Conference

Closing or opening proteasome doors by porphyrins.

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The role of proteasome in the regulation of all cellular functions, is so relevant that its modulation became a useful therapeutic strategy for a large variety of diseases.[1] Besides the potential clinical usefulness, proteasome regulators provide interesting and important tools for cell and molecular studies. Some years ago we have proposed cationic porphyrins as a new class of proteasome inhibitors,[2] extending a new regulatory function to the broad-spectrum activities of these "multi-purpose" molecules. The external face of the 20S CP, the α ring, has its own regulation system consisting of dynamic gate that constantly switches between closed and open state. These physiological receptorial regions of canonical regulatory particles are characterized by a regular arrangement of charged aminoacids that represent a sort of "electrostatic code" regulating the "state" of the gate; the peripheral porphyrin charges represent a key able to interfere with the gate "door lock".[3] Thus, porphyrins behave as gatekeepers of 20S CP,[4] either inducing a partial gate occlusion (e.g., H_2T4) or allosterically, triggering a conformational change that affect the open-closed equilibrium (e.g., pTMPyPP4).[3] Finally, in the case of tricationic porphyrin Tris-T4, 20S CP activation has been observed, as the result of a new proteasome functional state characterized by a much higher substrate affinity and a higher catalytic efficiency. According to our hypothesis, supported by NMR and computational data, the h20S activation observed upon Tris-T4 binding, might simulate to some extent the allosteric activation by regulatory proteins. These results coupled with porphyrin's versatile chemistry, position porphyrins as a novel class of CP conformational modulators of proteasome with a significant pharmacological potential.

References

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