An insight into epithelial cells through rare disorders

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Disorders of amino acid transport have been very influential in the elucidation of amino acid absorption in the kidney and intestine. Molecular identification of the transport systems mutated in these disorders highlights the complexity of amino acid transport and demonstrates its links to more complex pathologies such as blood pressure regulation and epithelial cell differentiation. Hartnup disorder is an autosomal recessive disorder. Analysis in 17 families up to now confirms that SLC6A19 is the only gene involved in the disorder. A variety of alleles have been identified, of which only one (R240Q) did not abolish transport. This allele could be clarified after the discovery that SLC6A19 requires one of the two auxiliary proteins collectrin or ACE2 for surface expression. Collectrin is predominantly found in the kidney, whereas ACE2 is found predominantly in the intestine. The association of SLC6A19 with two different proteins in kidney and intestine offers an explanation for Hartnup disorder variants that affect only renal or only intestinal amino acid transport. Coexpression of SLC6A19(R240Q) with ACE2 or collectrin shows reduced transport activity, thereby explaining the onset of Hartnup disorder in individuals with this allele. Iminoglycinuria (IG) was first described fifty years ago as an autosomal recessive abnormality of renal transport of glycine and of the imino acids, proline and hydroxyproline. Hyperglycinuria (HG) has been attributed to heterozygosity of a putative defective glycine, proline and hydroxyproline transporter. Unconfirmed associations have been reported with hypertension, glycosuria, nephrolithiasis, and various neurological diseases. A candidate gene sequencing approach was applied in seven families first identified through newborn screening programs. Electrophysiological studies and a molecular splicing assay were used to demonstrate aberrant transporter function in affected families. Mislocalization of mutant aminoacid transporters and their normal physiological distribution was defined by immunofluorescence. We identified a common proline and glycine transporter as the major responsible gene and demonstrate consistent inheritance and functional studies. In some of the pedigrees the observed mutations of this transporter retained residual transport activity. In those cases the urinary phenotypes were modified by additional mutations in additional proline and glycine transporters. The model consistent with the observed pattern of inheritance is classical semi-dominant inheritance in which two inherited non-functional alleles of the major gene conferred the complete IG phenotype whereas one non-functional allele was sufficient to confer the HG phenotype. Despite the apparently simple urinary phenotypes of IG and HG, this study has revealed unexpected multigenic complexity as an explanation for the observed reduced penetrance. The contributions of mutations in multiple transporters in these discrete phenotypes provide a model for dissecting the molecular etiology of a major gene modified by genes with related functionalities.