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MiRNA-directed gene activation during tuberculosis infection

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Motivation and Aim: Tuberculosis pathogen, Mycobacterium tuberculosis (Mtb), remains successful due to the ability to get through adverse macrophage environment. MiRNAs play a role in the response to Mtb infection. Yet only regulation via mRNA repression has been investigated so far. Recent studies show that miRNAs act in an unconventional way – by activating enhancers with miRNA seed [1]. We wonder if such regulation is possible during Mtb infection.
Methods and Algorithms: We sought for enhancer-miRNA-gene trios assuming that a miRNA up-regulates a gene by targeting its enhancer. We used a time-course expression dataset from [2] and enhancer-gene interactome from [3]. Since the exact mechanism of enhancer regulation by miRNA remains unclear, we used various strategies to determine enhancers possibly targeted by differentially expressed (DE) miRNAs: we examined if miRNA could form either duplex or triplex with an enhancer sequence. To look for miRNA:enhancer duplexes we either (1) selected active enhancers containing seed sequence of any DE miRNA and high identity of the rest miRNA to surrounding DNA (Needle); or (2) sought for miRNA targets with MiRanda. Additionally, we predicted RNA:DNA triplex formation (Triplexator). Then, Spearman correlation coefficient was calculated for each DE miRNA-gene pair for genes with enhancer targeted by a miRNA.
Results: Among highly correlated trios we found a small regulatory network of Klf6 and BC016423, regulated by the same enhancer via duplex formation with miR-22 and miR-221. Klf6 could also be regulated by miRNA miR-221 via RNA:DNA triplex formation with another enhancer. KLF6 is a transcription factor essential for macrophage motility and plays an important role in the regulation of macrophage polarization promoting M1 phenotype.
Conclusion: We conclude that miRNA-directed activation of enhancers and their target genes is possible in Mtb infection at least for several DE miRNAs. Yet experimental validation is crucial (such as enhancer activity assays and chemiluminescent EMSA for validation of miRNA-DNA interaction).
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