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The University of Osaka

Abstract of Thesis

Name (Bakhtiyor NOSIROV)

Title

Systematic study of circulating microRNAs and their immune-related target genes

(分泌型microRNAとその免疫関連のターゲット遺伝子の系統的解析)

Since microRNAs (miRNAs) were discovered, they have been subject of many studies to elucidate their role and functional mechanisms in various biological processes, including host defense. It has been argued that post-transcriptional regulation of immune responses is at least as important as transcriptional-level regulation and miRNAs are well suited for regulating inflammation and immunity because miRNA system can evolve rapidly to create new regulatory features. One important class of miRNAs is cell free, extracellular miRNAs that exist and circulate with bodily fluids (e.g. serum, urine, breast milk, etc.). They, called circulating miRNAs, are highly stable and have attracted much attention in biomarker research, as they are readily accessible and have been shown to correlate with various disease states. However, very little is known about the function of most circulating miRNAs as the source cells secreting these circulating miRNAs and destination cells where they perform their functions are usually unknown.

As a first step to understanding the system-wide functions of circulating miRNAs, this study describes a bioinformatics approach to examine the relationship between circulating serum miRNAs (referred to here as "serum miRNAs") and target messenger RNAs (mRNAs) preferentially expressed in immune cells. Our study is based on our speculation that serum miRNAs preferentially target mRNAs that are highly expressed in immune cells. Specifically, we hypothesized that immune-specific mRNAs would have more predicted serum miRNA binding sites than other mRNAs, and, reciprocally, that serum miRNAs would have more predicted immune-specific mRNA targets than non-serum miRNAs. Because immune cells co-localize with serum miRNAs in the serum, molecular-level interaction data – either observed in large-scale experiments, or inferred from a predictor trained on such data – can be considered both physically and biologically plausible.

To test our hypotheses, we took a bottom-up approach: 1) To prioritize miRNA-mRNA pairs, we developed a robust consensus miRNA target predictor, based on Random Forest algorithm, integrating several established tools and trained as a meta-predictor on currently available small-scale and large-scale miRNA-mRNA interaction experiments. 2) We then looked for target mRNAs with high expression in immune cells in human and mouse which are the model organisms considered in this study.

First, we show that the consensus predictor performs well using curated small-scale data. However, its performance, along with that of other predictors, generally declines as new, high-throughput experimental data is added. This trend might reflect the inherent noisiness of CLIP-based data or a bias in the current set of established tools. In any case, we find that, for all compositions of small- and large-scale experimental training data, the consensus predictor

performs better on an independent test set than any of the individual established tools.

Next, our systematic and quantitative testing of the hypotheses on the relationship between miRNA subtypes (serum and non-serum) and immune-specific mRNAs demonstrated the results are highly consistent between humans and mice in spite of the fact that independent data sources were utilized. Interestingly, although we found that immune related mRNAs were predicted to be targeted by serum miRNAs modestly more than other mRNAs, and that serum miRNAs were predicted to target many more immune-specific mRNA targets than non-serum miRNAs, the two phenomena are, in fact, independent. That is, immune-specific mRNAs have more miRNA binding sites in general, not just for serum miRNAs; reciprocally, serum miRNAs target many more mRNAs in general, not just immune-specific mRNAs. In spite of this independence, the combined miRNA and mRNA biases result in a much greater number of serum miRNA-immune mRNA interactions than expected by chance. Then, we surveyed on the nucleotide content in miRNAs and found statistically significant differences in nucleotide usage between serum and non-serum miRNAs. To contextualize the biological significance of these results, we clustered serum miRNAs in terms of their mRNA binding profiles, and recapitulated the myeloid and lymphoid immune cell lineages. We also investigate gene ontology analysis for the targets of serum miRNAs in order to understand what kind of immune related biological processes serum miRNAs might play a key role in.

Finally, we introduce miRImm, a resource for systematically identifying interactions between miRNAs and target mRNAs that are specifically expressed in immune cells. Our goal by developing miRImm was to facilitate similar automated environment to study relationship between any other set of miRNAs, researchers might be interested in, and immune genes. miRImm uses a novel consensus-scoring scheme calculated by the consensus method, then finds the intersection between predicted targets and immune-specific mRNAs. Examination of miRImm output using known immune-regulating miRNAs as input indicates that both well-established immune-specific interactions and previously unreported high confidence interactions can be identified.

様式 7

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

Bakhtiyor presented his thesis, “Systematic study of circulating microRNAs and their immune related target genes”. In this talk he first introduced the main idea that co-localization suggests that miRNAs circulating in serum are likely to target genes expressed in immune cells. Next, he presented two testable hypotheses: (1) that circulating miRNAs have more immune-related targets than non-circulating miRNAs and (2) that immune-related targets have more circulating miRNA binding sites than non-immune related genes. He used published data to define these different miRNA and gene sets and developed a novel consensus-based method to predict miRNA-mRNA interactions.

Bakhtiyor presented results that showed the consensus-based predictor was more accurate than several established target prediction method over a wide-range of inputs. Next, he showed that the two hypotheses (above) were supported by his data. In particular, circulating miRNAs have many more immune-related targets than non-circulating miRNAs. However, he further found that circulating miRNAs have many more targets in general than non-circulating miRNAs, and suggested that this was due to an inherent difference in the composition of the miRNAs. Further analysis showed that the immune-related genes have longer 3’ UTRs on average, explaining their larger number of miRNA binding sites.

In the Q&A, Bakhtiyor was asked to explain how many parameters were optimized in his Random Forrest method, to which he answered that there were three main parameters. He was also asked whether the individual predictors might be correlated, and, if so, whether removing one might improve the prediction. To this, Bakhtiyor answered that he had not tried it. He was also asked if the circulating miiRNAs have higher expression rates (and are thus more likely to be found in the serum), but Bakhtiyor didn’t have any knowledge of such a relationship. After discussing his presentation, thesis and publication the committee was satisfied with Bakhtiyor’s progress to PhD.