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Editorial Open Access

Drug-Tolerant Mycobacteria: Are Biofilms or Signaling Mechanisms Controlling its Production an Option to Find New Drugs?

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Human tuberculosis (TB) is a reemerging disease caused mainly by bacilli of the *Mycobacterium tuberculosis* (Mtb) complex. In its 2012 Global Tuberculosis Report, the World Health Organization (WHO) estimated 1.4 million deaths in 2011 due to this disease, and almost one million of these deaths were among HIV patients. Also, 6.8 new million cases were notified, and WHO estimates that 19% correspond to multi-drug resistant TB (MDR TB), this is TB resistant to isoniazid (INH) and rifampicin (Rif), the two principal drugs used for TB treatment.

Chemotherapy of drug-susceptible TB requires a long period of time: the first phase lasts about 2 months, and the second one from 4 to 7 more months. This period becomes longer when treating MDR TB. This prolonged regime is thought to be required given that TB patients might contain bacilli distributed among heterogeneous populations: those that are actively replicating (and fully susceptible to first-line drugs) and those that sporadically replicate and become persistent. In order to reduce the duration of the treatment is necessary to study the physiology of persistent bacilli.

Recently, Ojha et al. proposed a new approach to study this persistent population: biofilms [1]. Biofilms are communities of microorganisms immersed into a matrix formed by secreted polymers such as polysaccharides, lipids or nucleic acids. This phenotype has been extensively studied in pathogens capable of causing persistent infections and it has been noted also that a microorganisms within biofilm are more tolerant to antibiotic than the same microorganisms grown planktonically [2]. When screening for molecules against biofilm formation in *M. smegmatis*, Wang and cols. found that one of their tested molecules, named TCA1, was able to inhibit production of biofilm by Mtb, and showed bactericidal activity *in vitro*, and in both an acute and a chronic infection mice model [3], therefore indicating that screening for biofilms inhibitors might lead to discover or rationally design new anti-TB drugs.

In many microorganisms biofilm formation is triggered by high concentrations of the second messenger bis-(3′-5′)-cyclic dimeric guanosine monophosphate (c-di-GMP) where synthesis and degradation occur by the action of the diguanylate cylases (DGC) and phosphodiesterases (PDE), respectively [4]. Mtb H37Rv spontaneously forms biofilm *in vitro* when cultured on detergent free media and possess genes (*Rv1354c* and *Rv1357c*) whose products are respectively responsible for synthesizing and degrading c-di-GMP *in vitro*.

A recent study suggests that c-di-GMP regulate dormancy and virulence in Mtb H37Rv, by a mechanism independent of the transcriptional regulator DosR [5]. There, an Mtb H37Rv strain lacking *Rv1357c*, the gene that codes for the PDE in this strain, was less able than wild type Mtb to sustain a chronic infection in C57BL6 mice infected by tail vein injection [5]. These findings are somewhat opposed to the demonstration of activity of TCA1 against biofilm production and chronic TB [3], as well as to the general observation in several microorganisms where biofilm formation is triggered by high c-di-GMP concentration [4]. This is so because deletion of the c-di-GMP PDE is expected to increase second messenger concentrations, which would probably lead to increased biofilm production and, hypothetically, to a sustained, chronic infection. In *Vibrio cholerae*, to cite one example, compounds that inhibit DGC activity, inhibit biofilm production [6], and it seems worthwhile assessing these compounds during *in vivo* infection for several model microorganisms. A clear elucidation of a possible relation between inhibitions of biofilm production via new drugs affecting c-di-GMP signaling would help us on the quest for new drug candidates to improve current TB treatment.

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