

Slit/Robo Pathway - Neurogenesis to Cancer Progression: A Potential Therapeutic Target

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Abstract

Slit-Robo could be a cell signaling pathway with numerous functions such as axon steering and ontogenesis. Slit is a secreted macromolecule and most generally referred to as a repulsive axon steering cue, and Robo as its trans-membrane macromolecular receptor. This ligand-receptor combination has been concerned in different kind of neuronal and non-neuronal processes starting from cell migration to ontogenesis, tumorigenesis and organogenesis like kidneys, lungs and breasts, etc.

Roundabout receptors (Robo) and their Slit ligands were detected in axon steering. Slit was primarily associated degree extracellular matrix super molecule and expressed by plane interstitial tissue in fruit fly. Slits acted as chemo-repellents for axons crossing the plane in vertebrates and invertebrates. The origin of Robo proteins were from fruit fly in an exceedingly mutant screening for genes concerned with the regulation of plane crossing. This ligand-receptor try has been involved exceedingly in somatic cell and non-neuronal processes starting from cell migration to maturation, tumorigenesis and organogenesis of tissues like kidneys, lungs and breasts, etc. This pathway act as a substance receptor pathway where Slit proteins bind with Robo receptors and convert signals for axon steering through plane commissures. Recent studies have confronted the role of this signal in numerous fields outside ontogeny like maturation and cancer progression. Here the fundamental framework of Slit/Robo structure and its general pathway with special stress on its operation in stomach cancer are summarized.

Keywords: Slit; Robo; Neurogenesis; Cancer progression

Introduction

Neurogenesis, a way of producing new neurons from neural precursor cells observed through neuronic migration and regionalization, is an inevitable incident for the occasion of systema nervosum. In each invertebrates and vertebrates, plane cells, a group of sign molecules, play a key role in the formation of the nerve fiber commissures that adjoins left and right sides of the forming central systema nervosum permitting communication between each side of the body. The formation of commissures and connectives involves each nerve fiber attraction and nerve fiber repulsion towards or away from the plane that is radio-controlled by nerve fiber steering molecules. Recently, studies have shown that Slit and Roundabout (Robo) were thought to be the nerve fiber steering molecules as Slit/Robo sign pathway directs nerve fiber walking, neuronic movement yet because it promotes nerve fiber branching. Slit proteins are secreted glycoproteins, extremely preserved in its structure that intervene their functions by binding to their trans-membrane receptors referred to as Robo receptors [1]. Slit acts as a chemo-repulsive sheet cue that binds to the trans-membrane receptor Robo, that is expressed on the expansion cones of target axons, to mediate sheet crossing [2-5]. Besides dominant in the repulsion and migration of the axons, Slit/Robo pathway conjointly contributes in ontogeny and tumor-endothelial cell communication. Though it's illustrious that the angiogenic stimuli created by growth cells drives the epithelial tissue cells towards them, the explanation behind the directional movement is unknown. Wang Associate in nursing colleagues delineated a quirky mechanism for growth-driven ontogeny by stating that tumor cells manufacture the Slit macromolecule which will acknowledge tube-shaped structure epithelial tissue cells through their expressed cognate receptor Robo [6]. Angiogenesis, being one among the most important attributes of cancer progression, are often targeted and Slit/Robo sign pathway is often targeted for the therapeutic approach towards cancer.

Molecular framework of Slit/Robo

Initially, Slit proteins were known in pomace fly by the technique of screening that was chiefly performed to observe patterns and morbidity [7]. These square measure secreted proteins enabled to link with extracellular matrix. Though these proteins share nearly similar structures, they're extremely preserved among species [8]. 3 Slit genes square measure found among vertebrates; Slit 1, Slit 2, Slit 3 that code ~200 kDa of proteins. Each of those super molecules is formed from four stretches of leucine-rich repeat (LRR) domains (D1-D4), seven to nine cuticular protein repeats, one Agrin-Perlecan-Laminin-Slit (ALPS) or Laminin G like domain and an amino acid knot at C terminal.

Robo receptor genes were additionally found in *Drosophila melanogaster* [3,5,9]. The Roundabout conformation owing to interruption of the commissural axons on the plane of the ventral nerve twine resulted in the naming of Robo receptors. These receptors are giant trans-membrane proteins composed of 1000-1600 amino acids having no chemical activity and are entirely addicted to downstream communication for their functions. The Robo receptor ortholog varies with species from being just one in *Caenorhabditis elegans*, 3 in chick and *Xenopus* four in mammals and zebrafish [10]. Except in class

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Robo4, all alternative animate thing domains of those receptors have 5 immunoglobulin (Ig) like domains (Ig 1-5) and 3 fibronectin repeats (FNIII 1-3). A protoplasm tail, being variable among species, with many preserved motifs follows the transmembrane domain. Robo4 is exclusive by having solely 2 immune globulin and FNIII domains [11]. Robo receptors are characterised by its substance binding activity through that it binds specifically with the secreted Slit proteins throughout steering.

Signaling pathway and mechanism of Slit/Robo

Signal transduction through Slit/Robo is principally downstream and effectively mediated by protoplasm enzyme Abelson (Abl) and simple protein and tubule complex body part influenced by Abl and its effectors. Role of Abl is contradictory as its performance has been argued to vary in several species. In pomace fly its Associate in Nursing repressive result upon Robo activity [12] whereas in another study [13] it has been shown to own a promoting result of repulsive plane steering on Robo receptors by Abl macromolecule. In chick retinal cells, a molecular advance is created between Robo1 and N-cadherin that is totally controlled by Abl effector. This advance is snapped followed by the engagement of Slit ligands which ends within the loss of N-cadherin mediated cellular division through β -catenin by Abl [14,15]. GTPase, small GTP binding macromolecule, is meticulously concerned during this sign pathway because it will modulate cell polarity and movement by rearranging the complex body part. Dock/Nck protein forms a crucial association between GTPase and upstream sign wherever it binds to pomace fly and class Robo receptors, activating nerve fiber branching and outgrowth in plant tissue neurons *in vitro* [16-18]. Slit/Robo GTPase activating macromolecule (srGAPs) illustrious for dominant GTPase were found in Yeast [19] and srGAP2 mediate downstream sign controls Rac1 activity in protrusion of cell in cell overlapping zone. Directed movement at the forefront is non-heritable by the repolarization of the cell referred to as contact inhibition of locomotion (CIL). Recent studies have urged another RhoA dependant GTPase activating macromolecule, Myo9b which may bind on to the living organism domain of Robo1 [20] inflicting inhibition of Myo9b and in broader sense inhibiting carcinoma cell metastasis.

Slit/Robo signaling in cancer development

Slit/Robo signal has been found to own an inevitable link with cancer progression. Once the initial report of gradual studies have shown the deletion of deoxyribonucleic acid two of Robo1 in respiratory organ and breast tumor cell lines [21,22]. In many forms of cancer epigenetic modulations are found like hypermethylation of Slit and Robo proteins. Activation of Slit/Robo pathway successively activates completely different oncogenic pathways that terminate in cancer. In most cases lowering of Slit/Robo expression is taken into account to be the cause behind tumorigenesis since Slit/Robo will inhibit cell invasion and migration. Slit/Robo trigger necrobiosis in body part cancer by Slit2-Robo4 interaction wherever the activated Robo4 subdue the expression of netrin-1 (a tumor suppressor protein) by interacting with it leading to the dissociation of netrin-1 from its receptor DCC (axon steering receptor deleted in body part cancer) resulting DCC regulated necrobiosis in cancer cells by activation of caspase-3 and caspase-9 [23,24]. This inhibition of netrin-1 binding to its receptor may also be non-heritable with Slit2 interaction with netrin-1. the foremost operation of Slit/Robo pathway in bar of cancer is suppression of metastasis of cancer cells as according to carcinoma and body part cancer wherever cell invasion has been ceased by interaction of Slit/Robo with E-cadherin and β -catenin [25,26]. In cancer of the liver, hepatocyte protein mediated

cell invasion is prevented by Slit2/Robo4 interaction [27]. HGF is activated by its substance Met through substance receptor binding that promotes tumor cell metastasis and formation of various carcinomas. Not solely cancer cells, recent study have unconcealed the prospect of Slit-3 macromolecule in the migration of malignant melanoma cells by modulating matter protein-1 [28]. Supported the signal mechanism and kinds of cancer, Slit/Robo pathways otherwise management cell movement and invasion. Though the reason for this differential activity in numerous forms of cancer remains unclear, it is believed that Slit-2 binds additional specifically with its Robo-1 receptor than different 2 slits (Slit-1 and Slit-3). On the context of cancer progression Slit/Robo pathway suppresses tumorigenesis by modulating activities like cell metastasis, cell necrobiosis and cell migration. Whether Slit/Robo axis will initiate cancer or not is unknown however its expression can undoubtedly inhibit cancer progression.

Role of Slit/Robo signaling in gastric cell carcinoma

The major action of Slit/Robo pathway is to hinder cell migration and metastasis however in some sort of cancer this activity differs and there Slit/Robo pathway acts favorably to growth cell metastasis. Such incidence is seen in viscous cell malignant neoplastic disease (GC) where Slit/Robo interaction triggers growth metastasis. Microribonucleic acids (miRNAs or microRNAs) play an important role within the regulation of viscous malignant neoplastic disease. These square measure short, present, non-coding polymer molecules generated from pre-miRNAs that negatively modulates organic phenomenon. This square measure found to integrate into RNA-inducing silencing complexes and try with the 3'untranslated regions of specific mRNAs to induce degradation or to forestall the interpretation of the mRNA [29]. Cell proliferation, apoptosis, invasion and metastasis is regulated by miRNAs. In studies regarding invasive and noninvasive cells, a complete of 45miRNAs square measure found to be otherwise expressed among that miR-218 is found to be closely correlative with rate metastasis and invasion. Recent experiments and diagnosis have reported concerning the lowering of miR-218 expression in many solid tumors that features rate, glandular cancer, carcinoma [30-33]. Bioinformatics dependent studies have discovered that miR-218 interacts with Robo1 receptor to alter the cell motility in rate. A feedback loop is created between Slit, miR-218 and Robo1 within which miR-218 comes from either of 2 genes placed within the introns of 2 distinct Slit super molecule friends. As Slit act as the substance of Robo receptors, miR-218, happiness from same molecular family, conjointly act as the substance of Robo1 receptors. Slit3, one among the host genes, is suppressed at the side of miR-218 in malignancy cells. Suppression of miR-218 upregulates Robo1 (one of the many Slit receptors) expression by elimination of Robo1 repression and leads to the interaction of Slit2/Robo1 that facilitates growth metastasis. Restoring high level of miR-218 will forestall Slit2/Robo1 interaction and inhibits cell invasion. This phenomenon not solely provides associate degree insight to the differential activity of Slit proteins however conjointly discovered a completely unique miRNA mediate regulative mode of receptor sign. Therefore miR-218 is a possible target for interference growth metastasis.

Conclusion

Though at first Slit/Robo signal was concerned exceedingly in axon steering however recent studies and experiments were incontestable and used it in a broader facet outside the system. Its diversity and specificity in varied species have additionally shown its biological process multiplicity. Class Robo3 and Robo4 don't bind Slit as ligands and have non-heritable different molecules as ligands, creating them totally

different from authentic Robo1 and Robo2 receptors. Equally totally different Slit receptors like Eva1C, plexin A1, Dscam1 and dystroglycan have additionally been known. Slit/Robo pathway has anticancer result and thus therapeutic approach towards varied cancer can be achieved by targeting this pathway. Simple protein deacetylase inhibitors may be used to revive Slit/Robo expression. Researches and studies on Slit/Robo pathway remains within the basic and initial level as there are several queries relating to varied mechanism of Slit/Robo area unit still unrequited. Multiple XT signal has to be studied and regarded before declaring any conclusion. There's an enormous potentiality of this pathway to be thought-about as a therapeutic target of assorted kinds of cancer however a large analysis and studies are required.

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