial activity, inhibition of angiogenesis and interference with memory formation. Aim of the present commentary is to draw attention on these less well-known and sometimes controversial roles of Nogo-A. Furthermore, we are addressing the role of Nogo-A in neuropathological conditions such as ischemic stroke, schizophrenia and neurodegenerative diseases.

1. Introduction

Almost 30 years ago, Schwab and Caroni discovered that myelin from the central nervous system (CNS) inhibits neurite outgrowth in contrast to myelin from the peripheral nervous system (PNS) [1]. In further studies they identified a high molecular weight component from the CNS myelin called NI-250, which was responsible for these inhibitory actions and was later on renamed Nogo-A. Since then, several other neurite growth inhibitors such as myelin associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), semaphorins and ephrins as well as chondroitin sulphate proteoglycans have been discovered [2,3]. Nogo-A also called reticulon 4 belongs to the reticulon family that consists of four genes named RTN1, RTN2, RTN3 and RTN4. RTN4 encodes for three major isoforms (Nogo-A, B and C) [4]. These three isoforms are generated by alternative promoter usage (Nogo-C) and alternative splicing (Nogo-A and B) [5] and have a conserved carboxyl terminus containing two hydrophobic domains separated by the Nogo-66 domain. Nogo-66 is one of Nogo-A's ligand domains and is located on the extracellular endoplasmatic reticulum (ER) membrane or the plasma membrane [6]. A second ligand domain is Nogo Δ-20 that is located on the N-terminus and uniquely characterizes Nogo-A (for structural details of the different ligand domains, see [7]). Nogo-66 binds the Nogo-receptor 1 (NgR1) that lacks an intracellular domain and therefore necessarily requires the interaction with co-receptors in order to

Abbreviation: ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CA1 and CA3, cornu ammonis area 1 and 3; CNS, central nervous system; CRMP2, collapsin response mediator protein 2; CSF, cerebral spinal fluid; DC, dendritic cells; EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ER, endoplasmatic reticulum; FGF2, fibroblast growth factor 2; FGFR1, fibroblast growth factor receptor 1; GABA, γ-aminobutyric acid; GPI, glycosylphosphatidylinositol; HUVEC, human umbilical vein endothelial cells; IGF-1, insulin-like growth factor 1; LINGO-1, leucine-rich repeat and immunoglobulin domain-containing 1; LTD, long-term depression; LTP, long-term potentiation; MAG, myelin associated glycoprotein; MCAO, middle cerebral artery occlusion; MOD, monocular deprivation; MS, multiple sclerosis; MVECs, microvascular endothelial cells; NGF, nerve growth factor; NgR1, Nogo-receptor 1; NPCs, neural progenitor cells; NSCs, neural stem cells; OD, ocular dominance; Olig2, oligodendrocyte transcription factor; OMgp, oligodendrocyte myelin glycoprotein; OPC, oligodendrocyte progenitor cells; P75, low affinity nerve growth factor receptor p75; PD, Parkinson's disease; PirB, paired immunoglobulin-like receptor; PNS, peripheral nervous system; RGC, retinal ganglionic cells; RhoA, ras homolog gene family member A; RTN, reticulon; ROCK, rho-associated protein kinase; S1PR2, sphingosine-1-phosphate receptor 2; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; Stat3, signal transducer and activator of transcription 3; SVZ, subventricular zone; TrkB, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B; TROY, tumor necrosis factor receptor superfamily member 19.

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transmit the signal. NgR1 forms a complex with Leucine-rich repeat and immunoglobulin domain-containing 1 (LINGO-1), a tumor necrosis factor receptor superfamily member 19 (TROY) and/or low affinity nerve growth factor receptor p75. p75 interacts with glycosylphosphatidylinositol (GPI) and activates the Rho/ROCK pathway leading to growth cone collapse [8]. Moreover, Nogo-66 can bind to the paired immunoglobulin-like receptor (PirB) [9] that also activates the Rho/ROCK pathway. The Nogo Δ-20 domain acts through a different receptor, namely the sphingosine-1-phosphate receptor 2 (S1PR2). Yet, also this signaling converges in the Rho/ROCK pathway (for more details on signaling see [8]). Notably, Nogo-A is not the only binding partner for NgR1, as Nogo-B, Nogo-C and also MAG and OMgp can interact with NgR1 [3]. The NgR1 complex and Nogo-A have been extensively studied in the brain over the past few years, which revealed distinguished expression patterns, regulation of various physiological functions, tissue recovery following injuries as well as involvement in several diseases.

2. Expression and function of Nogo-A under physiological conditions

Nogo-A is enriched in oligodendrocytes and mostly associated with the ER, but is also found on the surface of oligodendrocytes in the outermost and innermost adaxonal myelin membrane. Importantly to note, new findings showed that Nogo-A is not only expressed on oligodendrocytes but also in various brain areas and in several types of neurons and glial cells [10]. Accordingly, Nogo-A has been detected in the spinal cord, in the hippocampus, in the cerebral cortex, in the cerebellum and in the brain stem of humans, whereas it is fundamentally absent in the cerebral blood vessels and the meninges (Table 1). Neuronal Nogo-A is highly expressed during development and down-regulated in adults [11]. Yet, its differential distribution throughout the adult mature brain hints to a range of different functions in addition to axonal inhibition (Figs. 1 and 2). In this first part of the present commentary we will focus on the role of Nogo-A signaling in the regulation of physiological functions of the brain, the immunsystem and in angiogenesis.

2.1. Regulation of oligodendrocyte maturation and myelin formation

The expression of Nogo-A and the other molecules associated with Nogo-A signaling in oligodendrocytes has largely been described in the literature and are not discussed in the present commentary (for review see [12]). In contrast to mature oligodendrocytes that only express Nogo-A, oligodendrocyte progenitor cells (OPCs) contain both Nogo-A and NgR1 [13], which play a critical role in the control of differentiation into mature oligodendrocytes [13,14]. In fact, Nogo-A knock-out caused a transient impairment in oligodendrocyte differentiation as well as in the production of myelin [14]. In contrast to Nogo-A, LINGO-1 functions as an inhibitor of OPCs differentiation likely through activation of RhoA and suppression of Fyn kinase activity, which is known to be involved in oligodendrocyte differentiation. Several studies revealed that blocking LINGO-1 enhances OPC differentiation and that LINGO-1 knock-out mice show an early onset of OPC differentiation during development [15,16]. Finally, in Nogo-A knock-out animals the structures of the myelin sheaths and Ranvier nodes do not differ from wild type animals, suggesting that Nogo-A does not play a role in the formation of myelin structures [14].

2.2. Regulation of neuronal stem and progenitor cells

Nogo-A and Nogo-B as well as its receptor NgR1 are expressed on blastocysts and on cultured embryonic stem cells of mice. NgR1 contributes to the maintenance of pluripotency of murine embryonic stem cells by increasing expression levels of the transcription factor Nanog *via* the Stat3 pathway resulting in an inhibition of cell differentiation [17]. In contrast, Nogo-66 administration increased differentiation of neural progenitor cells (NPCs) into astro-glial lineage in the mouse embryonic forebrain [9] and antagonization of LINGO-1 during the first days of neural differentiation decreased neuronal maturation in the mouse embryonic cortex [18]. In the forebrain of mouse embryos, NgR1 and PirB are expressed in neural stem cells (NSCs) of the subventricular zone (SVZ) and together with LINGO-1 in NPCs of the cortex [9,18]. Stimulation of cortical NSCs with Nogo-66 promotes their survival and proliferation *via* NgR1/Rho or PirB pathways [9]. On the other hand, Nogo-A signaling inhibition enhances proliferation of NPCs *via* Notch pathway in the rat embryonic hippocampus [19].

In addition to its function in regulating NPCs differentiation and proliferation, Nogo-A signaling controls the adhesion and migration of NPCs during radial migration in cortical development. Embryonic cortical NPCs of Nogo-A null mice showed defects in migration as displayed by decreased adhesion and increased motility. Similar results were gathered when neurospheres were treated with antibodies against Nogo-A, LINGO-1 or NgR1 [20]. Nogo-A not only controls radial migration but also regulates tangential migration of cortical GABAergic interneurons. Cortical GABAergic interneurons are generated in the ganglionic eminences and migrate through the SVZ before they integrate into the cortical plate. It has been shown that in Nogo-A/B/C deficient mice the tangential migration is delayed [21]. NPCs also migrate out of the SVZ along the rostral migratory stream into the olfactory bulb. In this so called SVZ-olfactory bulb system Nogo-A and NgR1 are differentially expressed in the mouse brain, whereby Nogo-A identifies immature neuroblasts and NgR1 germinal astrocytes [22]. Rolando et al. demonstrated that NgR1 antagonization increases the proliferation in the SVZ *in vivo* [22]. Yet, anti-Nogo-A antibody treatment could not reproduce the results obtained by NgR1 antagonization. These results led to the hypothesis that Nogo-A exerts a negative feedback through NgR1 on NSCs proliferation in the SVZ, thereby limiting the rate of neurogenesis [22]. On the other hand, Nogo-A supports the migration of the neuroblasts towards the olfactory bulb *via* Nogo Δ-20 domain, *i.e.* through a NgR1 independent signaling [22].

2.3. Regulation of immune cells

NgR1 and its co-receptors are expressed on peripheral blood mononuclear cells. Several lymphocytes including B cells and T cells express NgR1 and further up-regulate it upon activation of the immune response. Additionally, B cells and T cells express also NgR1 co-receptors p75, LINGO-1 and TROY [23]. Inhibition of NgR1 signaling, however does not affect *in vitro* human immune cell proliferation or cytokine secretion, but reduces adhesion on myelin and enhances motility of the cells [23]. On the other hand, Nogo-A neutralization in hippocampal slice cultures increased several genes involved in the immune response and inflammation [24]. These results imply that NgR1 expression may influence the immune cell infiltration or motility within the CNS [23]. T cells are activated by antigen-presenting dendritic cells (DCs) in the lymph nodes. Tissue resident immature DCs express high levels of NgR1 and NgR2 (NgR1/2) and down-regulate their expression upon maturation. Hence, the expression level of NgR1/2 is inversely correlated with adherence to myelin [25]. In line with this notion, McDonald et al. demonstrated that mature DCs from NgR1/2 knock-out mice adhere to a higher extent to myelin compared to wild type DCs, supporting the concept that the adherence of DCs to myelin is dependent on NgR1/2 [25]. Differently from DCs, the majority of activated macrophages,