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Leucine rich-repeat sequence and the related protein in glioma

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Abstract. Leucine rich-repeat sequence (LRR sequence) is a special class of polypeptide sequences composed of several adjacent leucine residues. LRR sequence participates in evolution between species and across species. This sequence is widespread in a variety of proteins and has important biological functions. LRR protein plays a major part in the development of the nervous system and the maintenance of normal function. In addition, a large number of leucine repeats are closely related to the occurrence of a variety of diseases, such as leucine-rich repeat disease, leucine-rich peptide aggregate. Most importantly, it correlates with the development of brain tumors like glioma. This article is primarily focused on the structure and function of LRR sequence and the associated LRR proteins. Moreover, we summary the LRR-contain transmembrane proteins in nerve system and highlight the function of these proteins in glioma progression which takes the sequencing of LRR a potential personalized diagnosis and treatment of brain tumors.

Keywords: leucine rich-repeat sequence, glioma, LRR transmembrane proteins.

1. Introduction

LRR is a common motif shared in several different kinds of nervous system proteins which shows a complicated biological function. LRR transmembrane protein plays a significant part in the formation and differentiation of synapses, the growth of axons, neurotransmitter transmission and other physiological processes. Moreover, related studies have found that Leucine repeat and immunoglobulin like domain 1 (LRR immunoglobulin domain 1, LRIG 1) are down regulated in several types of cancers which is a potential tumor suppressor gene. Glioma is a glial tumor derived from the neural ectoderm lobe. It is the most usual primary malignant tumor in the skull. It mainly results from the brain or myeloid glia, and originates from the neuroepithelium, which is called neuroepithelial tumor. Pertinent data show that in recent years, the prevalence of primary malignant glioma has increased year over year, with a yearly growth rate of approximately 1.2%, especially in the middle-aged and elder population. Surgery is now the preferred treatment for glioma, which can significantly improve the condition of patients, but the prognosis of patients is relatively poor, prone to relapse and has a short overall survival. This article is centered around the kidney the structure and

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function of LRR and propose the important role of related LRR proteins in brain tumors, providing insights for clinical research [1].

2. Leucine rich-repeat sequence

Leucine rich-repeat sequences are short sequence modes that are prevalent in a variety of proteins and vary in their cellular distribution and function. It is generally composed of 20 to 29 amino acid residues and is named for the hydrophobic-rich leucine. From 2 to 45 curved spatial structures formed in tandem of LRR, conserved sequences form a hydrophobic core that readily binds to other proteins, enhancing affinity and interactions between proteins [2]. The proteins containing leucine rich-repeat sequences, are widely distributed in eukaryotes and prokaryotes, are reflected in various tissues and cells, and the specificity of their localization and the complexity of the proteins they interact with determine the diversity of LRR protein functions (Table 1). Contemporary studies have confirmed that LRR proteins can serve as RPTKs, CAM, and extracellular matrix glycoproteins involved in many biologically important approaches, such as hormone-receptor interactions, cell adhesion, and intracellular transport. Many LRR proteins are relatively specifically

expressed in the nervous system, which are essential for the development and differentiation of the nervous system. Notably, the vast majority of LRR proteins highly expressed in the nervous system belong to transmembrane proteins [3].

3. Leucine rich-repeat sequence protein in neutral system

3.1. Structural features of LRR transmembrane proteins in neural tissue

The fixed arrangement order of nLRR + / -Ig-C2 + / -FN-constitutes the main feature of the extracellular structure of the LRR transmembrane protein. Leucine-rich repeats (LRR) are the joint protein domain. Besides the LRR (C-terminal) and LRRNT (N-terminal) structures, LRS contains Ig-C2-like domain (immunoglobulin C2-set domain) and (or) FN-like domain (fibronectin type III) (Table 1). Ig-C2-like domains are sandwich structures composed of several β folds that are common in the communal cell recognition, cell surface receptors and autoimmune system. The FN-like domain is a dimer comprised of two similar polypeptide chains, mainly involved in cell adhesion, growth, migration, and differentiation. The interaction between the three domains has been rarely reported. Only in the study that the Ig-C2-like domain formed nearly 90 angles with the LRR, riding the convex surface of the LRR close to each other.

In recent years, a variety of proteins containing LRR structures have been found within the nervous system. NLRR1/2/3, containing 11 LRR domains, role in the process of developing and regeneration of the nervous system. zfNLRR with 12 LRR domains and 1 Ig domain, participating in the repair course of nervous system injury in zebrafish [4]. Also, the intracellular structures of LRR transmembrane proteins contain different protein sites of protein action, such as the PDZ binding region of NGL-1, and the protein kinase c phosphorylation site of LRIG-1. The intracellular and outer structures are linked by the transmembrane regions (TM). These features are the structural basis for the diversity of roles of LRR transmembrane proteins in the nervous system. Mainly used as cell adhesion molecules and ligand-binding proteins involved in the formation of synapses, the growth of neurites and the transport and release of neurotransmitters. (Table 1)

3.2. Functional studies of LRR transmembrane proteins in neural tissue

3.2.1. Formation of LRR transmembrane proteins with synapses. Synapses are the fundamental unit of nervous system activity. The extracellular LRR structure of LRR transmembrane proteins provides a framework for protein adhesion and, binding, while the intracellular protein binding sites are in a position to interacting with different effector proteins. This is a critical factor in spanning the gap between two neurons and forming synapses. Us are mainly distributed in the post synaptic membrane of nerve cells, and they bind through LRR structures to netrin-G1, netrin-G2 and LAR proteins of the

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presynaptic membrane, respectively, forming trans-synaptic connections. Netrin-G1-NGL-1, netrin-G2-NGL-2, LAR-NGL-3 can encourage the aggregation of PSD-95, GKAP, Shake and other proteins in nerve cells, and promote the formation of post synaptic membrane. Meanwhile, LAR-NGL-3 induces the aggregation of the presynaptic structural proteins and promotes the formation of the presynaptic membrane. Functionally similar are LRRTMs and SALMs, which promote post synaptic membrane formation mainly by interacting with PSD-95 proteins and direct presynaptic membrane formation during axonal contacts with other cells to form synaptic junctions [5]. NGL-1 is mostly released during the month of the distal end of dendrites, whereas NGL-2 prefers the proximal end of dendrites, and they determine the shaping of local segments of dendritic membrane by recruiting different intracellular proteins in neural cells. The above illustration demonstrates that transsynaptic adhesion of LRR transmembrane proteins plays a crucial role in synapse formation and differentiation.

3.2.2. Growth and development of LRR transmembrane proteins and neurites. Neurites include axons and dendrites, and the presence of various guidance factor receptors on the surface of the growth cones at the most anterior edge of the neurites can recognize and transmit attractive or repellent signals in the environment, and guide neurite growth along specific routes by regulating cytoskeleton restructuring within the growth cones. The role of LRR containing protein Slitrks regulating neurite growth is dual: on the one hand, due to the high homology of its extracellular structure and Slits, it may be an axon guidance factor; on the other hand, the specific tyrosine residue fragment in Slitrks intracellular structure is similar to NGF (nerve growth factor) receptor TrkA, Slitrks may act as a nutrient factor receptor or receptor copestone to promote neurite outgrowth. After binding to the corresponding ligand, FLRT-1 is phosphorescent and mediated by the non-receptor tyrosine kinase SFK (sic family kinase), and participates in the regulation of neurite outgrowth by regulating the signaling pathways related to the FGF (fibroblast growth factor) receptor [6]. AMIGOs need to be able to bind to certain neurotrophic factors and promote the formation of axonal nerve bundles.

Table 1. The LRR transmembrane proteins in the nervous system.

family	family member	positioning	protein structure		intracellular	biological function	disease
			extracellular LRR IgC2 FN III	TM			
LINGOs	LINGO-1 LINGO-2 LINGO-3	Specific and sexually expressed in the nervous system, mainly in the hippocampus neocortex and striatum.	12 1-TM		Tyrosine kinase, and the phosphorylation sites	Negative regulation in regulating axonal regeneration and myelination.	Repair after a nerve injury
LRIGs	LRIG-1 LRIG-2 LRIG-3	LRIG-1 is expressed in various tissues and highest in brain, tissues.	15 3-TM		Protein kinase-c-phosphorylation sites	Candidate tumor suppressor genes.	Multiple types of tumors
NGLs	NGL-1 NGL-2 NGL-3	Relative-specific proteins of brain tissue, mainly localized in the excitatory postsynaptic membrane.	9 1-TM		PDZ, bonded pad	Promote synapse formation and shaping of synapsis and guide axon growth and migration.	neurogliocytoma
LRRTMs	LRRTM-1 LRRTM-2 LRRTM-3 LRRTM-4	LRRTM-1 is mainly expressed in the cerebral cortex, with widespread expression of other members.	10--TM		Probably the PDZ, binding region	Promote synapse formation, and the transport of synaptic vesicles.	schizophrenia
SALMs	SALM-1 SALM-2 SALM-3	Of various nerve cells, axons, dendrites, and growth cones.	6 1 1 TM		PDZ, bonded pad	Promote nerve growth.	not quite clear

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Table 1. (continued).

SLITRKs	SALM-4 SALM-5 SLITRK-1 SLITRK-2 SLITRK-3 SLITRK-4	SLITRK 1-5 are nervous system-specific proteins, mainly distributed in the cerebral cortex.	11 TM				Tyrosine kinase and the phosphorylation sites	SLITRK-1 promotes nerve growth, while other SLITRKs inhibit nerve growth.	Neurotic psychosis
FLRTs	SLITRK-5 SLITRK-6 FLRT-1 FLRT-2	Widely distributed in brain tissue.	10-1 TM				Unknown special domain	Promote the growth of nerve cells.	not quite clear
AMIGOs	FLRT-3 AMIGO-1 AMIGO-2 AMIGO-3	AMIGO is a brain tissue-specific protein and is mainly localized in hippocampal neurons.	6 1-TM				Unknown special domain	It promotes the growth of nerve cells, promotes the formation of axonal nerve bundles, and promotes the formation of myelin and sheath.	not quite clear
Alivins	Alivin-1 Alivin-2 Alivin-3	Widely distributed, mainly in cerebellar granule neurons and the region between CA1 and CA3 in the hippocampus.	7 1-TM				Unknown special domain	Maintain neuronal activity and antiapoptotic, the release of synaptic vesicles.	Familial Alzheimer's disease, Parkinson's syndrome
NLRR	NLRR-1 NLRR-2 NLRR-3 NLRR-4 Pal LRRC4	Widely expressed in the nervous system. Retinal-specific proteins. Relative-specific proteins of the brain tissue.	12 11 5 7	1 1 1	1 1 1 	TM TM TM TM	Clathrin-mediated conduction of the endocytic mold bodies Unknown special domain. PDZ binding domain	NLRR-3 promotes the Ras-MAPK pathway NLRR-4, is associated with hippocampal-dependent long-term memory. Light stimulation switches to neural impulses, neurotrophin receptors. Candidate tumor suppressor genes.	not quite clear Retinitis pigmentosa syndrome gliocytoma

Its expression, synchronized with the oligodendrocyte marker protein α -CNPase, contributes to the association between axons and glia and promotes myelin formation. The above examples demonstrate that LRR transmembrane proteins mainly participate in neurite growth and development as ligand-binding proteins.

3.2.3. Transfer and release of LRR transmembrane proteins with neurotransmitters. In the CNS, the most important mode of synaptic transmission is the delivery of chemical neurotransmitters. The Ca^{2+} influx is a critical factor for this process. The expression of Alivin-1 was positively correlated with Ca^{2+} influx and was significantly inhibited with the Ca^{2+} channel antagonist tetrodotoxin [7], indicating that Alivin-1 is linked to neurotransmitter release. NGL-3 binds to LAR and participates in the transport of synaptic vesicles by the liquid- α proteins interacting with the presynaptic membrane active zone proteins RIM and ELKS / ERC. LRRTM controls the release of synaptic vesicles by regulating the distribution of glutamate transporter VGLUT-1 [8].

3.2.4. LRR transmembrane proteins and other biological functions of the nervous system. Clathrin endocytosis in the cytoplasmic tail of NLRR-3 promotes the internalization process of EGF (epidermal growth factor), affects the Ras-MAPK signal pathway, and participates in the physiological activities of nerve cell growth, development and apoptosis. NLRR-4-deficient mice have severely impaired hippocampus-dependent long-term memory, while hippocampus-independent short-term and permanent memory not was affected. NLRR-4 may participate in memory conversion and storage by changing the CREB (cAMP responsive element binding protein) signal pathway. Pal is a retina-specific protein that is mainly expressed in rods and related, bipolar cells and is involved in the conversion of photo stimulation into neural impulses [9].

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3.3. LRR transmembrane proteins and neurological disorders

LRRC4 is a gene specifically expressed in brain tissue cloned from chromosome 7q31-32. Woo team in 2006 identified LRRC 4 as a ligand protein for nerve growth factor (netrin-G ligand) and named it NGL-2. The study showed that LRRC4 expression is weak or absent in gliomas. LRRC 4 protein relies on the LRC domain to inhibit ERK / AKT / NF- κB signaling, and the coordinated regulation of STAT 3 or JNK 2 / c-Jun / p53 signaling by LRC, IgC 2 and TM domains, which jointly arrest U251 cells in the G_0 / G_1 phase and inhibit the growth and invasion of U251 cells. Methylation of the promoter and interference with hsa-miR-381 may account for LRRC 4 inactivation. LRRTM is linked to paternally inherited left-handed individuals and schizophrenia. The Alivin-1 gene is situated on chromosome 12q13.11 and may be the causative gene for familial Alzheimer's disease and Parkinson's syndrome. The LRIG-1 gene is localized to chromosome 3p14, and multiple types of human tumors have loss of heterozygosity in this region and may be a potential tumor suppressor gene. Moreover, the abnormal expression of Slitrks is closely associated with the onset of neurotic psychosis.

4. Potential leucine rich-repeat sequence

Glioma is a common brain malignant tumor, and its occurrence and development are the result of the joint action of numerous genes and cytokines. It has the characteristics of fast progression, strong aggressiveness and poor differentiation, and is also the main reason for testing clinical treatment and poor prognosis of patients [10]. Studies have shown that the biological behavior of different grades of glioma is malignant. Although the treatment of glioma through surgery, the pathogenesis of glioma is complicated and the boundary with normal tissue is unclear, which can significantly affect the effect of surgical resection and the prognosis of patients. Therefore, it is important to find the pathogenic mechanisms and targets of glioma. Studies have confirmed that the emergence and development of glioma is the consequence of the cooperative action of a variety of protein genes and cytokines. Therefore, looking for molecular markers of glioma has become the current research direction of glioma.

LRR sequences participate in evolution between species and across species. LRR-containing proteins consist of tyrosine kinase receptors, cell adherence molecules, viral factors, and so on. These proteins participate in several psychological processes: signal transduction, cell adhesion, DNA repair, cell remodeling, RNA processing and transcription, cell apoptosis, innate immune response, regulation of the cell cycle, cell scaffold, enzyme inhibition, interaction between hormone receptors, etc. Numerous studies have shown that LRR proteins participate in early mammalian development, neurodevelopment, polar differentiation of cells, and the regulation of gene expression, most importantly, LRR proteins like LRRC-4 are brain tumor candidates. The L-seq showed potential clinical applications.

5. Progress in the application of the L-seq sequencing technology

5.1. Transcriptome and expression profiling

Gene expression profiles refer to all genes expressed by a cell under a given condition. Analysis of gene expression profiles is an important means to understand the molecular basis of the function of tissues or organs and the molecular mechanisms of the environment and lesions affecting organisms. Previous gene expression profiling mainly relies on gene chip technology, which relies on known gene sequences to design probes, through fluorescent labeling and hybridization, according to the intensity of fluorescence expression, large error, and cannot detect the expression of unknown genes [11]. L-seq sequencing technology can sequence all RNA in a single cell sample, that is, the entire transcriptome, and detect genes expressing 1-50,000 copies of mRNA in each cell. The technology can also detect not previously detected genes or new transcripts (transcript), and quantitatively determine the expression pattern of genes.

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5.2. miRNA analyze

Research L-seq sequencing technology has been widely used in the study of the expression of different kinds of RNAs, among which non-coding small molecule RNAs are involved in many important biological developmental processes [12]. Their sequences are very short, with only 18 – 40 nucleotides, well within the read lengths of next-generation high-throughput sequencing technologies. The L-seq sequencing method also enables the discovery of new small-molecule RNA. For example, using the analysis of next-generation sequencing of Illumina before and after their development, the expression profiles of 334 known and 104 newly discovered small RNA were obtained.

6. conclusion

In this review, we have given an account of the current understanding on the structure of LRR proteins. The LRR fold is very versatile, playing a crucial role in the development of the nervous system, and it also has some links to the development of brain tumors. The pioneering elucidation of the glioma has shown that the prognosis of glioma remains to be improved. Therefore, we discuss a new idea of classification and differential diagnosis of brain tumors by using leucine-rich sequencing (L-seq), so as to provide new ideas for clinical diagnosis and treatment. We summed up and found that the abnormal gene expression of L-seq was closely related to the malignancy of brain tumors, but its correlation with clinical prognosis needs to be further studied. We hope that this review will provide an important theoretical basis for finding the molecular markers of L-seq expression in brain tumor cells and tumor malignancy, and to realize the personalized diagnosis and treatment of brain tumors.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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