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Mycobacterial Adenylyl Cyclases: Potential Drug Targets

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Tuberculosis is a disease caused by the bacterium *Mycobacterium tuberculosis*, which has co-evolved with the human population. According to the World Health Organization in its 2011 report, this intracellular bacterium kills approximately 1.4 million people every year, including 350,000 people co-infected with HIV. During the past years, drug-resistant TB cases have raised. For example, the multidrug-resistant strains (MDR) (resistant to isoniazid and rifampicin), the extensively drug-resistant (XDR) (MDR tuberculosis with additional resistance to kanamycin and ofloxacion) and more recently the totally drug resistant strains present in India [1] have prompted concerns about how likely would it be to stop the spread of these microorganisms in our globalized era. In 2007, an American citizen, diagnosed with XDR-TB, was able to travel from the United States to Europe; in this scenario, we can wonder how many other infected and not diagnosed people could be sources of this type of infection throughout the world.

Cyclic adenosine 3'5'-monophosphate (cAMP) is a second messenger that is used widely among bacteria, fungi and complex organisms including mammals. This molecule regulates many pathways inside the cell in response to environmental changes conditions. This molecule is synthesized by the conversion of adenosine triphosphate by specialized enzymes called Adenylyl Cyclases (ACs). *M. tuberculosis* complex bacteria encode an unusually large number of class III ACs; for example, *M. tuberculosis* H37Rv contains 15 complete AC genes and one pseudogene, *M. tuberculosis* CDC1551 strain contains 17 genes and more interestingly, *M. marinum* contains 31 genes related with ACs. In contrast, many bacteria and fungi, such as *Escherichia coli*, *Candida albicans* among others have only a single AC gene. So, why *M. tuberculosis* complex bacteria have retained this number of AC genes during its evolution? Is there a metabolic advantage for the bacteria in changing environmental conditions?

Excellent reviews of the biochemical structure and function of ACs can be found in recent reports [2-4]. Part of the success of these bacteria is due to its capacity to modulate persistence factors that are associated with the formation of granulome, which contains the infection. However, a recent report by Davis JM and co-workers, using a zebrafish model infected with *Mycobaterium marinum*, indicate that granulome formation may be a mechanism of dissemination [5]. Granulome formation is dependent on the recruitment of innate and adaptative immune cells at the site of infection, besides the production and secretion of high levels of pro-inflammatory cytokines such as TNF-α. The main sources of this cytokine are the monocytes and macrophages; the latter being the main target of infection of *M. tuberculosis*.

Some reports have found that high levels of cAMP synthesized by mycobacterial species have an impact in inhibition of phagosome maturation in macrophages or in modifying the innate and adaptative immune response in order to maintain its survival. Agarwal et al. [6] reported that a loss of function mutant of the *M. tuberculosis* Rv0386 gene diminished its ability to survive during macrophage infection. They concluded that Rv0386 adenylyl cyclase synthesize cAMP that is delivered into macrophage during infection. This event leads to high levels of TNF-α production that is dependent of PKA/CREB phosphorylation pathway. Although TNF-α is a important cytokine that is needed to control the infection, some evidence indicate that high levels promote dysregulation on the site of infection by inhibiting maturation of dendritic cells, for example. It is important to note that PKA/CREB phosphorylation pathway not only promotes the transcription of TNF-α, also induces the transcription of IL-2, IL-6 and IL-10 related genes, which play an important role during macrophage infection.

Considering these evidences, it seems worth looking at defining the role of particular adenylyl cyclases during mycobacterial replication and survival within their hosts and multiple microenvironments. Although more in depth research on *M. tuberculosis* adenylyl cyclases is necessary, given the urgent need of new antimycobacterial drugs, we think adenylyl cyclases-specific inhibitors could be promising new drug candidates. Previous reports have shown the feasibility of the design and testing of specific inhibitors against class III adenylyl cyclases, such as the heat-labile enterotoxin (LT) and CyaB, present in enterotoxigenic *Escherichia coli* and *Pseudomona aeruginosa*, respectively. The molecule KH7.148 inhibited CyaB *in vitro* [7], whereas the fluorenone-based molecule DC5 decreased colonization of ETEC to epithelial cells [8]. In light of these results, it would be worthwhile to test these molecules if a class III general inhibition mechanism exists, or develop, by Medicinal Chemistry approaches, new *M. tuberculosis*, AC-specific drug candidates and evaluate them for their capacity to halt bacterial replication and determine their potential side effects, so that the class III AC mycobacterial enzymes could be exploited as drug targets.

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