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Structure and mode of action of chagasin, a protease inhibitor from *T. cruzi*

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Chagasin, expressed by the parasite *Trypanosoma cruzi*, the pathogen of Chagas disease, is a potent inhibitor of papain-like cysteine proteases. It can control the activity of both endogenous (cruzipain) and host (cathepsins) enzymes. The structure of recombinant chagasin in free form and in complex with a variant of human cathepsin L reveals both the novel fold of this protein and novel mode of enzyme inhibition. In terms of the folding pattern, chagasin, together with the recently determined NMR structure of a related inhibitor from *Leishmania*, defines a new structural family, with some resemblance to immunoglobulin domain, which can be described as a distorted jelly-roll barrel with an intrusion of an N-terminal (-hairpin in parallel orientation to the neighboring strands. This folding pattern has no analogy to any of the known classes of cysteine protease inhibitors, such as cystatins or staphopains. In this topology, three loops aligned at one edge of the molecule are inserted into the catalytic cleft of cathepsin L. This ″three-prong″ inhibition mode resembles somewhat that of cystatins, but the topology of the three elements forming the epitope is entirely different, and the inhibitor molecule approaches the enzyme from a different angle. The inhibition mode of chagasin is also very different from that of staphostatin, which uses one long β-strand to span the entire length of the catalytic cleft of the enzyme in a substrate-like fashion.

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Structure of the class D β-lactamase OXA-29, a different carbonated dimer

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The most widespread resistance mechanism developed by bacteria to fight β-lactam antibiotics is the expression of enzymes capable of degrading them. We present here the crystal structure of such enzyme, the class D β-lactamase OXA-29 at 2.3Å resolution. Like the other enzymes of this class, OXA-29 is characterized by a carbonated lysine in the first of the three conserved motif characteristic of the Penicillin Recognizing Proteins (PRP). OXA-29 is only found as a dimer while OXA-1, its closest related protein with a known structure is always monomeric. The stability of the OXA-29 dimer is mostly provided by extended hydrophobic interactions and no cation are found at the dimer interface. Surprisingly the dimer formed by OXA-29 is significantly different from the one of OXA-2 and OXA-10 enzymes, raising the question of a specific Role for the dimerization in that class of β-lactamases.