ICGEB International Centre for Genetic Engineering and Biotechnology | Developing Knowledge

ICGEB International SEMINAR PROGRAMME 2018

Monday, 8 January 2018 | 12:00 noon | ICGEB Seminar Room, W building | Padriciano, 99, Trieste, ITALY

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Using CAGE transcriptomics we redefined the transcriptional regulatory dynamics of differentially activated classical (M1) or alternative (M2) macrophages and identified new genes and noncoding RNA species. We uncovered a novel transcription factor Batf2 in macrophages and demonstrated that Batf2, together with Irf1, induces inflammatory responses in classically activated macrophages, lipopolysaccharides, as well as mycobacterial infection. Subsequent experimental *Mycobacterium tuberculosis* (Mtb) infection in Batf2 deficient mice resulted in reduced pulmonary inflammation with increased survival compared to infected wild type mice. Mechanistically, we identified Batf2 as a transcriptional inducer of inflammatory responses during Mtb infection in mice and showed that BATF2 is a predictive biomarker for TB disease in humans in a prospective cohort study in adolescents. We further demonstrated that Mtb exploits the host cholesterol pathway for its survival and we were able to increase host protection against tuberculosis by reducing cholesterol by statins. Isolated human monocytes and macrophages from statin-treated patients show significantly reduced bacterial burden compared to the cells of healthy donors. Mechanistically, statins increased phagosomal maturation and autophagy as host-protective functions to contain and reduce Mtb growth within macrophages. New classes of drugs are constantly being evaluated for anti-mycobacterial activity with currently a very limited number of new drugs approved for TB treatment. We show minor groove binders (MGB) with novel anti-mycobacterial activities against intracellular clinical Beijing strain HN878 in macrophages. We further employed non-ionic surfactant vesicles as a drug delivery system to deliver entrapped MGB with increased intracellular drug activity against a clinical strain of Mtb. Taken together we report that minor groove binders constitute an important new class of drug/chemical entity, which holds promise in future pathogen-directed therapy for tuberculosis. In addition, targeting Batf2 and its transcriptional pathway together with repurposed drugs such as statins offers possible adjunctive host-directed drug therapy that may reduce the burden and pathological inflammation of tuberculosis.

"Host transcriptomics of tuberculosis to statins and minor groove binders as host/pathogen-directed drug therapy for tuberculosis"

Host: A. Marcello

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