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Regulation of Amino Acid Transport System

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The transport of amino acid across the plasma membranes of mammalian cells is a process of fundamental physiological importance and has been the object of extensive study. The characteristics, kinetics and regulation of various transport systems have been understood in general terms for many years, but until recently little was known about the structure and molecular properties of amino acid transport proteins.

For the past 30 years, the field of mammalian amino acid transporter biology has relied on functional characteristics to distinguish between specific transporters, an effort largely initiated and advanced by Christensen and colleagues in the 1960s using radiolabeled amino acids and amino acid analogs. Among these functional characteristics are substrate specificity, kinetic and regulatory properties, ion dependence and pH sensitivity. On the basis of these characteristics, a classification of the discriminated activities termed "systems" was developed. In general, the transporters known as System A and System ASC are responsible for Na+ dependent concentrative uptake of aliphatic neutral amino acids in most cell types, while System L is responsible for the Na+ independent uptake mainly of branched chain and aromatic amino acids. In epithelial brush borders, these three systems are less important, and a broad specificity system termed System B is responsible for the Na+ dependent uptake of branched chain, aromatic and aliphatic neutral amino acids. Basic amino acids are transported on a separate system termed System y+, while acidic amino acids are transported mainly by System X^{-}_{AG}. Both these systems are widely distributed. In some cell types, two additional broad specificity systems occur. These are the Na+ dependent System $B^{0,+}$ and the Na+ independent System $b^{0,+}$ both of which catalyse the transport of both neutral and basic amino acids. This list of transporters is not exhaustive and several other transport activities have been identified in particular tissues. The above nomenclature for amino acid transporters has been based on their kinetically determined amino acid specificity; very little is known at present about the actual molecular bases for this specificity

In cases where the transport protein cannot be identified directly, the technique of expression cloning has been employed to isolate cDNA clones encoding the transporter.
The first mammalian amino acid transport system to be identified was System y+ (now called cationic amino acid transporter 1 or CAT1), which was found to be identical with the mouse ecotropic virus receptor. This was soon followed by the isolation and sequencing of

a number of other clones encoding amino acid transporters. The amino acid transporters cloned can be grouped in four protein families: 1) the family of sodium-independent cationic amino acid transporters(CAT); 2) superfamily of sodium- and chloride-dependent, neurotransmitter transporters, which includes amino acid transporters; 3) the superfamily of sodium-dependent, and in some cases potassium-dependent, anionic or zwitterionic amino acid transporters; and 4) putative subunits of sodium-independent cationic and zwitterionic amino acid transporters. Not all these clones can yet be identified with the kinetically defined transport systems. In particular no clones corresponding to the important transport activities known as System A and System B have yet been isolated. In addition, the role of certain 'transport-activator' protein is still unclear.

A particular feature of certain amino acid transporters is that their expression in cells is highly regulated by a number of factors including hormones, growth factors and hyperosmotic medium and by amino acid deprivation. The molecular mechanisms involved in this regulation are only just beginning to be understood and are of considerable interest.

The study of inherited pathology due to defective amino acid transport in the plasma membrane of human cells has been give a new impetus. The molecular basis for tissue and development dependent expression of transporters and their regulation will be of importance in the elucidation of the probable role of amino acid transport systems in many pathophysiological conditions, such as neoplasia and amino aciduria.