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Århus University

Investigating regulatory motif perturbation during SARS-CoV-2 infection in a single-cell setup

Paula Rodrigo Martín

Supervisor: Jakob Skou Pedersen

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ABSTRACT

Post-transcriptional regulation is a cellular mechanism for gene expression control that constitutes a complex network of many factors. SARS-CoV-2 is known to take over the host's transcriptional and translational machinery leading to perturbations in normal gene expression. We therefore ask whether post-transcriptional regulators are also perturbed under SARS-CoV-2 infection. The overall study objective is to investigate the perturbation of microRNAs (miRNAs) and RNA binding proteins (RBPs) during SARS-CoV-2 infection. For that purpose, we analyze a single-cell atlas, comprising approximately 1.4 million healthy and SARS-CoV-2 infected cells. We aim to identify regulatory molecules with known target motifs that substantially up- or downregulate target genes. By using the miReact pipeline, we systematically screen all 7-mer motifs found in 3′UTRs for significant association with target gene perturbation during infection. We have developed a framework that, through systematic annotation with signals indicative of biological function, generates catalogs of motifs that can be ranked by biological interest and hence allow hypothesis generation and identification of candidates for further study.

This approach identifies mechanisms in epithelial cells that are related to viral infection. We found the miR-20b-3p activity to be perturbed during SARS-CoV-2 infection of epithelial cells. We hypothesize the presence of an analogous viral miRNA (v-miRNA) to miR-20b-3p to be targetting genes related to transcription. miR-640 shows potential sponging by the viral genome and we discover a 13 nucleotide long motif associated with Von-Hippel-Lindau (VHL) complex deregulation in squamous cells. Our analysis points to significant post-transcriptional deregulation of specific miRNAs during SARS-CoV-2 infection. The results show-case the usefulness of expression-coupled motif analysis in detecting differential miRNA activities, which are otherwise unobserved.

Keywords Post-transcriptomic deregulation · SARS-CoV-2 · miR-20b-3p · motif · miR-640 · miReact · longermer