Molecular pathology and therapy in heterogenic and multigenic diseases

Our research efforts focus on the molecular bases of renal reabsorption of amino acids, the physiopathology of the inherited aminoacidurias cystinuria and lysinuric protein intolerance (LPI), the structure-function relationship in heteromeric amino acid transporters (HATs) and the study of the multiple functions of heavy chains of HATs. With regards to the molecular bases of renal reabsorption of amino acids, we address the generation and characterisation of mutated mouse models of renal amino acid transporters. In the physiopathology of inherited aminoacidurias, our goal is to develop animal models to study the impact of several renal amino acid transporters on cystinuria; to identify mechanisms of pathology in this inherited disorder; to search for new drugs for the treatment of lithiasis in cystinuria; and to generate and characterise a mouse model for LPI. Finally, our group works towards developing the 3D structure of HATs, using both human transporters and prokaryotic homologues.

The molecular bases of renal reabsorption of amino acids

Our laboratory has identified three amino acid transporters involved in the renal reabsorption of amino acids: systems b₀⁺ (heterodimer rBAT-b₀⁺AT), y⁺L (heterodimer 4F2hc-y⁺LAT1) and exchanger L (heterodimer 4F2hc-LAT2). We also demonstrated the role of systems b₀⁺ and y⁺L in cystinuria and LPI. This has allowed us to propose a mechanism of reabsorption in which these amino acid exchangers participate. This model requires basolateral transporters with a net flux of neutral amino acids. The search for these transporters is done mainly with functional studies of orphan transporters within the described amino acid transporter families. Characterisation of mutated mouse models of LAT2 and EEG1 might shed light on this issue. Moreover, in collaboration with Paolo Gasparini, we are studying whether there is an association between amino acid transporter polymorphisms and renal reabsorption of amino acids in genetically isolated human populations. This activity was initiated within the European Union project EUGINDAT.

Physiopathology of inherited aminoacidurias cystinuria and lysinuric protein intolerance (LPI)

Our laboratory has identified the genes involved in cystinuria (system b₀⁺; heterodimer rBAT-b₀⁺AT) and LPI (system y⁺L; heterodimer 4F2hc-y⁺LAT1), and within the International Cystinuria Consortium, which we founded, we have identified most of the mutations causing these diseases. We have established a wide genotype-phenotype correlation in cystinuria that has allowed us to propose a new classification of the disease: type A, caused by SLC3A1 mutations, and type B, caused by SLC7A9 mutations. The objectives that we are currently pursuing are: a) the identification of molecular mechanisms to explain the distinct phenotypes in cystinuria, using animal and cell models; b) the identification of modulator genes of lithiasis in cystinuria, using animal models; c) the search for new drugs to treat lithiasis in cystinuria, using our murine cystinuria model Stones; and d) the identification of the mechanisms that lead to alveolar proteinosis in LPI, using a newly generated LPI mouse model.

Structure-function relationship in heteromeric amino acid transporters (HATs)

Our laboratory has identified most of the members of the heteromeric amino acid transporters (HATs). Moreover, we have approached the structure-function relationships of HATs by defining: the oligomeric state of HATs, the atomic structure of the ectodomain of 4F2hc (CD98hc) (in collaboration with IRB Barcelona researcher Ignasi Fita), the light subunit as the catalytic component, the membrane topology of the light subunits and the key residues for transport. At present we are developing the 3D structure of prokaryotic homologues of the light subunits with Dimitrios Fotiadis (University of Bern) and within the
European Union project EDICT (European Drug Initiative on Channels and Transporters). Functional studies in parallel seek to identify key residues for amino acid transport function within HATs.

Study of the multiple functions of heavy chains of HATs

One of the heavy subunits of HATs identified, 4F2hc (CD98), is involved in many cellular functions such as cellular transformation, adhesion and fusion. Very recently we have developed the 3D structure of the extracellular domain of 4F2hc (PDB 1Y4N and 1Y5Z). This allows us to study the role of the extracellular domain of 4F2hc in its multiple functions, including interaction with β1 integrins. Moreover, the recombinant extracellular domain of 4F2hc is a powerful tool for the identification of potential ligands of 4F2hc.

Publications


**Research Networks and Grants**

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**Research Director:** Manuel Palacín

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**Research Director:** Peter Henderson

**Group Leader:** Manuel Palacín

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**Research Director:** Manuel Palacín

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