Transcriptomics to identify host/pathogen-directed drug therapy for tuberculosis

11.00 ~ 12.00, Fri. August 3, 2018

Institute of Bioengineering, pr. 60-letya Oktyabrya, 7/1
Conference room, 3 flour, 304

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Biosketch

Reto Guler is a Senior Research Officer based at the Division of Immunology, University of Cape Town (UCT), South Africa and an associate member of the Institute of Infectious Disease & Molecular Medicine (IDM). In 2003, he completed his training in Immunology with a PhD degree from the University of Geneva, Switzerland where he investigated the role of TNF and TNF related molecules in mycobacterial infection and inflammation. For this work he was awarded the Swiss TB award. He then subsequently joined UCT for his postdoctoral studies. His current research focuses on pathogen and host-directed drug therapy for tuberculosis. This includes the identification of statins and host non-coding RNAs as host-directed drug therapy for TB and the role of epigenetics in host immunity to TB. He is a member of the international FANTOM consortium on genome-wide transcriptome analysis. He further investigates minor groove binders as novel anti-mycobacterial agents and non-ionic surfactant vesicles as a drug delivery system for tuberculosis. In collaboration, he investigates remodelling of mycobacterial peptidoglycan during cell division and in tuberculosis disease. His current work is supported by grants from the Swiss-South Africa Joint Research Programme as Co-PI and the BRICS multilateral joint science and technology research collaboration as PI.

Abstract

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.

Selected publications

1. Roy S, et. al. Transcriptional landscape of Mycobacterium tuberculosis infection in macrophages. *Sci Rep*. 2018 Apr 30;8(1):6758.
2. Roy S, et al. Redefining the transcriptional regulatory dynamics of classically and alternatively activated macrophages by deepCAGE transcriptomics. *Nucleic Acids Res*. 2015 Aug 18;43(14):6969-82.
3. Arner E, et. al. Transcribed enhancers lead waves of coordinated transcription in transitioning mammalian cells. *Science*. 2015 Feb 27;347(6225):1010-4.
4. Forrest AR, et. al. A promoter-level mammalian expression atlas. *Nature*. 2014 Mar 27;507(7493):462-70.