International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 2, No. 3, 2023

Research Progress on RGMb and its Signaling Pathway

Shucheng Li [1], Rongrong Zhang [1], Lei Zhang [2], Xinyue Qin [1, *]

[1] Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[2] Department of Rehabilitation Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

*** Corresponding author:** Xinyue Qin (Email: lsccqchina@163.com)

Abstract: Repulsive guidance molecule b (RGMb) is a member of RGM family, which is structurally composed of an N-terminal signal peptide, a vWFD domain and a C-peptide. RGMb is widely expressed in different systems in order to regulate various physiological and pathophysiological processes. So RGMb involves in tumor progression, immune regulation, retinal network, neural network reconstruction and other important aspects. Recently, numerous studies reflect the diversity and complexity of RGMb signaling pathway. This paper will focus on RGMb, and introduce its molecule structure, function, related signaling pathway, and above all, the research progresses.

Keywords: Repulsive Guidance Molecule b (RGMb); Molecular Structure; Negative Regulator; Mechanism Complexity; Nerve System.

1. Introduction

Repulsive guidance molecule b (RGMb) is an important member of the RGM family. RGMb, along with RGMa, RGMc, and recently discovered RGMd that is only expressed in fish, form the currently known RGM family [1-3]. Early 21st century, when Monnier et al. investigated the influencing factors of nervous system development process, they discovered a series of cytokines which expressed in the optic tectum region of chicken embryos and played a negative role in neuronal growth. Then they named the cytokines Repulsive Guidance Molecules [4]. As a member of the RGM family, RGMb was found to share high homology with other members such as RGMa [5]. And it is wildly expressed in brain, spinal cord, lung, kidney, muscle, bone, heart, reproductive axis and other important organs [6, 7]. Therefore, in recent years, the molecular signaling pathway of RGMb and its association with different diseases have been intensively discussed by experts both domestic and overseas. A large number of experiments have proved that RGMb, as a growth regulatory factor, is involved in various human physiological and pathological processes by influencing the activity of downstream signaling pathways, such as embryonic development, immune regulation, inflammatory activation, cancer progression, damage repair and neural network reconstruction [8-11].

In this review, starting from the molecular structure of RGMb, the signaling pathways and research progress of RGMb in tumor progression, immune inflammation regulation, retinal network formation, nerve damage repair and other aspects will be introduced in detail. At last, we will discuss the current research hotspots and propose the possible research direction in the future.

2. Molecular Structure and Expression Distribution

As a member of the RGM family, Repulsive guidance molecule b shares high homology in structure with other members, but there are still significant differences in other aspects like expression distribution in vivo and downstream signaling pathways. For example, the primary amino acid homology between RGMb and RGMa is as high as about 50%. But according to Jorge's report, there is still a dramatic difference in the spatial distribution of RGMb and RGMa in the embryo [12]. Secondly, in the Central nerve system (CNS), RGMb is highly expressed during the neurodevelopment stage and then gradually decreases to low expression along with the CNS maturity. However, RGMb expression is increased after central nervous system injury [13, 14]. Moreover, according to Li's report, RGMa that expressed in colon cancer cells can only inhibit intercellular adhesion, while RGMb can not only inhibit adhesion but also simultaneously inhibit cell growth, migration, and invasion [15]. As for the molecular structure of RGMb, it is a glycoprotein anchored to the cell membrane through the combination of C-peptide terminus and Glycosyl phosphatidyl inositol (GPI) [1]. And it composed of an N-terminal signal peptide, a local von Willebrand Factor type D (vWFD) domain and a GPI-anchored C-terminus [16]. RGMb N-terminal and C-terminal signal peptides bind to Bone morphogenetic protein (BMP) and type I transmembrane protein Neogenin with high affinity, which are regulating downstream signaling pathways [2, 3, 16]. Thus, RGMb is involved in cell adhesion, migration, invasion, regeneration and apoptosis [17-19], as well as regulating embryonic development, immune activity, inflammatory response, cancer progression and other physiological and pathological processes [8-11].

3. The Mechanism and Research Progress of RGMb

3.1. Tumor Progression

As mentioned above, RGMb can bind to BMP or Neogenin via its N-terminus and C-terminus to regulate the downstream signaling pathway. For example, RGMb can bind to Neogenin as a ligand to promote apoptosis of renal tubular epithelium under hypoxic conditions [20]. Meanwhile, RGMb can also act as a co-receptor to enhance BMP-induced downstream phosphorylation pathway and thus inhibit the growth of renal cysts [21, 22]. By knocking out the RGMb gene in breast cancer cell and mouse models, Li and his team found that the proliferation, adhesion and migration of tumor cells and the

ability of the tumor to metastasize in the body were greatly enhanced. Therefore, they speculated that it was related to the decreased expression activity of caspase-3 and the inhibition of MAPK-JNK pathway caused by the loss of RGMb expression [19]. Meanwhile, Jing et al. found that RGMb expression was reduced in Non-small Cell Lung Cancer (NSCLC) cells and tissues. Through Through extensive experiments, they proved that up-regulation of RGMb expression may inhibit their migration and invasion ability [23], slow down the proliferation rate of cancer cells, and initiate cell apoptosis by affecting the downstream Smad1/5/8 pathway [24]. This is the first report that RGMb negatively regulates the progression of breast cancer and NSCLC, and indicated the relationship between RGMb levels and overall survival in patience. At the same period, Ye et al. observed a similar phenomenon in prostate cancer cells. After downregulating the expression of RGMb, the malignancy of prostate cancer cells increased, such as the abilities of migration and proliferation were significantly enhanced [15]. In the case of squamous cell carcinoma, invasion and metastasis are also important causes of recurrence and progression. The experimental results of Zhang et al. in 2020 showed that Mir-93-5p inhibits the expression of RGMb in squamous cell carcinoma through an oncogene-like effect, thus regulating the migration and invasion of tumor [25]. In addition to the above effects on the proliferation and invasion of tumor cells, in 2018, Sanders and his group found that RGMb can also regulate the human vascular endothelial cells' responsiveness to hepatocyte growth factor, thereby inhibiting the generation of tumor neovascularization and ultimately affecting the deterioration of tumors [26]. In 2022，Zhang et al. also found that RGMb affected the clinical prognosis of patients by affecting the epithelial-mesenchymal transition and the malignant degree of tumors in nasopharyngeal carcinoma, through their research of the mechanism of LncRNA RGMb-AS1 in nasopharyngeal carcinoma [27]. In a nutshell, RGMb can inhibit cell proliferation, transformation, migration and invasion, initiate cell apoptosis, and interfere with tumor neovascularization so as to inhibit tumor progression.

3.2. Inflammation and Immune Regulation

RGMb is expressed in macrophages within various tissues, including lung interstitium, lung epithelium and nerve tissue [28]. For example, in an allergic asthma model, RGMb is expressed by activated eosinophils, interstitial macrophages, and airway epithelial cells. After inducing airway inflammation, the related cells simultaneously express RGMb and its ligand Neogenin to jointly regulate the secretion level of interleukin-4 (IL-4) which is the typical cytokine in typeII inflammatory response [9]. In their vitro experiment, IL-4 expression level was reduced after intervention with RGMb monoclonal antibody. It has been demonstrated that the RGMb-Neogenin signaling pathway maybe associated with type 2 inflammatory response and other types of inflammatory diseases [29]. At the same time, studies have proved that interleukin-6 is up-regulated in macrophages and dendritic cells of lung tissue in RGMb-knockout mice [8]. Together with the findings of Shi, it proved that RGMb is an important negative regulator of interleukin-6 expression [30]. In 2021, Ying et al. induced colitis in RGMb knockout mice and continued to detect the colony composition and abundance of gut microbiota. The results showed that the expression of RGMb did indeed alter the diversity of gut microbiota, leading to biological imbalance and affecting the occurrence and prognosis of colitis [8]. Similar results have also been obtained in the early inflammatory stage of colitis-associated colon cancer [30]. In summary, RGMb overexpression can inhibit the development of airway hypersensitivity and colitis, which suggests that RGMb may play an important role in immune and inflammatory diseases.

The inhibitory receptor Programmed Death-1 (PD-1) is the cornerstone of immune regulation, which exists two ligands, PD-L1/L2 [28]. Studies have found that RGMb is also a binding ligand of PD-L2, and the binding ability of RGMb is similar to PD-L2-PD-1. Its main role is to regulate respiratory tolerance by affecting the production of IL-4 and the proliferation of T cells after antigen presentation. The BMP pathway mentioned above is also related to it. PD-L2 and BMP can simultaneously bind to RGMb at different binding sites to form a more complex trimeric complex [31, 32]. RGMb is also a binding ligand of PD-L2, found by recent studies. And RGMb shares the same binding ability like PD-1, so it can regulate respiratory tolerance by affecting the production of IL-4 and the proliferation of T cells after antigen presentation [32]. The BMP pathway mentioned above is also related to this process. RGMb can simultaneously bind with PD-L2 and BMP at different binding sites to form a more complex trimeric complex [31]. Further studies have shown that Neogenin and BMP-RGMb-PD-L2 complex are not independent of each other [31]. Xiao et al. proposed an RGMb interaction model in which RGMb binds to the BMP-BMPR complex and then integrates to Neogenin in cis, that forms the BMP-BMPR-RGMb-Neogenin super-complex which regulates downstream pathways such as MAPK and ERK [16, 30, 33]. And PD-L2 may act as an upstream signaling molecule and regulate immune tolerance by trans-binding with RGMb super-complex [31]. However, further research is needed to be done on the specific mechanism of PD-L2 in this super complex and the interaction between its four molecules.

Therefore, based on the different receptors interacting with RGMb, it has different regulatory effects on inflammation. RGMb may inhibit the occurrence of inflammatory reactions directly, or it may affect the progression of inflammation by regulating the body's tolerance to different inflammatory factors.

3.3. Retinal Cellular Neural Network

In the retina of the human eye, ganglion cells express different levels of Low density lipoprotein receptor related protein 5 (LRP5) at different stages of development, which generates corresponding Wnt-signal through the concentration gradient of LRP5 on both sides of the retina, thereby affecting axonal growth and regulating the proper formation of retino-tectal/collicular map [6]. In the retinal network, as a GPI-anchored extracellular protein, RGMb is a novel extracellular substrate of the Vertebrate lonesome kinase (VLK). When VLK and RGMb interact with each other, the phosphorylated RGMb will be internalized into the cell and carries LRP5 during the transport process. By reducing the level of LRP5 on the membrane surface, Wnt-signal is down-regulated [34]. Therefore, RGMb can affect cell-autonomous axon guidance through LRP5-Wnt signaling pathway. So RGMb plays an important regulatory role in the establishment of optic nerve network.

Similarly, Ma et al. observed in developing RGMb mice that the protrusions of newly formed neurons in their dorsal

root ganglia were fewer and shorter than those in the same nest of RGMb silenced mice [33]. This also suggests that RGMb does not only serve as a repulsive guiding factor, but also regulate the speed of axon growth. This pathway may be the first example of neuron targeted connections to achieve cell-autonomous axon guidance independent of the influence of paracrine signals [6].

3.4. Neural Network Repair and Reconstruction

In the CNS, injured axons fail to regenerate in a short time. It's not because they are not regenerative, but the nascent growth cones formed at the lesion site show typical poor growth trend or even collapse under the limitation of the CNS environment [35]. A large number of studies on neural network repairmen and reconstruction have shown that both positive and negative growth factors in the glial environment are crucial for axon regeneration and other processes. For example, Myelin-associated glycoprotein (MAG), Nogo, and oligodendrocyte myelin glycoprotein (OMgp) have been characterized as inhibitors of axonal regeneration [36, 37]. Therefore, amplifying the effect of positive growth factors and early intervention of negative growth factors has a great positive effect on the repair and reconstruction of neural networks and the improvement of the prognosis of patients [36].

A large number of experiments have proved that RGM family is related to neural network repairmen and reconstruction [38-41]. Among them, RGMa and RGMb are highly expressed in CNS [6] and play an important role in inhibiting axon growth, formation and synaptic maturation [38-41]. In the study of Zhang et al., it was found that RGMa promoted gliosis and scar formation in the CNS injury site through ALK5-TGFβ1 pathway, thus inhibiting the reconstruction of neural network after stroke [42]. Unlike RGMa, RGMb is highly expressed during the neurodevelopment stage and then gradually decreases to low expression along with the CNS maturity. However, RGMb expression may increase again after central nervous system injury [13, 14]. And the role of re-expression or overexpression may be mainly due to the inhibition of nerve regeneration. And participate in subsequent apoptosis [14, 22, 43]. Its overexpression may take part in nerve regeneration inhibition and the subsequent apoptosis process [14, 22, 43]. Schwab et al. found that RGMb expression was significantly increased at the injured site after spinal cord injury in rats, and speculated that RGMb-RhoA pathway was involved in the subsequent growth cone development disorder and scar tissue formation, thereby inhibiting axon regeneration [44]. In 2020, a MCAO animal experiment found that RGMb level in the cerebral core infarction area of rats upregulates its expression by activating RhoA-Rho kinase pathway, thereby mediating neuronal apoptosis, destroying nerve fiber myelination and inhibiting nerve axon growth [45]. When Li et al. studied the effects of lead on the development of hippocampus and cerebral cortex in rats, they found that the expression of RGMb was related to the apoptosis activation in cerebellar neurons and granulosa cell axons inhibition. And they speculated it is realized through the activation of classical RhoA-ROCK and PKC signaling pathways [46]. Liu et al. found in vitro experiments that upregulating the concentration of RGMb level resulted in axonal growth inhibition in neurons of spinal cord injury rats [43].

Therefore, it is currently believed that the expression level of RGMb in the nervous system may be related to neuron survival, apoptosis, differentiation and the reconstruction processe [1, 28]. However, as far as we know, there is limited research on the mechanism of RGMb in CNS, and it still needs extensive data to explore the relationships.

4. Complexity and Contradiction

Although due to the wide distribution of RGMb in vivo, it has aroused intense discussion in various fields worldwide, the interaction between it signaling pathways is still unclear, even contradictory. For example, in terms of tumor progression, RGMb can inhibit cell proliferation, transformation, migration and invasion, initiate cell apoptosis, and interfere with tumor neovascularization in NSCLC [23], breast cancer [19, 23], liver cancer [47], squamous cell carcinoma [25], nasopharyngeal carcinoma [27] and other related tumors, so as to inhibit tumor progression and even improving survival ratio. However, Song et al. mentioned in their study that LncRNA RGMb-ASI promoted cell proliferation and migration through miR-574-3p/PIM3 and inhibited cell apoptosis, thus leading to the progression of pancreatic cancer [48]. In 2019, Pan et al. also found that silencing RGMb significantly inhibited cell proliferation and migration, and even made tumor cells stagnant in order to reduce the malignant degree [49]. In the same time, Zhang et al. reported that down-regulation of RGMb inhibited cell proliferation, epithelial cell transformation and promoted cell apoptosis in gastric cancer cells [50]. It is diametrically opposite to the inhibitory effect on tumor progression mentioned above.

At the early 21st century, it was generally believed that the RGMb related BMP signal and the Neogenin signal were independent of each other [51, 52]. However, with the breakthrough in PD-1, whether RGMb can also regulate immune tolerance capacity through programmed death has attracted attention worldwide. As mentioned above, RGMb-BMP-PD-L2 formed a complex trimer complex, and Neogenin could also interact with this trimer. Meanwhile, recent studies have found that Neogenin may act as an upstream molecule to promote the activation of BMP signaling pathway. What's more, Neogenin may also be the receptor of BMP [32]. This overturns the previous belief that they do not affect each other.

Samad et al. found that GPI anchored RGMb plays a negative role in promoting BMP-related-signal, but in contrast, the dissociated RGMb. Fc soluble residues show an inhibitory effect. They speculated that RGMb. Fc residues can bind to the ligands of BMP and prevent them from approaching the receptors on the cell surface [21, 53]. Moreover, this inhibitory ability is highly specific [16]. However, Kanomata et al. found that the differentiation and proliferation capacity of C2C12 osteoblasts were simultaneously inhibited by RGMb anchoring glycoprotein and RGMb. Fc residues in subsequent studies [52]. So, we speculate that there may be a novel molecule which preferentially recognizes cell surface receptors after binding to RGMb, and then decides whether to present RGMb binding sites in a cell type-dependent manner to inhibit the BMP pathway. However, the specific molecular mechanism is still unclear and needs further study.

RGMb is a negative regulatory factor and is currently believed to take part in inhibiting axonal regeneration and neural network reconstruction process in CNS [28, 33, 46]. However, Ma et al. found that the early axonal regeneration

of peripheral nerves in mice after injury was promoted by the RGMb-BMP pathway [33]. In RGMb-knockdown-mice, axon regeneration after sciatic nerve crush injury was significantly reduced compared with normal group [33]. This may be related to the diverse mechanism of RGMb in their different development processes, and the different extracellular microenvironment between the central and peripheral areas. And Mill et al. speculated that the positive regulatory effect of RGMb may be realized through another signaling pathway or another growth regulatory factor indirectly. Or there may be a situation in which positive and negative growth factors exert their effects at the same time [54].

5. Summary

Repulsion guidance molecule b is wildly expressed in nervous system, reproductive system, immune system, respiratory system, musculoskeletal system and other important systems. It is involved in cell adhesion, migration, invasion, regeneration, differentiation and apoptosis, and is related to various physiological and pathological processes such as embryonic development, immune activity, inflammatory response, cancer progression and damage repair. As an inhibitor of neuronal regeneration protein with great research potential, RGMb is related to the occurrence, development and prognosis of a variety of diseases. RGMb is a protein molecule worthy of further study, but the research on RGMb is still shallow, and its research in the neural direction needs a large number of experimental and clinical data for further discussion.

Acknowledgments

The authors thank Dr. Zhang from The First Affiliated Hospital of Chongqing Medical University for her advice and guidance.

References

[1] C. Siebold, T. Yamashita, and P.P. Monnier (2017). RGMs: Structural Insights, Molecular Regulation, and Downstream Signaling. Trends Cell Biol, vol.27, no.5, p.365-378.

[2] C.J. Severyn, U. Shinde, and P. Rotwein (2009). Molecular biology, genetics and biochemistry of the repulsive guidance molecule family. Biochem J, vol.422, no.3, p.393-403.

[3] C.H. Bell, E. Healey, and S. van Erp (2013). Structure of the repulsive guidance molecule (RGM)-neogenin signaling hub. Science, vol.341, no.6141, p.77-80.

[4] P.P. MONNIER, A. SIERRA, and P. MACCHI (2002). RGM is a repulsive guidance molecule for retinal axons. Nature, vol.419, no.6905, p.392-395.

[5] V. Niederkofler, R. Salie, and M. Sigrist (2004). Repulsive guidance molecule (RGM) gene function is required for neural tube closure but not retinal topography in the mouse visual system. J Neurosci, vol.24, no.4, p.808-818.

[6] H. Harada, J. Charish, and P.P. Monnier (2020). Emerging evidence for cell-autonomous axon guidance. Dev Growth Differ, vol.62, no.6, p.391-397.

[7] M. Metzger, S. Conrad, and G. Alvarez-Bolado (2005). Gene expression of the repulsive guidance molecules during development of the mouse intestine. Dev Dyn, vol.234, no.1, p.169-175.

[8] Y. Shi, L. Zhong, and Y. Li (2021). Repulsive Guidance Molecule b Deficiency Induces Gut Microbiota Dysbiosis and Increases the Susceptibility to Intestinal Inflammation in Mice. Front Microbiol, vol.12, p.648915.

[9] S. Yu, K.M. Leung, and H.Y. Kim (2019). Blockade of RGMb inhibits allergen-induced airways disease. J Allergy Clin Immunol, vol.144, no.1, p.94-108 e111.

[10] T. Malinauskas, T.V. Peer, and B. Bishop (2020). Repulsive guidance molecules lock growth differentiation factor 5 in an inhibitory complex. Proc Natl Acad Sci U S A, vol.117, no.27, p.15620-15631.

[11] C. Meng, N. Guo, and Q. Wei (2014). Expression of repulsive guidance molecule b (RGMb) in the uterus and ovary during the estrous cycle in rats. Acta Histochem, vol.116, no.8, p.1231-1236.

[12] E.C. Jorge, M.U. Ahmed, and I. Bothe (2012). RGMa and RGMb expression pattern during chicken development suggest unexpected roles for these repulsive guidance molecules in notochord formation, somitogenesis, and myogenesis. Dev Dyn, vol.241, no.12, p.1886-1900.

[13] J. Oldekamp, N. Kraemer, and G. Alvarez-Bolado (2004). bHLH gene expression in the Emx2-deficient dentate gyrus reveals defective granule cells and absence of migrating precursors. Cereb Cortex, vol.14, no.9, p.1045-1058.

[14] J.W. Kam, E. Dumontier, and C. Baim (2016). RGMB and neogenin control cell differentiation in the developing olfactory epithelium. Development, vol.143, no.9, p.1534-1546.

[15] J. Li, L. Ye, and H.G. Kynaston (2012). Repulsive guidance molecules, novel bone morphogenetic protein co-receptors, are key regulators of the growth and aggressiveness of prostate cancer cells. Int J Oncol, vol.40, no.2, p.544-550.

[16] E. Corradini, J.L. Babitt, and H.Y. Lin (2009). The RGM/ DRAGON family of BMP co-receptors. Cytokine Growth Factor Rev, vol.20, no.5-6, p.389-398.

[17] T. Iezaki, Y. Onishi, and K. Ozaki (2016). The Transcriptional Modulator Interferon-Related Developmental Regulator 1 in Osteoblasts Suppresses Bone Formation and Promotes Bone Resorption. J Bone Miner Res, vol.31, no.3, p.573-584.

[18] J.M. Wardlaw, P. Koumellis, and M. Liu (2013). Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. Cochrane Database Syst Rev, vol., no.5, p.CD000514.

[19] J. Li, L. Ye, A.J. and Sanders (2012). Repulsive guidance molecule B (RGMB) plays negative roles in breast cancer by coordinating BMP signaling. J Cell Biochem, vol.113, no.7, p.2523-2531.

[20] W. Liu, B. Chen, and Y. Wang (2018). RGMb protects against acute kidney injury by inhibiting tubular cell necroptosis via an MLKL-dependent mechanism. Proc Natl Acad Sci U S A, vol.115, no.7, p.E1475-E1484.

[21] T.A. Samad, A. Rebbapragada, and E. Bell (2005). DRAGON, a bone morphogenetic protein co-receptor. J Biol Chem, vol.280, no.14, p.14122-14129.

[22] J. Liu, W. Wang, and M. Liu (2016). Repulsive guidance molecule b inhibits renal cyst development through the bone morphogenetic protein signaling pathway. Cell Signal, vol.28, no.12, p.1842-1851.

[23] J. LI, L. TE, and X.S. SHI (2016). Repulsive guidance molecule B inhibits metastasis and is associated with decreased mortality in non-small cell lung cancer. Oncotarget, vol.17, no.13, p.15678-15689.

[24] X.F. Jing, M.Y. Ren, and Y.S. Fan (2021). Circular RNA_0001073 (circ_0001073) Suppresses The Progression of Non-Small Cell Lung Cancer via miR-582-3p/RGMB Axis. Cell J, vol.23, no.6, p.684-691.

[25] S. Zhang, Y. He, and C. Liu (2020). miR-93-5p enhances migration and invasion by targeting RGMB in squamous cell carcinoma of the head and neck. J Cancer, vol.11, no.13, p.3871-3881.

[26] A.J. Sanders, L. Ye, and J. Li (2014). Tumour angiogenesis and repulsive guidance molecule b: a role in HGF- and BMP-7-mediated angiogenesis. Int J Oncol, vol.45, no.3, p.1304-1312.

[27] T. Zhang, Y. Jin, and X. Luo (2022). Long non-coding RNA RGMB-AS1 represses nasopharyngeal carcinoma progression via binding to forkhead box A1. Bioengineered, vol.13, no.3, p.5564-5580.

[28] K.E. Pauken, J.A. Torchia, and A. Chaudhri (2021). Emerging concepts in PD-1 checkpoint biology. Semin Immunol, vol., p.101480.

[29] Y. Iwai, S. Terawaki, and T. Honjo (2005). PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol, vol.17, no.2, p.133-144.

[30] Y. Xia, V. Cortez-Retamozo, and V. Niederkofler (2011). Dragon (repulsive guidance molecule b) inhibits IL-6 expression in macrophages. J Immunol, vol.186, no.3, p.1369-1376.

[31] Y. Xiao, S. Yu, and B. Zhu (2014). RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. J Exp Med, vol.211, no.5, p.943-959.

[32] M. Perez-Cruz, B.P. Iliopoulou, and K. Hsu (2022). Immunoregulatory effects of RGMb in gut inflammation. Front Immunol, vol.13, p.960329.

[33] C.H. Ma, G.J. Brenner, and T. Omura (2011). The BMP coreceptor RGMb promotes while the endogenous BMP antagonist noggin reduces neurite outgrowth and peripheral nerve regeneration by modulating BMP signaling. J Neurosci, vol.31, no.50, p.18391-18400.

[34] H. Harada, N. Farhani, and X.F. Wang (2019). Extracellular phosphorylation drives the formation of neuronal circuitry. Nat Chem Biol, vol.15, no.11, p.1035-1042.

[35] A.J. Mothe, N.G. Tassew, and A.P. Shabanzadeh (2017). RGMa inhibition with human monoclonal antibodies promotes regeneration, plasticity and repair, and attenuates neuropathic pain after spinal cord injury. Sci Rep, vol.7, no.1, p.10529.

[36] T. YAMASHITA,M. FUJITANI, and S YAMAGISHI (2005). Multiple signals regulate axon regeneration through the Nogo receptor complex. Molecular neurobiology, vol.32, no.2, p. 105 -111.

[37] J.W. Fawcett, and J.C.F. Kwok (2022). Proteoglycan Sulphation in the Function of the Mature Central Nervous System. Front Integr Neurosci, vol.16, p.895493.

[38] J. Yoshida, T. Kubo, and T. Yamashita (2008). Inhibition of branching and spine maturation by repulsive guidance molecule in cultured cortical neurons. Biochem Biophys Res Commun, vol.372, no.4, p.725-729.

[39] H. Brinks, S. Conrad, and J. Vogt (2004). The repulsive guidance molecule RGMa is involved in the formation of afferent connections in the dentate gyrus. J Neurosci, vol.24, no.15, p.3862-3869.

[40] K. Hata, M. Fujitani, and Y. Yasuda (2006). RGMa inhibition promotes axonal growth and recovery after spinal cord injury. J Cell Biol, vol.173, no.1, p.47-58.

[41] D.M. van den Heuvel, A.J. Hellemons, and R.J. Pasterkamp (2013). Spatiotemporal expression of repulsive guidance molecules (RGMs) and their receptor neogenin in the mouse brain. PLoS One, vol.8, no.2, p.e55828.

[42] R. Zhang, Y. Wu, and F. Xie (2018). RGMa mediates reactive astrogliosis and glial scar formation through TGFbeta1/ Smad2/ 3 signaling after stroke. Cell Death Differ, vol.25, no.8, p.1503-1516.

[43] X. Liu, M. Hashimoto, and H. Horii (2009). Repulsive guidance molecule b inhibits neurite growth and is increased after spinal cord injury. Biochem Biophys Res Commun, vol. 382, no.4, p.795-800.

[44] J.M. Schwab, S. Conrad, and P.P. Monnier (2005). Spinal cord injury-induced lesional expression of the repulsive guidance molecule (RGM). Eur J Neurosci, vol.21, no.6, p.1569-1576.

[45] X. Wang, J.L. Cheng, and Y.C. Ran (2017). Expression of RGMb in brain tissue of MCAO rats and its relationship with axonal regeneration. J Neurol Sci, vol.383, p.79-86.

[46] N. Li, M. Qiao, and Q. Zhao (2016). Effects of maternal lead exposure on RGMa and RGMb expression in the hippocampus and cerebral cortex of mouse pups. Brain Res Bull, vol.127, p.38-46.

[47] N. Sheng, Y. Li, and R. Qian (2018). The clinical significance and biological function of lncRNA RGMB-AS1 in hepatocellular carcinoma. Biomed Pharmacother, vol.98, p. 577-584.

[48] W. Song, and C. Shi (2021). LncRNA RGMB-AS1 facilitates pancreatic cancer cell proliferation and migration but inhibits cell apoptosis via miR-574-3p/PIM3 axis. Am J Physiol Gastrointest Liver Physiol, vol.321, no.5, p.G477-G488.

[49] B. Pan, M. Zhao, and N. Wang (2019). LncRNA RGMB-AS1 Promotes Glioma Growth and Invasion Through miR-1200/HOXB2 Axis. Onco Targets Ther, vol.12, p.10107-10114.

[50] W. Zhang, F. Zhan, and D. Li (2020). RGMB-AS1/miR-22-3p/NFIB axis contributes to the progression of gastric cancer. Neoplasma, vol.67, no.3, p.484-491.

[51] W. Liu, X. Li, and Y. Zhao (2013). Dragon (repulsive guidance molecule RGMb) inhibits E-cadherin expression and induces apoptosis in renal tubular epithelial cells. J Biol Chem, vol.288, no.44, p.31528-31539.

[52] K. Kanomata, S. Kokabu, and J. Nojima (2009). DRAGON, a GPI-anchored membrane protein, inhibits BMP signaling in C2C12 myoblasts. Genes Cells, vol.14, no.6, p.695-702.

[53] B. Andriopoulos, Jr., E. Corradini, and Y. Xia (2009). BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. Nat Genet, vol.41, no.4, p.482-487.

[54] C.D. Mills, A.J. Allchorne, and R.S. Griffin (2007). GDNF selectively promotes regeneration of injury-primed sensory neurons in the lesioned spinal cord. Mol Cell Neurosci, vol.36, no.2, p.185-194.