Pathophysiology of protein and vitamin handling in the proximal tubule

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Abstract

The two membrane receptors megalin and cubilin are highly expressed in the endocytic pathway of the renal proximal tubule. Numerous ligands have been identified, and these receptors appear to be the main players responsible for the tubular clearance of proteins filtered in the glomeruli. Cubilin does not have an endocytosis signalling sequence and, since it binds to megalin, it appears that megalin in addition to internalizing its own ligands is also responsible for internalization of cubilin and its ligands. The importance of the receptors is underscored by the proteinuria observed in megalin-deficient mice and in dogs lacking functional cubilin.

Keywords: cubilin; megalin; proximal tubule; receptors

The molecular events responsible for the very efficient renal tubular clearance of protein have been largely unknown until recently. However, within the last few years, two multiligand, endocytic receptors, megalin and cubilin, have turned out to be extremely central for the reabsorption of protein in the renal proximal tubule. The two receptors are co-localized and heavily expressed in the brush border and the apical endocytic apparatus (Figure 1) consisting of coated pits and vesicles, endosomes, dense apical tubules and lysosomes [1]. Megalin, previously named gp330, is a 600 kDa transmembrane protein belonging to the low-density lipoprotein (LDL) receptor family [2]. The complete cDNA sequences have been characterized for rat [3] and human megalin [4]. The cytoplasmic tail contains three NPXY motifs which mediate the clustering in coated pits. These and other cytoplasmic motifs are possibly involved in signalling functions. The extracellular domain contains four cysteine-rich, complement-type repeats, probably constituting the ligand-binding regions. Cubilin, also known as the intestinal intrinsic factor cobalamin receptor, is a 460 kDa receptor with no transmembrane domain and no known signal for endocytosis. The complete cDNA sequences have been identified for rat [5], human [6] and canine cubilin [7]. Cubilin contains 27 CUB domains responsible for the ligand binding and eight epidermal growth factor (EGF)-type repeats preceded by a stretch of 110 amino acids, where the N-terminal region appears essential for membrane anchoring. The two receptors bind each other with high affinity [5] and co-localize in several tissues, and it is therefore highly conceivable that megalin mediates internalization of cubilin and its ligands.

While megalin is expressed in many epithelial cells, at present it appears that the expression of cubilin is more restricted [1]. The two receptors are co-localized in the proximal tubule, the small intestine, the visceral yolk sac and the cytotoxic blast of the placenta. Megalin, in addition, has been demonstrated in glomerular podocytes, type II pneumocytes, thyroid and parathyroid cells, the choroid plexus, the endometrium, the oviduct, epididymis, ependymal cells, labyrinthic cells of the inner ear and the ciliary epithelium of the eye.

Both receptors are important for normal reabsorption of proteins in the renal proximal tubule. Among the proteins normally filtered in the glomeruli, cubilin has been shown to bind albumin [8], transferrin [9], immunoglobulin light chains [10] and apolipoprotein A-I [11,12]. The variety of filtered ligands identified for megalin include transcobalamin–vitamin B12 [13], 25-(OH) vitamin D3 [14], retinol-binding protein vitamin A [15], hormones, enzymes, apolipoprotein H [16], albumin [17], β2γ [18] and α1-microglobulin [19], transthyretin [20] and α-amylase [21]. The ligand binding is Ca²⁺ dependent, and calcium itself binds strongly to megalin [22].

Several of the ligands have been found using megalin-deficient mice [23] or dogs lacking functional cubilin [24]. Lack of proximal tubular accumulation of these proteins and vitamins and their loss in the urine of...
megalin-deficient mice and cubilin-deficient dogs illustrate the physiological importance of these receptors. Megalin- and cubilin-deficient mice and the cubilin-deficient dogs will be important tools for studying tubular and interstitial lesions induced by proteins and other substances reabsorbed by the proximal tubule.

References

2. Rajchowdhury R, Niles JL, McCluskey RT, Smith JA. Autoimmune target in Heymann nephritis is a glycoprotein with homology to the LDL receptor. Science 1989; 244: 1163–1165