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MEGALIN: Unveiling its Multifaceted Role in Organ Function and Disease Pathogenesis. MEGALIN STRUCTURE

Dr Namitha D[1], Dr Asharani N[2*], Dr Shilpashree Y D[3], Dr Aliya Nusrath[4], Dr Rajeshwari A[5]

[1]Associate Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

[2]Professor and HOD, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

[3]Associate Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

[4]Vice Principal & Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya- 571448.

[5]Associate Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

***Corresponding Author:** Dr Asharani N

Professor and HOD, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.ashanellore@gmail.com

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ABSTRACT

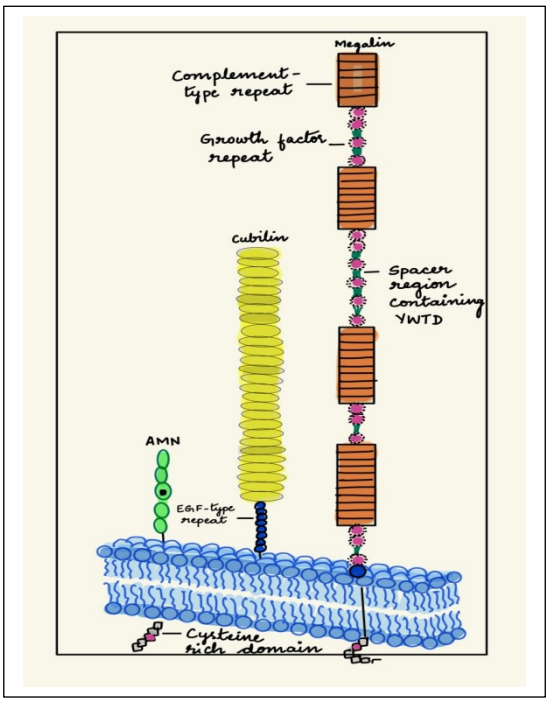
Megalin is a large transmembrane glycoprotein was discovered in early 1980s as a autoantigen in Heymann nephritis [1], and then it was characterized as a large glycosylated receptor (gp330) of 600 kDa (4655 amino acids) associating its important role in renal functions. It is also known as low-density lipoprotein receptor-related protein 2 (LRP2).[2-4] Megalin consists of a large extracellular domain, a single transmembrane domain and a short cytoplasmic tail, a member of LRP2 family of proteins. The single transmembrane domain consists of 23 amino acids, and the receptor with an intracellular C-terminal cytoplasmic tail of 209 amino acids. The cytoplasmic domain of megalin involved in regulating receptor trafficking and endocytosis. [5-7] Whereas extracellular domain consists of 4 clusters of cysteine-rich complement-type repeats that are involved in ligand binding. [8,9]

INTRODUCTION

Megalin is a large transmembrane glycoprotein was discovered in early 1980s as a autoantigen in Heymann nephritis [1], and then it was characterized as a large glycosylated receptor (gp330) of 600 kDa (4655 amino acids) associating its important role in renal functions. It is also known as low-density lipoprotein receptor-related protein 2 (LRP2).[2-4]

Megalin consists of a large extracellular domain, a single transmembrane domain and a short cytoplasmic tail, a member of LRP2 family of proteins. The single transmembrane domain consists of 23 amino acids, and the receptor with an intracellular C-terminal cytoplasmic tail of 209 amino acids. The cytoplasmic domain of megalin involved in regulating receptor trafficking and endocytosis. [5-7] Whereas extracellular domain consists of 4 clusters of cysteine-rich complement-type repeats that are involved in ligand binding. [8,9]

Megalin forms a complex with the extracellular protein cubilin in a ratio of 1:1. The ligand-binding regions and the gross structural composition of extracellular motifs of megalin are identical in humans and rats.[6]



Megalin are expressed in epithelial cells of several tissues, including apical membranes of proximal tubule, endocytic vesicles, dense apical tubules of kidney also expressed in several extrarenal, absorptive epithelia such as the choroid plexus, intestine, lung alveoli, tissues involved in maternal-to-fetal exchange, endocrine glands, sense organs and the genital system.[8]

The presence of megalin at the cell surface is regulated by multiple mechanisms. These include the phosphorylation of its cytoplasmic domain by GSK3, the proteolysis (shedding) of its extracellular domain at the cell surface, the intramembrane proteolysis of its transmembrane domain by the gamma-secretase complex, and exosome secretion. After internalization, the ligands bound to megalin are either directed to the lysosomal degradation pathway or transported by transcytosis to the opposite membrane of the cell. [10]

MEGALIN IN DEVELOPMENT

There is evidence that LRP2 plays a vital role during embryogenesis. Remarkably, LRP2 and cubilin are already expressed in 8-cell stage embryos to supply the foetus with nutrients. Throughout development, they remain important for the maintenance of normal embryonal growth. Moreover, due to its function as a receptor for signaling proteins and morphogens expression of LRP2 in the neuroepithelium is essential for proper forebrain development. Mice lacking LRP2 show specific brain and facial malformations, for example forebrain fusion resulting in one single ventricle (holoprosencephaly) and lack of the olfactory bulb. Most of these animals die perinatally from respiratory insufficiency, indicating a vital role during respiratory tract development. Additionally, LRP2 contributes to the development of reproductive organs, primarily by uptake and delivery of carrier-bound sex steroids in target tissues. Despite its important function in renal filtration, it is dispensable for murine kidney development.[11]

MEGALIN FUNCTIONS

Megalin plays a pivotal role in the endocytosis of diverse glomerular-filtered substances into PTECs, allowing it to bind >40 different ligands.[12] Megalin along with cubilin are involved in the endocytic uptake of ligands including nutrients, lipoproteins, vitamin-binding proteins and iron-carriers, hormones and their carrier proteins, insulin, leptin, angiotensin II signaling molecules, morphogens, and extracellular matrix proteins including, other carrier proteins, hormones, enzymes and drugs in several epithelia. The receptors might work independently, but have also been shown to interact to facilitate the uptake of several ligands. [10]

Furthermore, several urinary biomarkers filtered by glomeruli such as α1-microglobulin [α1-MG], ß2-microglobulin [ß2-MG], liver-type fatty acid-binding protein, neutrophil gelatinase associated lipocalin are known endocytic ligands of megalin.[13,14]

In healthy conditions, proximal tubule epithelial cells (PTECs) reabsorb nearly all serum proteins from the ultrafiltrate via the combined effort of megalin (LRP2) and cubilin (CUBN). These receptor proteins form a complex at the PTEC brush border where either member can independently bind to a number of substrates. [15]

Megalin expression and trafficking are likely implicated in diseases that affect the functioning of organs such as the kidneys, brain, mammary glands, thyroid, and gallbladder. Furthermore, megalin ligands such as vitamin D binding protein (VDBP), albumin, insulin, and angiotensin II are associated with pathological conditions like diabetes, hypertension, and obesity. These disease-related conditions can severely impair megalin expression, leading to common features such as low molecular weight proteinuria and albuminuria.[16]

ROLE OF MEGALIN IN LIPID METABOLISM

Megalin also plays a significant role as a lipoprotein receptor involved in cholesterol transport, particularly evident during development in conjunction with its coreceptor cubilin. Besides apoE, megalin serves as the receptor for apoJ/clusterin, which is associated with HDL particles, as well as for Lp(a), an atherogenic particle. Apolipoprotein M, a lipocalin with antiatherogenic properties, is found in pre-ß-HDL particles, chylomicrons, VLDLs, and LDLs secreted by the liver and kidney, all of which use megalin as a receptor. In addition to apoM, megalin, along with cubilin, internalizes apoA-I and apoA-II, the structural components of HDLs. This highlights megalin's role in regulating HDL metabolism. [17]

Mii et al, reported that plasma cholesterol levels and LDL cholesterol have been associated with genetic variations in the megalin gene in the Japanese population, further suggesting that this receptor has a systemic function in cholesterol homeostasis. [18]

Nielsen R et al, in their study showed the Receptor gene knockout animal models have identified important functions of the receptors and have established their essential role in modulating urinary protein excretion in disease conditions such as chronic kidney disease, diabetes, and hypertension. [15]

ROLE OF MEGALIN IN DIABETES MELLITUS

Regulation of glucose homeostasis: Megalin is involved in the reabsorption of several proteins and hormones, including insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding

proteins (IGFBPs). IGF-1 is related to insulin and plays a role in glucose metabolism. Megalin's function in reabsorbing these molecules can indirectly influence insulin signaling and glucose homeostasis.[19] Impaired metabolism of these bioactive proteins in proximal tubule cells may lead to compensatory cellular hypertrophy and sustained Na+ reabsorption, causing systemic hypertension and glomerular hyperfiltration.[20] This suggests that megalin-mediated metabolic overload in proximal tubule cells may contribute to the pathogenesis of diabetes mellitus.[21]

Diabetes is associated with chronic low-grade inflammation and oxidative stress. Megalin has been implicated in the regulation of inflammatory processes and the handling of oxidative stress. Deregulations of megalin in the kidneys can contribute to inflammation and oxidative damage, which are associated with diabetes complications.

In diabetes, Advanced glycation end products (AGE) generation is increased, and the handling mechanisms in PTC are likely associated with the pathogenesis of tubulointerstitial injury. A number of studies have indicated that AGE are associated with PTC injury. [22-24]

A study by Saito A et al, performed AGE uptake analysis using the rat yolk sac-derived L2 cell line system suggested that megalin is also involved in the endocytosis of AGE in PTC and could thus be a therapeutic molecular target for preventing AGE accumulation in the cells. [25]

Thrailkill KM et al, have demonstrated decreased megalin and cubilin expression in animals with type 1 diabetes mellitus (T1DM) and these reports have led investigators to propose that this reduction leads to less proximal tubular protein reabsorption and contributes to proteinuria in Diabetic Nephropathy. [26]

ROLE OF MEGALIN IN RENIN-ANGIOTENSIN SYSTEM HOMEOSTASIS

Megalin participates in the reabsorption of renin in the proximal tubules of the kidneys. By reabsorbing renin, megalin helps control the availability of renin in the circulation, which, in turn, influences the rate at which angiotensinogen is converted into angiotensin I. Megalin also contributes to the reabsorption of angiotensinogen in the proximal tubules of the kidneys. By reabsorbing angiotensinogen, megalin helps control the amount of angiotensinogen that is excreted in the urine. This, in turn, affects the availability of angiotensinogen for renin-mediated conversion into angiotensin I.

The mechanisms underlying megalin down regulation in pathological conditions are not known, but they could be related to the activation of the renin-angiotensin system, increased TGFß signaling and increased albumin overload in the lumen of the PT.[16]

Megalin-mediated renin reabsorption amounts to ≈95%. Consequently, even small variations in megalin may cause great variation in urinary renin levels for a given plasma renin level, thus explaining why plasma and urinary renin are often unrelated. Ang II (angiotensin II) negatively regulates megalin expression at both the mRNA and protein levels through its type 1 receptor. [27,28]

ROLE OF MEGALIN IN VITAMIN D HOMEOSTASIS

Megalin is an endocytic receptor that plays a crucial role in vitamin D homeostasis. It is abundantly expressed in various cells, including proximal tubular epithelial cells, bone cells, and parathyroid cells. [29,30] Megalin facilitates the uptake of the vitamin D-binding protein (DBP) complexed to 25-hydroxyvitamin D3 (25(OH)D3) and promotes the intracellular conversion of precursor 25(OH)D3 to the active form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3).[31] This receptor is involved in the reabsorption of 25(OH)D3 and 1,25(OH)2D3 in the kidneys, as well as in regulating vitamin D homeostasis in other tissues such as mammary cells, fat, muscle, and mesenchymal stem cells.[32] Megalin also has potential cross-talk with calcium signaling in the parathyroid gland.[33] Furthermore, megalin is required for the actions of 25(OH)D3 and 1,25(OH)2D3 in human mesenchymal stem cells, including osteoblast differentiation and biosynthesis of 1,25(OH)2D3 . Additionally, megalin is also involved in the reabsorption of retinol-binding protein (RBP) and vitamin D-binding protein (VDBP) . The expression of megalin increases during kidney development, and its abundance in the kidney is inversely correlated with the urinary loss of vitamin carriers in preterm infants. Overall, megalin plays a crucial role in the absorption and reabsorption of vitamin D and its carriers, contributing to vitamin D homeostasis.

Elsabbagh RA et al studied the association of megalin and cubilin genetic variants with serum levels of 25-hydroxvitamin D and the incidence of acute coronary syndrome in Egyptian population (n=185, 27-60 years). This study reported that megalin (rs2075252 and rs4668123) and cubilin (rs1801222 and rs12766939) are associated with a higher ACS incidence, further multivariate analysis showed megalin rs4668123 SNP as independent ACS risk factor. [34]

ROLE OF INSULIN IN MEGALIN EXPRESSION

PI3K and Akt are pivotal in initiating insulin signaling, orchestrating various cellular processes such as proliferation and glucose uptake. mTOR, a serine/threonine kinase, is integral to two complexes, mTORC1 and mTORC2, each serving distinct functions. mTORC1 regulates protein synthesis and cell growth when activated by insulin signaling through PI3K and Akt, while mTORC2, located at the plasma membrane, fully activates Akt. Insulin initiates a dynamic signaling cascade where class I PI3K elevates intracellular PIP3 levels, leading to the translocation and activation of Akt. Upon insulin binding to its receptor, a signaling cascade is triggered via IRS, activating PI3K, which converts PIP2 to PIP3. The elevated PIP3 levels prompt Akt to translocate to the plasma membrane, where PDK1 phosphorylates it at Thr308, and mTORC2 phosphorylates it at Ser473. The fully activated Akt then triggers signals that lead to mTORC1 activation. mTORC1's downstream effector, p70S6K, provides negative feedback at IRS, halting further signal transduction. Additionally, Akt interacts with Dab2, a megalin-associated protein, enhancing endocytosis in certain cells. Overall, fully active Akt, phosphorylated at both Thr308 and Ser473, emerges as a principal mediator of the increased megalin expression following insulin treatment.[35]

CONCLUSION

Megalin, also referred to as low-density lipoprotein receptor-related protein 2 (LRP2), is a large protein pivotal in endocytosis, notably within the kidneys and other epithelial cells, facilitating the reabsorption of diverse substances—such as proteins, vitamins, and hormones—from the renal filtrate back into circulation. Predominantly located in the proximal tubules of the kidneys, megalin forms a complex with cubilin, orchestrating the retrieval of filtered proteins (e.g., albumin), vitamins (e.g., vitamin D-binding protein), and hormones (e.g., insulin-like growth factor 1). This process is vital for upholding bodily homeostasis by averting the loss of essential substances through urine. Megalin also exhibits presence in various tissues, including the brain, where it participates in transporting select molecules across the blood-brain barrier. Dysfunctions or alterations in megalin can significantly impact physiological processes, particularly those related to renal function and the central nervous system. Comprehending megalin's role in these diseased conditions is crucial for devising potential therapeutic strategies and diagnostic approaches aimed at alleviating associated complications and enhancing patient outcomes.

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