Clues for innovative therapies targeting the c-ring of the F1FO-ATP synthase

Increasing evidence points out that the ATP synthase/hydrolase, also known as F_1F_O-complex, can be the key enzymatic switch between cell life and death. So, the enzyme complex, which bears the task of building most cellular ATP, the energy currency of the cell, in organisms from bacteria to humans, has awaken increasing interest in pharmacology, leading to think that its quenching in selected cells could be extremely useful in therapy to fight worrisome human diseases. An emerging pharmacological challenge is to exploit the slightly different functional and structural properties of the enzyme complex in different organisms, as well the chemical modulation of its functionality, to selectively kill noxious cells. This strategy may be extremely useful to treat diseases resistant to traditional therapies or based on mitochondrial dysfunctions, which could be potentially overcome by chemical manipulations. Within the enzyme complex multisubunit structure, the *c*-ring, a polymeric cylinder embedded in the membrane enzyme portion, seems the master player of the whole catalytic machinery which builds and destroys ATP. As a matter of fact the *c*-ring is able to clockwise or counterclockwise rotate, according to the direction of protons across the membrane. So, if it does not work, catalysis is prevented. Due to its key role, the *c*-ring becomes a sort of Achille's heel of the enzyme complex, and, consequently, one of the most suitable protein structures to be targeted by drugs. In this perspective, selected compounds which may be also helpful in drug design are considered. The *c*-ring can bind a number of natural macrolide antibiotics, produced by bacterial fermentation and structurally related to the classical F_1F_O inhibitor oligomycin. These structurally akin compounds block the enzyme through a mechanism which strictly mimics that of oligomycin, which prevent the proton flux through the membrane which drives catalysis.

All the macrolides tested, bafilomycin, venturicidin and oligomycin bind to the same binding region of the enzyme. The inhibition potency depends both on the compound structure and the protein target, since the strength of the binding depends on the chemical interactions which can be established between the inhibitor and the protein. Other than macrolides, which differently modulate the F_1F_O-complexes depending on their structure, also some man-made compounds such as some diarylquinolines (bedaquiline) and organotin compounds (tributyltin) bind to the *c*-ring and modulate the enzyme activity. The attractiveness of the *c*-ring as a drug target is shouldered by its structural plasticity. The most recent advances suggest that the drug effects on the enzyme complex could be manipulated not only by aminoacid substitutions (mutations) but also by chemical (post-translational) modifications of *c*-subunits. Drugs targeting the *c*-ring could act as antiproliferative agents by blocking the enzyme of life in selected cells, thus disclosing new potentialities to fight cancer and infections sustained by therapeutically recalcitrant microorganisms. Additionally, compounds which selectively block the microbial *c*-ring may also represent innovative tools to eradicate undesired biofilms which cannot be removed in other ways. Finally, drugs targeting the *c*-ring may address at the molecular level the therapy of mammalian diseases related to mitochondrial dysfunctions. Accordingly, in the future, it seems not impossible

to chemically inactivate changes in crucial amino acids associated with a decreased or defective functionality of the F_1F_O-complex in order to improve or recover the enzyme function.

Taken as a whole, the insights up to now available and the deepening of studies on the molecular interactions within the *c*-ring of the F_1F_O-complex may renew hope to counteract diseases insufficiently susceptive to the existing therapies. At the moment therapies based on the *c*-ring manipulation and/or on the use of new *c*-ring-targeting drugs prevalently remain a dream, but promising clues exist which may make all these potentialities somehow concrete and realistic in the next years.

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