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The Role of Lama2 in Cancer: Current Perspectives

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Abstract: Laminin is a large molecular glycoprotein heterotrimer assembled from different α, β, and γ chains. In 1979, Non-collagen glycoprotein were isolated from basement membrane-rich tumors and cells that produce basement membranes and purified into laminin. The LAMA2 gene encodes the subunit of Laminin α2 and is located on chromosome 6q22-q33. Recently, new evidence has emerged that LAMA2 is involved in the biological processes of extracellular matrix (ECM) tissue and adhesions, and is related to inflammatory breast cancer (IBC), pituitary adenoma (PitNET), ovarian cancer (OC), Laryngopharyngeal squamous cell carcinoma (L/P-SCC) and many other diseases. In addition, the role of LAMA2 gene in mutation, differential expression and in terms of signal pathways in many cancers and other diseases, as well as promoter DNA methylation, all show the important regulatory role of LAMA2 in molecular biological mechanisms. The review briefly generalizes the progress in deciphering this unique molecule in recent years, including molecular structure of Lama2 gene, Lama2 gene regulation and DNA methylation, Lama2 and its protein binding partners, clinical relevance of Lama2, prospective application in diagnosis and potential therapeutic application of Lama2, and summarizes the new frontiers of Lama2 research and predicts the new prospects of Lama2 as a diagnostic and prognostic indicator of cancer and other diseases.

Keywords: Lama2, Laminin, Gene, Gene Regulation, Epigenetic, Cancer

1. Introduction

Laminin is a large-molecular-weight glycoprotein heterotrimer assembled by three disulfide-bonded polypeptides, consists of different α, β, and γ chains. In 1979, Non-collagen glycoprotein were isolated from basement membrane-rich tumors and cells that produce basement membranes and purified into laminin. The whole is arranged in a cruciform. The intersecting short arms of laminin are formed by the individually folded N-terminal regions of each α, β, and γ chain, and all three chains form the long-armed stem [1]. LAMA2 encodes laminin α2 subunit, located on chromosome 6q22-q33 [2], and is expressed in a variety of tissues, including skeletal muscle, astrocytes, brain capillary pericytes and Schwann cells [2]. This review of the LAMA2 gene aims to provide new prospects for the diagnosis, treatment and prognosis of cancers and other diseases related to Lama2 in the future.

2. Section Snippets

2.1. Lama2 Gene Regulation and DNA Methylation

Searching the previous literature, regarding LAMA2, the most is LAMA2 has been shown to be mutated in patients with congenital muscular dystrophy [3]. In addition, through targeted high-throughput sequencing (NGS) of breast tumor tissues of inflammatory breast cancer (IBC), the results showed that LAMA2 is one of the most frequently mutated genes [4]. Study by Vossen DM et al. showed that LAMA2 mutations are enriched in laryngopharyngeal squamous cell carcinoma (L/P-SCC), compared with locally advanced oral squamous cell carcinoma (OSCC) [5]. Recent studies have shown that patients with ventricular tachycardia (VT) secondary to coronary artery disease (CAD), dilated cardiomyopathy (DCM) or idiopathic causes, mutations in the LAMA2 gene predominate [6].

In addition to gene mutations, LAMA2 gene is differentially expressed and also plays an important role in the signaling pathways it participates in. A study have shown that human limbal niche cells (LNC) exhibit differential expression of LAMA2 and other genes in the extracellular matrix (ECM) receptor interaction pathway and Wnt signaling pathway from medullary mesenchymal stem cells (MMSC), indicating that LNC has its unique signaling pathway to support the limbal stem cell niche [7]. In addition, Liang J et al. showed that a new type of tumor-promoting RNA binding protein (RBP) Mex3a can promote lung adenocarcinoma cell metastasis through the PI3K/AKT signaling pathway mediated by LAMA2 [8]. In addition, a recent new study have shown that the treatment of follicle-stimulating hormone (FSH) in human umbilical vein endothelial cells (HUVEC) up-regulates the expression of LAMA2, triggers and activates the cAMP-PKA, JAK-STAT, PI3K-AKT and JNK-MAPK signaling pathway; Follicle Stimulating Hormone Receptor (FSHR) as a GPCR, its RNAi's inhibitory effect on LAMA2 attenuates the promotion of FSH on HUVEC migration [9]. Recently, expanded research has determined that LAMA2 inhibits the osteogenesis of MSCs (mesenchymal stem cells) and promotes adipogenesis by regulating the hedgehog signaling pathway [10].

The first exon of LAMA2 is full of CpG islands, which are reported to be hypermethylated in a variety of cancers, and promoter hypermethylation is usually associated with decreased expression of tumor suppressor genes [8]. Consistent with these studies, recent quantitative proteomics methods have shown that CpG methylation of the LAMA2 promoter down-regulates LAMA2 expression, while demethylation of LAMA2 affects the PTEN-PI3K/AKT signaling pathway and matrix metalloproteinase-9 (MMP- 9), which can inhibit the invasion of pituitary adenoma (PitNET) cells [11].

In general, the role of LAMA2 gene in mutation, differential expression and in terms of signal pathways in many cancers and other diseases, as well as promoter DNA methylation, all support the tumor suppressor effect of this gene, and show the important regulatory role of LAMA2 in molecular biological mechanisms.

2.2. Tissue Distribution and Subcellular Localization of Lama2 and Its Protein Binding Partners

The coordinated integration of morphogenetic signals and the proper regulation of cell adhesion and migration include ligand-receptor interactions between cells and surrounding components. LAMA2 is an important part of basement membrane, which can stabilize cell structure and promote cell migration. Integrins, dystroglycans, matriglycans, transmembrane heparan sulfate proteoglycans (Syndecans) and other cell surface molecules are the cell receptors of LAMA2. As an important function, integrins mediate bidirectional signal transduction to trigger various regulatory cascade, affecting various cellular processes, such as growth, differentiation, adhesion, migration, and apoptosis [12]. A recent study has shown that the interacting molecular set of LAMA2 genes includes integrin subunits ITGA1, ITGA2, ITGA3, ITGA4, ITGA6, ITGA7, ITGA9, ITGB1 genes, DAG1 (a dystroglycan gene), and nidogens NID1 and NID2 genes [12]. Another study showed that Dystroglycan is a receptor on muscle and nerve cells. It mainly interacts with the LG4 domain of LAMA2 in a Ca^{2+} dependent manner and uses a unique Carbohydrate modification to bind LAMA2. LAMA2 binds to glucuronic acid-xylose (a matrix glycan synthesized by a bifunctional glycosyltransferase called LARGE), whose heptasaccharide linker is linked to core protein of dystroglycan [13]. In addition, longer matriglycan chains can additionally bind to the LG4 basic residues of LAMA2 to form heparan sulfate proteoglycans. Besides, the LG1-3 region of LAMA2 has additional dystrophin binding sites [13]. Moreover, LAMA2 interacts with multiple calcium sensitive receptors (CaSR). CaSR, a prototype receptor activated by extracellular calcium, activates the MAPK and NF-κB pathways, leading to the production of pro-inflammatory cytokines IL-6 and TNF-β, which play an important role in the immune response. LAMA2 directly binds to superantigens and connects staphylococcal superantigens with CaSR type G protein-coupled receptor (GPCR) activation to enhance the activation of T cells. This mechanism helps to provide new treatment strategies for bacterial superantigen-induced diseases [14].

2.3. Clinical Relevance of Lama2

It has been reported that about half of the cells in the ovarian cortex express at least one laminin gene. LAMA2 is the laminin alpha chain that is more commonly expressed in the ovarian cortex. No xenogeneic growth substrates will be reserved by laminins that consist of lama2 on human ovarian tissue culture, which may help to further develop in vitro folliculogenesis for clinical practice [15]. The results of a recent study showed that the additive effect of the double-gene inheritance of heterozygous variants in LAMA2 and LOXL4 may lead to the onset of focal and segmental glomerulosclerosis (FSGS) in adults [16]. In addition, recent new evidence identifies that LAMA2 as an immune and locus-related gene, its high expression predicts the poor prognosis of pancreatic adenocarcinoma [17].

The mutation and differential expression of LAMA2 gene are closely related to clinical practice. A study has shown that LAMA2 is a component of the niche of the ventral midbrain (VM) midbrain dopaminergic neuron (mDA) progenitor cells. This mechanism provides a possible basis for autism-like behavior and brainstem hypoplasia in some individuals with LAMA2 mutations [18]. Recently, a study has identified and described the mutation and differential expression of LAMA2 in varicocele (VE) through bioomics for the first time, which is a new candidate gene and pathway in the occurrence and development of VE [19]. In addition, there is report showing that the basement membrane component LAMA2 is down-regulated after the dosing of cyclosporin A, which can lead to overgrowth of the gums [20]. A study has shown that LAMA2 is down-regulated in ovarian cancer (OC) tissues and is related to the progression of OC [21].

2.4. Prospective Application of Lama2 in Diagnosis

Recently, a study by Lin T et al. showed that LAMA2 is involved in the biological processes of extracellular matrix (ECM) tissue and adhesions, and may play an anti-cancer effect in HCC. Its progressive down-regulation in the liver may promote HCC occurrence or even intravenous metastasis, may be one of the potential biomarkers for the occurrence and prognosis of portal vein tumor thrombus (PVTT) in HCC patients [22]. A recent study has shown that LAMA2, mixed lineage leukemia 4 (MLL4), and plexin domain containing 2 (PLXDC2) are expressed in patients with prediabetes, but not in healthy volunteers. Further analysis shows that the combination of the three proteins is better than any single protein with greater diagnostic efficacy, it is a new and reliable serum protein marker for the diagnosis of human prediabetes [23]. In addition, Pan J et al. analyzed the proteomic analysis of fetal membranes and showed that there is a differential expression of LAMA2 between the preterm group and the term group. This molecular change in the fetal membranes provides important molecular features the premature rupture of the membranes (PPROM) in preterm labor syndrome [24]. In addition, research by Wang RQ et al. showed that the expression of LAMA2 is negatively correlated with the aggressiveness of pituitary adenoma (PitNET), and can be used as a biomarker for evaluating tumor malignancy and predicting the prognosis of PitNET patients [11]. However, more research should be conducted to confirm these results.

2.5. Potential Therapeutic Application of Lama2

Researchers have shown that pathogens penetrate the host cell barrier by attaching to extracellular matrix molecules (such as proteoglycans, laminin, and collagen), leading to the invasion of epithelial cells and endothelial cells. It has been confirmed that the invasion of cells by the human pathogen B group streptococcus, A group streptococci and staphylococcus aureus depends on the L4a domain of laminin α2 subunit. This discovery may provide new clues for the molecular pathogenesis of these bacteria and the development of new antibacterial drugs [25]. Study by Silva ME et al. showed that Lama2 acts on the resident pericytes (PC) of the central nervous system to activate oligodendrocyte progenitor cells (OPC), and OPC proliferates, migrates and differentiates into oligodendrocytes that produce myelin. Therefore, Lama2 was identified as a PC-derived factor that promotes OPC differentiation. This mechanism may pave the way for the development of new therapies for multiple sclerosis (MS) [26]. It is believed that more lama2-related therapeutic studies are underway.

Table 1. *Tissue expression of Lama2 and changes in the expression of clinically related diseases.*

Tissue	Clinically relevant diseases	Lama2 express alteration	Ref.
Skeletal muscle	Congenital muscular dystrophy	mutation	[3]
Breast	Inflammatory breast cancer (IBC)	mutation	[4]
Laryngopharyngeal	Laryngopharyngeal squamous cell carcinoma (L/P-SCC)	mutation	[5]
heart	Ventricular tachycardia (VT) secondary to coronary artery disease (CAD), dilated cardiomyopathy (DCM) or idiopathic cause	mutation	[6]
pituitary	Pituitary adenoma (PitNET)	Promoter methylation/Down regulation	[11]
Spermatic cord	Varicocele (VE)	Mutation, Differential expression	[19]
Ovary	Ovarian cancer (OC)	Down regulation	[21]

Table 2. *Lama2 interacting protein and its function.*

Identified partner	Function	Ref.
Integrin	Affect various cell processes such as cell differentiation and adhesion	[12]
Dystroglycan/ Matrix glycan/ Transmembrane heparan sulfate proteoglycan (Syndecans)	LAMA2 binds to glucuronic acid-xylose (a matrix glycan synthesized by a bifunctional glycosyltransferase called LARGE), whose heptasaccharide linker is linked to core protein of dystroglycan. Longer matriglycan chains can additionally bind to the LG4 basic residues of LAMA2 to form heparan sulfate proteoglycans.	[13]
CaSR type G protein-coupled receptor (GPCR)	Enhance the activation of T cells and affect the immune response	[14]

3. Conclusion

Overall, these findings indicate the importance of the extracellular matrix gene LAMA2 in the development of the disease and related clinical diagnosis and treatment. It will provide the basis for more LAMA2 gene-related research in the molecular biology mechanism in the future, and Lama2 gene provides new prospects for the diagnosis and prognosis of many cancers and other diseases.

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