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Mini-Review

Regulation of lateral olfactory tract development by Nogo-A, Nogo receptor-1 and LOTUS proteins

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ABSTRACT

During development, neuronal circuits are organized by various molecules. In the olfactory circuit, the axons emerging from the olfactory bulb (OB) form their fasciculate bundles termed lateral olfactory tract (LOT), and their collateral branches thereafter. We discovered LOT usher substance (LOTUS) as a novel protein that contributes to LOT formation through blockade of the binding of Nogo-A, an axonal growth inhibitor, to Nogo receptor-1 (NgR1). Furthermore, we found that up-regulation of Nogo-A in the LOT sprouts collateral branching of the LOT by overcoming the antagonism for NgR1 by LOTUS. In this review, we focus on the novel roles of Nogo-A, NgR1 and LOTUS in axonal bundling and branching of the LOT, and discuss the possible involvement of the molecular mechanisms regulated by these proteins in the development of other neuronal networks.

KEYWORDS: LOT, LOTUS, NgR1, Nogo-A.

ABBREVIATIONS

CNS, central nervous system; LOT, lateral olfactory tract; LOTUS, lateral olfactory tract usher substance; NgR1, Nogo receptor-1; OB, olfactory bulb.

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INTRODUCTION

Developing neurons migrate to specific regions, extend their axons to the target cells along the proper paths and form synapses with the target dendrites, leading to the establishment of functional neuronal circuits. These developmental processes are regulated by various repulsive and attractive guidance molecules and their receptors [1].

In the developing olfactory circuit, olfactory sensory neurons in the olfactory epithelium elongate their axons to single glomeruli in the olfactory bulb (OB) and synapse with the dendrites of tufted and mitral cells in the OB [2-4]. The axons emanate from these cells at embryonic day (E) 12 and course laterally and caudally along the surface of the telencephalon while forming a fasciculate bundle, termed the lateral olfactory tract (LOT), during the subsequent two days [5]. Afterward, the primary axons of these cells form their collateral branches [6, 7]. Collateral branches in the axons of tufted cells project only to some areas of the olfactory cortex such as the anterior olfactory nucleus and olfactory tubercle, whereas those of mitral cells innervate almost all areas of the olfactory cortex [4]. Through these olfactory circuits, odor information that is received by olfactory receptors expressed in the dendrites of olfactory sensory neurons is transmitted to the olfactory cortex [3, 4].

Axonal bundles and collateral branches of the LOT are shown to be controlled by Slit proteins [8, 9] and semaphorins [10, 11] that are axon guidance molecules [1, 12-15], and anosmin-1 [16],

a secreted and glycosylated extracellular protein [17]. Previously, we identified LOT usher substance (LOTUS) as a novel protein that plays an important role in LOT formation through the interaction with Nogo receptor-1 (NgR1) [18], a receptor for axonal growth inhibitors such as Nogo-A [19]. Moreover, we recently showed that Nogo-A, NgR1 and LOTUS also contribute to collateral branches of the LOT [20]. This review summarizes the novel function of LOTUS, the roles of Nogo-A, NgR1 and LOTUS in LOT development, and the possibility that LOTUS might participate in the development of other neuronal circuitry formation.

Identification of LOTUS serving for LOT formation

To identify the key protein(s) responsible for LOT formation, we previously established the organotypic telencephalon culturing method of embryonic mice combined with fluorophore-assisted light inactivation (FALI) technique [21, 22] using monoclonal antibodies (mAbs) produced by immunizing homogenates extracted from the developing mouse LOT and its surrounding areas [23]. FALI is a technique generally known as chromophore-assisted light inactivation and is able to inactivate the target antigen using antibodies, fluorescein isothiocyanate (FITC) and its excitation light. Light irradiation of approximately 490 nm wavelength renders FITC to locally generate oxygen radicals (singlet oxygen), and the radicals chemically inhibit the function of the antigen recognized by FITC-labeled antibodies through a strong oxidative reaction. FALI using a specific mAb causes defasciculation of the LOT in organotypic cultures of mouse embryonic telencephalon. By screening of COS7 cells, which are transfected with plasmids subdivided from a cDNA expression library in mouse embryonic OB and are immunocytochemically stained by this mAb, a cDNA clone is isolated from approximately 57,000 clones in the library. Sequence analysis of this cDNA clone shows that it encodes for cartilage acidic protein-1B (Crtac1B), identifying Crtac1B as the antigen of this mAb [18].

Human or mouse Crtac1B is reported to be specifically expressed in brain tissues [24]. Human Crtac1A, another splice variant of *CRTAC1* gene, is a secreted and glycosylated extracellular protein expressed in chondrocytes of articular cartilage [24]. 3'-rapid amplification of cDNA ends analysis reveals that no *Crtac1a*-specific sequences are found in several mouse tissues [24], suggesting that *Crtac1* gene in mouse encodes for only Crtac1B. Mouse brain-specific Crtac1B is termed 'lateral olfactory tract usher substance' (LOTUS) [18].

Identification of NgR1 as a LOTUS-binding protein

As LOTUS is considered to be a membrane protein without an intracellular domain [18, 24], LOTUS may bind to the protein(s) that is expressed on the cell surface and is involved in LOT development. Screening of the cells bound by soluble truncated form of LOTUS using the above cDNA expression library results in the isolation of a cDNA clone. By sequencing this cDNA clone, Nogo receptor-1 (NgR1) is identified as a LOTUS-binding protein [18]. NgR1 is a common receptor for axonal growth inhibitors such as Nogo proteins [19], myelin-associated glycoprotein (MAG) [25], oligodendrocyte myelin glycoprotein (OMgp) [26], B lymphocyte stimulator (BLyS) [27] and chondroitin sulfate proteoglycans (CSPGs) [28]. The interaction of these five molecules with NgR1 restricts axonal regeneration following damage to the central nervous system (CNS) [28-30].

Molecular function of LOTUS

LOTUS, NgR1 and Nogo-A, an NgR1 ligand [19], are expressed in growth cones of cultured OB neurons and in the LOT from mouse embryos at E13. A ligand-receptor binding assay of Nogo66, which is an NgR1-binding domain and an axonal growth inhibitory domain of Nogo-A [19, 31], reveals that the binding of Nogo66 is blocked in cells overexpressing both proteins NgR1 and LOTUS, suggesting that LOTUS may have an antagonistic activity on NgR1. In cultured chick embryonic dorsal root ganglion (DRG) neurons in which NgR1 [19] but not LOTUS is expressed, Nogo66 induces growth cone collapse in the DRG neurons without overexpression of LOTUS but the LOTUS-overexpressing growth cones in the DRG neurons are insensitive to

Nogo66-induced collapse. Furthermore, in cultured mouse embryonic OB neurons in which both LOTUS and NgR1 are expressed, Nogo66 does not induce growth cone collapse in neurons from wild-type mice, while growth cone collapse is induced by Nogo66 in neurons from *Lotus*-deficient mice. These results indicate that LOTUS inhibits Nogo66-induced growth cone collapse by blocking the binding of Nogo66 to NgR1 [18] (Fig. 1).

LOTUS forms axonal bundling of the LOT

Analysis of the LOT formation reveals that defasciculation of the LOT is observed in embryonic mice genetically lacking *Lotus* as well as in organotypic cultures of mouse embryonic telencephalon using FALI with the antibody against LOTUS. This suggests that the loss of LOTUS would allow Nogo-A to interact with NgR1 and thereby activate NgR1 signaling that may give rise to defasciculation of the LOT. The LOT forms as a normally fasciculate bundle in *Ngr1*-nullified mice and double gene (both *Lotus* and *Ngr1*)-deficient mice, indicating that NgR1 may mediate defasciculation of the LOT caused by null of LOTUS. Taken together, these results suggest that LOTUS contributes to LOT formation through its antagonism for NgR1 [18] (Fig. 2).

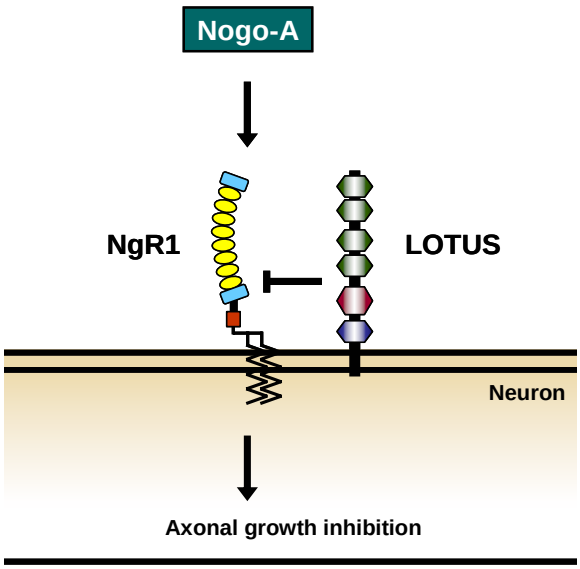

Fig. 1. Schematic drawing of the molecular mechanism of LOTUS.
Nogo-A induces axonal growth inhibition through its binding to NgR1. The interaction of LOTUS with NgR1 blocks the binding of Nogo-A to NgR1, thereby suppressing axonal growth inhibition induced by Nogo-A.

Nogo-A forms axonal branching of the LOT

Western blotting reveals that LOTUS, NgR1 and Nogo-A are expressed in the OB from E14 to E18 when the main shaft of the LOT had been formed. The expression level of NgR1 in the OB does not change during these stages. LOTUS expression level in the OB tends to increase mostly during these stages although it is significantly increased at E18. Nogo-A is up-regulated in the OB at E17 and E18 when collateral branches of the LOT are being formed [6, 7]. Furthermore, Nogo-A is found

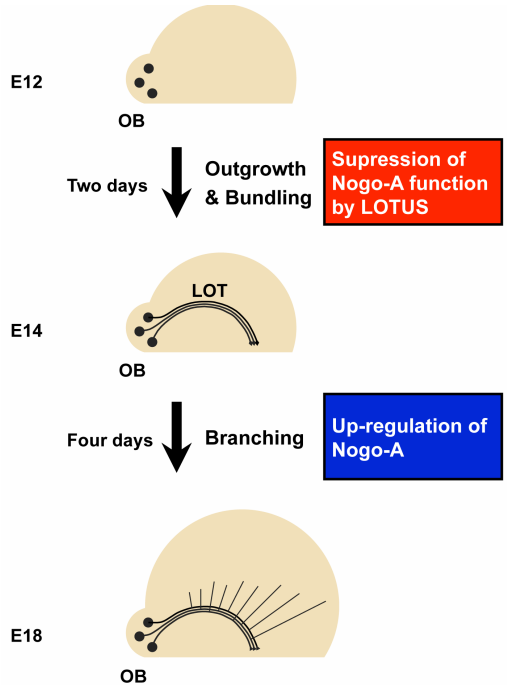

Fig. 2. Schematic illustration of axonal bundling and branching in the LOT controlled by Nogo-A, NgR1 and LOTUS.
The LOT primarily forms as a fasciculate axonal bundle during the early stages from E12 to E14. This formation is caused by LOTUS function that interrupts the interaction of Nogo-A with NgR1 and suppresses Nogo-A-induced axon growth inhibition. Thereafter, collateral branches sprout from the primary axons in the LOT during late developmental stages. This collateral sprouting is ascribed to the overcoming of the NgR1-antagonism by LOTUS *via* Nogo-A up-regulation in the LOT.

to be expressed in the mitral and tufted cells of the OB from E14 to E18 but not in the granular cells of the OB as evidenced by immunohistochemistry using antibodies against Nogo-A and T-box transcription factor, Tbx21, which is used as a marker for mitral and tufted cells [32]. The sprouting of collateral branches is reported to be inhibited in cultured DRG neurons and cultured mesencephalon neurons whose *Nogo-a* is nullified or those treated with function-blocking antibodies against Nogo-A or NgR1 [33, 34]. Analysis of *Lotus* or *Ngr1*-knocking out mouse embryos shows that axon collaterals are enhanced in cultured embryonic OB neurons from *Lotus*-deficient mice but reduced in those from *Ngr1*-knockout mice. *Nogo-a* knockdown inhibits axon collaterals in cultured embryonic OB neurons from wild-type mice and *Lotus*-deficient mice. Furthermore, axonal branches of the LOT are increased in *Lotus*-nullified mouse embryos, but decreased in *Ngr1*-deleted mouse embryos. Moreover, double gene (both *Lotus* and *Ngr1*)-ablated mouse embryos exhibit a reduction in axonal branches of the LOT compared with single gene (*Lotus*)-knockout mouse embryos. Therefore, these results suggest that up-regulation of Nogo-A induces collateral branches of the LOT through its binding to NgR1 by overcoming the antagonism for NgR1 by LOTUS [20] (Fig. 2).

From these observations, we conclude that axonal bundling of the LOT is formed by antagonistic action on NgR1 by LOTUS during the early developmental stages from E12 to E14 and thereafter axonal collateral branching of the LOT is formed by Nogo-A-NgR1 interaction during late developmental stages (Fig. 2).

Contribution of other proteins in LOT development

Most axons in each embryonic rat OB explant grow asymmetrically on the side distal to aggregates of the cell overexpressing Slit1 or Slit2 [9]. The axons of cultured mouse embryonic OB neurons are also repelled near the explant of the mouse embryonic septum that expresses the protein of Slit1 and Slit2 and mRNA of Slit2 [8, 9]. However, this repulsion is abolished in septum explants derived from *Slit1* or *Slit2*-deficient mouse embryos [9]. Furthermore, Slit2-overexpressing cells have no repulsive effect on the axons of cultured OB neurons from embryonic mouse knocking out both *Robo1* and *Robo2* [35], which are receptors for Slit proteins [13, 14] and are expressed in the LOT [35]. It remains unknown whether the embryonic OB axons derived from either *Robo1* or *Robo2*-deficient mice respond to Slit2-induced chemorepulsive activity. The LOT normally forms in single gene knockout mice embryos of either *Slit1* or *Slit2*, whereas in double gene (both *Slit1* and *Slit2*)-deficient embryonic mouse, the LOT projection is profoundly disorganized [9]. The LOT typically forms as a fasciculate bundle in *Robo1*-knockout mouse embryos, but *Robo2*-nullified embryonic mice exhibit thinned LOT spread along the ventrolateral surface of the telencephalon [35]. Moreover, the LOT is segmented into multiple axonal fascicles and fanned all over the ventral side of the telencephalon in double gene (both *Robo1* and *Robo2*)-deficient mouse embryos [35]. These studies show that both Slit1 and Slit2 secreted from the septum are responsible for LOT formation through their binding to Robo2 expressed in the LOT [8, 9, 35].

Axon outgrowth of embryonic rat OB explants is promoted on non-neuronal cell layers overexpressing semaphorin 7A (Sema7A) [11], which is categorized as axon guidance molecules [12, 15], and soluble truncated form of Sema7A [11]. This promotion on axon outgrowth is independent of PlexinC1 [11], a well-known receptor for Sema7A [12, 15]. It is inhibited by deletion of the integrin-binding motif, which is known as the Arg-Gly-Asp (RGD) sequence [36] and which is found in Sema7A [11]. It is also suppressed by treatment with neutralizing antibodies against Integrin β1 [11]. Sema7A mRNA is expressed along the presumptive LOT trajectory in rat embryos, and β1-Integrins mRNA is expressed in the mitral cells in the embryonic rat [11]. Furthermore, the *Sema7a*-knockout embryonic mouse displays an excessively fasciculate LOT and impaired outgrowth of LOT [11]. Thus, Sema7A expressed in the presumptive LOT trajectory participates in LOT formation by interacting with β1-Integrins expressed in the mitral cells [11]. The axons of cultured OB explants from embryonic rats are repelled when

co-cultured near semaphorin 3F-overexpressing cells or the olfactory epithelium, but attracted in the co-culture with semaphorin 3B-overexpressing cells [10]. Semaphorin 3F mRNA is expressed in the olfactory epithelium and the expression of semaphorin 3B mRNA is detected in the cells that are adjacent to the LOT [10]. These reports suggest that some semaphorins are associated with the formation of the LOT [10, 11].

Collateral branches from the axons of dissociated rat embryonic OB neurons are enhanced by treatment with anosmin-1 [16]. Anosmin-1 is a protein encoded by the *KAL-1* gene whose mutation causes Kallmann syndrome of the X-chromosome linked form [37], and is expressed in the LOT and the olfactory cortex of rat embryos [16]. This enhancement of axon collaterals is observed in embryonic rat OB neurons cultured for three days *in vitro* not at E15 when the LOT is devoid of collateral branching yet *in vivo*, but at E17 when LOT collaterals are seen in many primary axons *in vivo* [7]. Furthermore, the sprouting activity of anosmin-1 on axonal branching in cultured OB neurons from rat embryos is inhibited by function-blocking antibodies to anosmin-1 [16]. Moreover, axonal branches of the LOT are observed in the organotypic telencephalon cultures of rat embryos, and the branches of the LOT are induced by exogenously added anosmin-1 [16]. This induction is abolished by treatment with neutralizing antibodies against anosmin-1, although anosmin-1-neutralizing antibodies have no effect on LOT formation [16]. This study indicates that anosmin-1 secreted from the olfactory cortex and/or the LOT exerts the sprouting action on LOT collaterals [16], although the functional receptor(s) for anosmin-1 involved in collateral branching of the LOT is still unknown.

Involvement of Nogo-A and NgR1 in various functions during neuronal development

Nogo-A is well characterized as a protein that causes the failure of axonal regeneration after adult CNS injury through its binding to NgR1 [29, 30]. However, the functions of these proteins in CNS development are still poorly understood.

Nogo-A is expressed in radial glial cells and migrating and postmigratory differentiated neurons of the embryonic mouse cortex [38, 39]. The genetic ablation of *Nogo-a* shows more newborn cells remaining in the lower cortical layers and less newborn cells reaching the upper cortical layers in mouse embryos [39]. Furthermore, *Nogo-a*-deficient mice also exhibit a delayed migration of the early generated interneurons in the neonatal mouse cortex that expresses Nogo-A [38]. These reports suggest that *Nogo-a* is required for neuronal migration in the developing cortex [38, 39]. On the other hand, *in vitro* migration analysis shows that the motility of cells is enhanced in cultured neurospheres, which express Nogo-A and NgR1, generated from embryonic mouse forebrain lacking *Nogo-a* or in those treated with Nogo-A- or NgR1-neutralizing antibodies [39].

Nogo66 inhibits axonal length in cultured hippocampal neurons from rat embryos, and this inhibition is rescued by Nogo66-function-blocking antibodies [40]. Cultured DRG neurons are able to lengthen their neurites and to enhance their neurite fasciculation in Nogo-A- or NgR1-neutralizing antibodies-treated neonatal mice or in *Nogo-a*-deficient neonatal mice [33]. The DRGs are shown to express the mRNA and the protein of Nogo-A in neonatal mice [33, 41]. Furthermore, axonal outgrowth is promoted in cultured OB neurons from mouse embryos knocking down *Nogo-a* or knocking out *Ngr1* [20]. As such, the interaction of Nogo-A with NgR1 inhibits neurite outgrowth and fasciculation in embryonic neurons [20, 33, 40, 41].

Nogo protein is expressed in the radial glia at the chiasmatic midline in mouse embryos [42], and NgR1 is expressed in axons and growth cones of the ventrotemporal retina in the embryonic mouse [42, 43]. Neurites in the ventrotemporal retina from mouse embryos are repelled at the Nogo-coated spot, and this repulsion is abolished by treatment with an NgR1 antagonist that is specifically competitive with Nogo [43]. Furthermore, it has been suggested that the uncrossed axons in the optic chiasm fail to normally project in slices of optic pathway from mouse embryos treated with Nogo-A-neutralizing antibodies or an NgR1 antagonist specifically competitive with Nogo [43]. These reports suggest that Nogo-A-binding to NgR1 contributes to axon guidance in the embryonic optic chiasm [42, 43].

Collaterals sprout in cultured DRG neurons from neonatal mice, and this sprouting is attenuated in neonatal mouse DRG neurons cultured in the presence of neutralization antibodies against Nogo-A or NgR1 [33]. Furthermore, this attenuation is also observed in cultured DRG neurons from neonatal mice nullifying *Nogo-a* [33] or in cultured mesencephalon neurons, which express the protein of Nogo-A in the embryonic mouse, derived from *Nogo-a*-deficient embryonic mice [34]. Conversely, Nogo66 decreases axonal branches in cultured hippocampal neurons from the embryonic rat, and this decrease is attenuated by treatment with Nogo66-neutralizing antibodies [40]. Axonal branches are also observed in cultured mouse embryonic cortical neurons in which Nogo-A is expressed, and are induced in those knocking out triple gene of *Nogo-a*, *Nogo-b* and *Nogo-c* [38]. Although controversial, Nogo-A is likely to be involved in the regulation of axonal branching in embryonic neurons through its binding to NgR1.

Hence, Nogo-A and NgR1 participate in various developmental processes such as migration, neurite outgrowth, and axonal guidance, fasciculation and branching during the organization of neuronal circuitry. We demonstrate that Nogo-A, NgR1 and LOTUS are essential for axonal fasciculation and branching in LOT development [18, 20]. Our findings provide a new insight into neurodevelopmental mechanism, and raise the possibility that ingenious regulation of NgR1 signaling by Nogo-A and LOTUS might be associated with the above developmental processes in other neuronal circuitry formation.

CONCLUDING REMARKS

LOTUS functions in axonal bundling of the LOT by blocking the binding of Nogo-A to NgR1 and suppressing Nogo-A-induced axonal growth inhibition [18] (Figs. 1, 2). Thereafter, Nogo-A up-regulated in the LOT conquers the blockade of NgR1 by LOTUS and starts to interact with NgR1, resulting in sprouting of collateral branches of the LOT [20] (Fig. 2). These findings indicate that Nogo-A, NgR1 and LOTUS play crucial roles in LOT development. It will be interesting to examine whether the defect of LOT development due to loss of LOTUS influences the olfactory information system.

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CONFLICT OF INTEREST STATEMENT

We have no conflict of interest to disclose.

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