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Editorial Open Access

New Evidences Strengthening the Need for Considering *M. tuberculosis* Biofilms in Drug Development Pipelines

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Tuberculosis (TB) still remains a major health problem. Even in drug susceptible cases, the current chemotherapy may last up to nine months. This is thought to be the consequence of the arousal of a subpopulation of bacilli that replicates very slowly and thus might not be susceptible to drug treatment. So it is clear that new drugs are needed to shorten the present chemotherapy scheme, and Islam et al. [1] propose that this might be achieved by studying tuberculosis as a biofilm forming disease.

A biofilm is defined as a community of microorganisms that grow attached to a matrix composed of secreted polymers (such as lipids, polysaccharides, proteins or nucleic acids). Biofilm-forming pathogens cause recalcitrant infections that exhibit a drug tolerant phenotype, which are characteristics possessed by *Mycobacterium tuberculosis* (Mtb) as well.

Although the formation of biofilms *in vivo* by *M. tuberculosis* remains controversial, Wang et al. have found that a molecule capable of inhibit biofilm *in vitro* has bactericidal effect, in both a chronic and an acute mouse infection model, even when rifampicin or isoniazid-resistant strains were used for infection, so it is suggested that biofilm may be relevant for the disease [2].

Orme has recently proposed the presence of a biofilm-like structure present on the acellular rim surrounding primary lesions in infected Guinea pigs. He calls this structure NECs: Necrosis-associated Extracellular Clusters, and designate them as responsible of persistence and drug tolerance [3]. Also, Kerns et al. identified a set of *M. tuberculosis* H37Rv proteins that were recognized by sera obtained from experimentally-infected Guinea pigs, which were expressed during biofilm formation but not in shaken cultures [4]; this strongly suggests the presence of a biofilm-like structure *in vivo* or simply that conditions prevalent during biofilm life cycle resemble to some extent a stage found during infection.

In order to recreate what might be a more accurate environment for *in vivo* biofilm formation, Ackart et al. designed a model consisting on RPMI-1640 tissue culture media supplemented with lysed human peripheral blood leukocytes. They found that under this condition, communities of attached mycobacteria were formed and drug tolerance to isoniazid and rifampicine was observed, and this was reversed upon the addition of Tween-80, while DNAse I addition to aggregates already formed restored only susceptibility to INH [5].

On the other hand, Bacon et al. analyzed a model of non-replicating persistence (NRP) consisting on a batch culture with gradual depletion of nutrients, and found that NRP bacilli were surrounded by an extracellular matrix, somehow resembling a biofilm-like structure. Furthermore, transcriptome analysis showed up-regulation for some genes in NRP bacilli that were also up-regulated in bacilli present within granulomas [6].

All these evidences further support the notion that biofilm formation could provide an important condition to assess new anti-tuberculosis drugs, in order to possibly eradicate persistent bacilli, and thus shorten the current chemotherapy period of time needed to cure drug susceptible tuberculosis. It is noteworthy that further investigation is needed, especially when choosing animal models whose pathogenesis resembles that observed in human beings.

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