Towards the molecular mechanism of the *E.coli* exchanger AdiC

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AdiC is an exchanger used by enteric bacteria, like *E. coli,* to survive to extreme acidic conditions in the host stomach to further establish several types of gastrointestinal infections [1]. AdiC forms a homodimer in the plasma membrane exchanging extracellular Arg^{1+} by intracellular Agm^{2+}, in this process one proton is consumed increasing the internal pH of bacteria to 4.7 [2, 3]. Additionally, AdiC shares about 18% of identity with the light subunits of the eukaryotic L-Amino acid Transporters (LATs). LATs form with a heavy subunit (rBAT or 4F2hc) the Heteromeric Amino acid Transporters (HATs), which are involved in human pathologies like inherited aminoacidurias, tumor growth and invasion, viral infection and cocaine addiction [4]. AdiC and LATs belongs to the amino acid/polyamine/organocation (APC) superfamily of transporters, and structure-function studies suggest that AdiC and LATs share the LeuT-fold, characteristic of several transporter families [5, 6]. In these transporters, the internal pseudo two-fold symmetry dictates the conformational changes during the transport cycle [7, 8]. AdiC structure has been solved facing outwards: without substrate [9, 10], with substrate bound (mutant N101A) [11], and with substrate occluded (mutant N22A) [12], bringing insights about the substrate-induced fitting mechanism of AdiC. However the complete mechanism of transport (e.g., translocation) remains unknown because crystal structures of the inward-facing states are missing. In this regard, it is fundamental to solve inward-facing structures of AdiC. Thus the objective of this project is to solve the crystal structure of AdiC in inward-facing conformation. Guide by the outward-facing structural data and the inward-facing models of AdiC, we have been using point mutation as a strategy to stabilize the transporter facing inward. I have been crystalizing AdiC mutants designed to try to weaken the interaction of the substrate in the outward binding site or to strengthen the interaction in the inward binding site.

References

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