

The unfolding story of megalin (gp330): now recognized as a drug receptor.

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Editorial

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In this issue of *The Journal* Moestrup et al. (1) report that polybasic drugs such as aprotinin, aminoglycosides, and polymyxin B are taken up by the endocytic receptor, megalin/gp330. Antibiotics such as gentamycin and polymyxin B are well known to be both nephrotoxic and ototoxic, but the mechanisms by which these drugs become concentrated in lysosomes of the kidney and ear to produce tissue damage remain unknown. This carefully executed study demonstrates that they bind to megalin/gp330 both in vitro and in vivo and are taken up by receptor-mediated endocytosis in clathrin-coated pits. Thus, Moestrup et al. (1) provide a clear explanation of the molecular mechanisms by which the kidney and probably also the ear take up and concentrate these toxic, polybasic drugs. At the same time the authors have added another dimension, a pathologic dimension, to the story of megalin (gp330) by showing that it serves as a drug receptor.

What is megalin/gp330? gp330 (megalin) is one of the most abundant membrane proteins in the renal proximal tubule. It was originally identified as the target antigen of Heymann nephritis, a rat model of membranous glomerulonephritis (2, 3). Its location in clathrin-coated pits suggested from the beginning that gp330 is an endocytic receptor (3, 4). In addition to its expression in glomerular and proximal tubule epithelia, this receptor is expressed in a number of epithelia that are heavily engaged in receptor-mediated endocytosis, including type II cells of the lung and epithelial cells of the inner ear, epididymis, mammary gland, thyroid, parathyroid, yolk sac, and retina (5). Interest in this molecule was greatly enhanced when Raychowdhury et al. (6) obtained and sequenced a partial cDNA clone which clearly established that gp330 is a member of the LDL receptor gene family (7). The complete amino acid sequence was obtained only recently (8), and this receptor was found to possess all the structural motifs characteristic of the LDL receptor family, including ligand binding, growth factor and EGF repeats, YWTD spacer regions, and the consensus (FX)NPXY endocytic internalization signal. Structurally it is quite similar to the LDL receptor related protein/ α_2 -macroglobulin receptor (LRP), another LDL receptor family member. Based on its large size (517,715 mol wt) which proved to be larger than originally anticipated the name "megalin" was introduced as an alternative to gp330 (8).

Ligands that bind to megalin/gp330. In the meantime the search for its ligands has identified a surprisingly diverse group of molecules that are capable of binding to megalin/gp330 in vitro: RAP (receptor-associated protein), apoE-enriched β VLDL, lipoprotein lipase, plasminogen, tPA:PAI-1, and uPA:PAI-1 complexes, Ca^{2+} (for review see reference 9), and, most recently, clusterin/apolipoprotein J (10). All of these ligands except plasminogen and clusterin also bind to LRP. RAP has the interesting property that it prevents binding of ligands to both megalin (gp330) (11) and LRP. RAP (as well as megalin/gp330) also serves as a pathogenic antigen in Heymann's nephritis (12).

Little is known at present concerning the features of the ligands or megalin that lead to these diverse interactions. Moestrup et al. (1) provide an important insight into this problem by demonstrating the importance of charge interactions. Using recombinant aprotinin mutants these authors show that basic residues are crucial for binding and uptake. As a bonus these observations also point the way to rational design of antibiotics which remain effective in fighting infections with Gram-negative bacteria but are not taken up by endocytosis thus reducing the severe side effects on the kidney and ear.

Little is known either about the major functions of megalin in vivo where the receptors typically face specialized milieu such as the glomerular filtrate, airways, epididymal fluid, thyroid colloid, and yolk sac fluid, which are not expected to contain many of the above ligands. The paper by Moestrup et al. (1) provides an important new insight into the properties of megalin. Given the diverse interactions of this receptor there can be little doubt that there are still many more intriguing chapters to come as the biology and pathology of this receptor continue to unfold.

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