Nogo-B Receptor (NgBR): A New Receptor that Modulates Blood Vessel Formation

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Received: April 08, 2014
Published online: June 13, 2014

Nogo-B is an isoform of reticulon-4 (RTN4) that distributes mainly in the endoplasmic reticulum. Nogo-B binds to its receptor, Nogo-B receptor (NgBR), to modulate blood vessel formation. Animal with Nogo-B knockout is phenotypically normal. NgBR is a type I receptor with a single transmembrane domain that binds Nogo-B and probably other angiogenic factors. NgBR knockout in zebra fish leads to abnormal formation of intersomite vessels suggesting NgBR plays a more important role in the Nogo-B/NgBR signaling pathway. It is reported that NgBR plays a role in dolichol biosynthesis, protein N-glycosylation, stabilizes Niemann-Pick type C2 protein, regulates intracellular cholesterol trafficking, controls blood vessel development, and modulates breast cancer progression. However, the research in NgBR remains in its early stage and needs further exploration.

Introduction

Nogo system is a relatively newly found signaling pathway that is widely distributed in the biological system. It belongs to the reticulon family and binds to different receptors for specific function. Nogo system contains Nogo-A, -B, and -C isoforms. Nogo-B itself has two isoforms, -B1 and -B2, that bind to same receptor, Nogo-B receptor (NgBR). Nogo-B/NgBR distributes mainly in the vasculature and its role in vascular development was recently been explored. It is considered that NgBR may be more vital during vascular development than Nogo-B judging from the fact that Nogo-A/B knockout animal remains phenotypically normal whereas NgBR knockout leads to impaired vascular formation in zebra fish \(^1\) and is lethal in mouse embryo \([\text{Miao RQ personal communication}].\) NgBR also controls other biological functions and awaits further explorations.

Reticulons

Reticulon is a group of proteins and obtain its name due to its distribution mainly in endoplasmic reticulum. Morris \textit{et al} first described reticulon protein, vp20, in rats \(^2\). Neurite outgrowth inhibitor, also known as Reticulon-4, is a protein that in humans is encoded by the \textit{RTN4} gene that has been identified as an inhibitor of neurite outgrowth specific to the central nervous system and obtained the name as “Nogo” \(^2, 3\). Using either alternate splicing or different promoter region there are three isoforms of Nogo produced from \textit{RTN4} gene (Figure 1) \(^4-6\). The distribution of the three Nogo isoforms is different. Nogo-A and -C are mainly distributed in the nervous system whereas Nogo-B is distributed mainly in vasculature \(^6, 7\). There are at least
three receptors have been described to bind Nogo-A that lead to inhibition of neuronal growth [8]. Detailed description of Nogo-A system is beyond the scope of this review and readers are encouraged to refer to several recent review articles about this topic [9, 10].

Nogo-C has been described to play some roles in neurological disease [11, 12], induces apoptosis in vitro via JNK-c-Jun-dependent pathway [13]. Nogo-C expression in brain is increased in schizophrenic patients [14] and mutations in Nogo-C have been linked to hepatic carcinoma in specific Chinese population [15].

Nogo-B is widely expressed in the central nervous system and peripheral tissues, and is mainly located in endoplasmic reticulum and cell membrane. Previous studies have revealed that Nogo-B plays a key role in vascular injury [16, 17], tissue repair and inflammation process [18-20]. However, Nogo-A/B knockout is non-lethal but results in an exaggerated neointimal proliferation, abnormal remodeling and a deficit in ischemia mediated arteriogenesis and angiogenesis. Nogo-B may be critical for apoptosis of tumor cells [21, 22] and central nervous system diseases. Recent studies suggest plasma Nogo-B level may be an indicator for liver cirrhosis [23, 24] and idiopathic pulmonary arterial hypertension [25]. Evidence suggests increased Nogo-B level disrupts the ER-mitochondron unit and suppresses mitochondrion-mediated apoptosis especially in the pulmonary artery smooth muscle cells (PASMC) and leads to the thickening of the PASMC layer under pulmonary artery hypertension inducing environment. Two isoforms of Nogo-B are reported in the literature [16, 26, 27] but difference in their biological role remains unknown.

**Nogo-B Receptor (NgBR or NUS1)**

As the receptor for Nogo-B, it is also known as nuclear undecaprenyl pyrophosphate synthase 1 Homolog (NUS1). Miao et al first described this protein and its role in human umbilical vein endothelial cells as a receptor necessary for Nogo-B stimulated chemotaxis and morphogenesis of endothelial cells [28]. His work also indicated NgBR inhibits PDGF-mediated vascular smooth muscle cell migration. There is evidence suggests that VEGF also binds to NgBR offering ~40% of the effect on angiogenesis and may explain why Nogo-A/B knockout mouse is non-lethal and phenotypically normal.

**Structure of NgBR**

Li et al used bioinformatic methodology to study CD and NMR characterization of NgBR and its two dissected domains. They described that the NgBR ectodomain is intrinsically unstructured without both secondary and tertiary structures while the cytoplasmic domain is partially folded with secondary structures but without a tight tertiary packing [29]. Therefore, NgBR is a rare example with the entire ectodomain as a transmembrane receptor.

**Function of NgBR**

Other than originally described function in vascular endothelial cell migration [29], inhibiting PDGF-mediated PASMC migration, and vascular development [1], it is shown to stabilize Niemann-Pick type C2 protein and regulates intracellular cholesterol trafficking using yeast two-hybrid screen for interacting proteins [30]. Part of its function is believed to be through the binding with vascular endothelial cell growth factor. It is also needed for cellular dolichol biosynthesis, protein N-glycosylation [30]. Miao’s group identified NgBR binds farnesylated Ras and recruits Ras to the plasma membrane, which is a critical step required for the activation of Ras signaling in human breast cancer cells and tumorigenesis. Recently his group reported that expression modulates survivin level in estrogen-receptor positive breast cancer tumor cells which may contribute to the progression of breast cancer [31].

Using pulmonary artery endothelial cells (PAEC) and lung tissue obtained from fetal sheep after intrauterine ductus arteriosus constriction induced pulmonary hypertension model, intrauterine pulmonary hypertension (IPH), our group observed a decreased NgBR level in IPH PAEC and lungs [27]. The decreased NgBR level is associated with increased reactive oxygen species formation and decreased nitric oxide availability in PAEC (Figure 2). The changes in ROS and NO formation in

*Figure 1. Structure of the different isoforms of Nogo protein. All three major isoforms are encoded by RTN4 gene in human. There are two isoforms of Nogo-B identified.*
PAEC parallel to the in vitro angiogenesis assays (Figure 3) as we previously described [32]. We believe that increased NgBR level in PAEC helps eNOS activity through activation of Akt/PKB pathway. In the same report we also observed an increased GTP cyclohydrolase-1 level and MnSOD level/activity. Judging from the decreased GTP cyclohydrolase-1 level [33] and MnSOD level/activity in IPH PAEC [34] impair angiogenesis in IPH we believe NgBR provides several levels of benefit to vascular development in the developing lungs.

Conclusions

NgBR is a newly described protein with limited information available in literature to help us understanding its role in biologic system. Knockout animal models suggest NgBR is vital to normal embryo development. In human cancer tissue NgBR may modulate the disease progression. Manipulating NgBR level in PAEC demonstrates its function in angiogenesis is through eNOS coupling. Research in this protein remains in its early stage but its involvement in cancer progression and lung development deserve our endeavor for further explorations.

Conflicting interests

The authors have declared that no competing interests exist.

References


