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The regulatory impact of RNA-binding proteins on microRNA targeting

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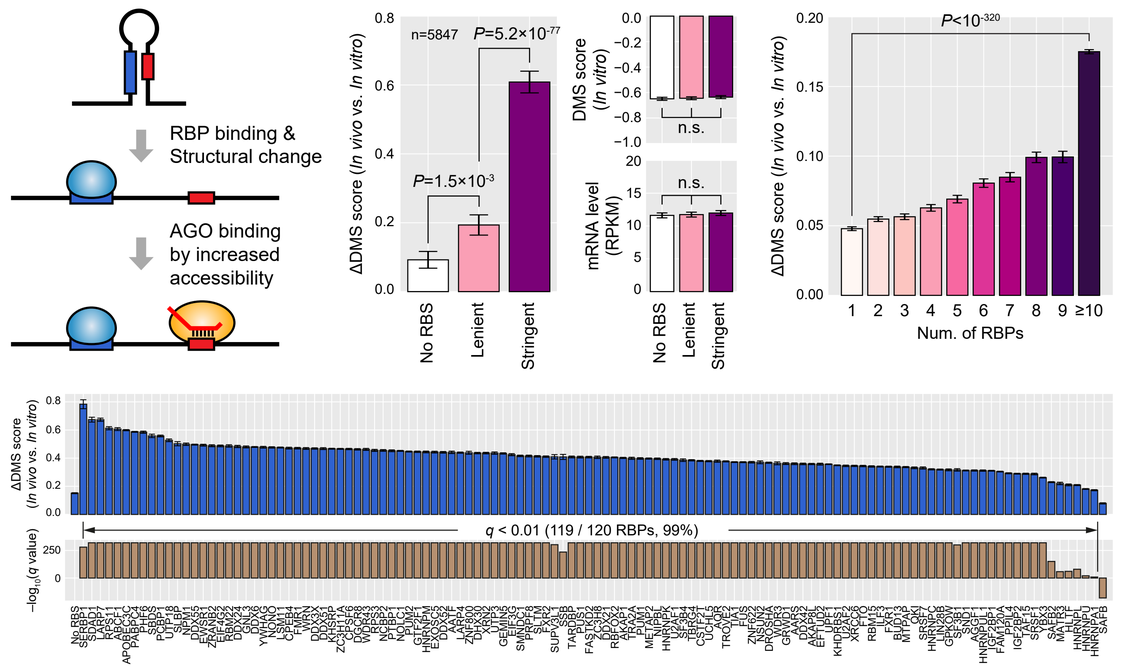
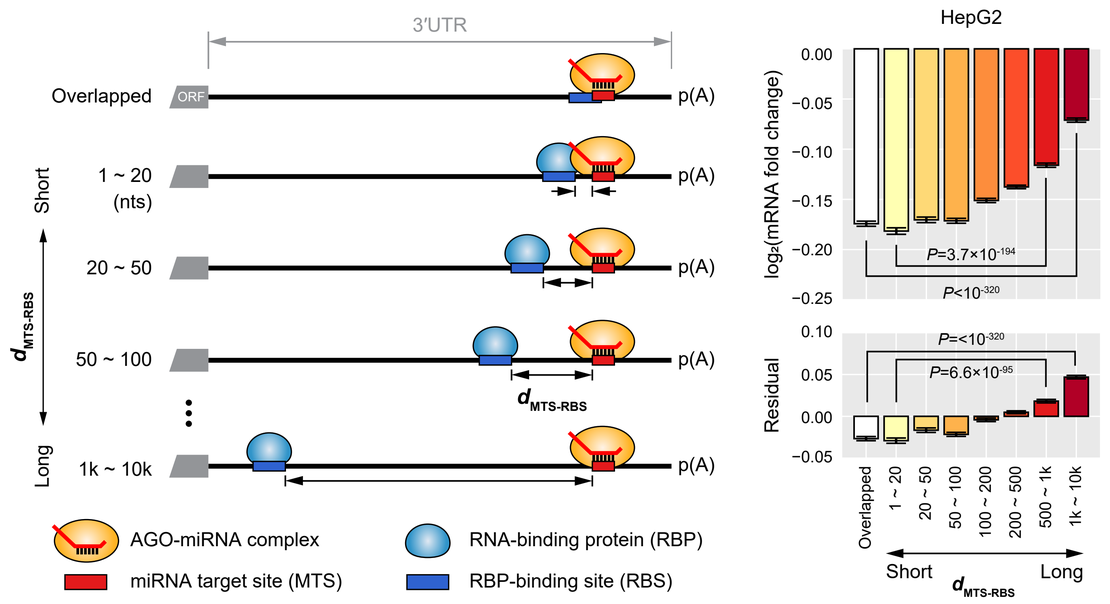
Abstract

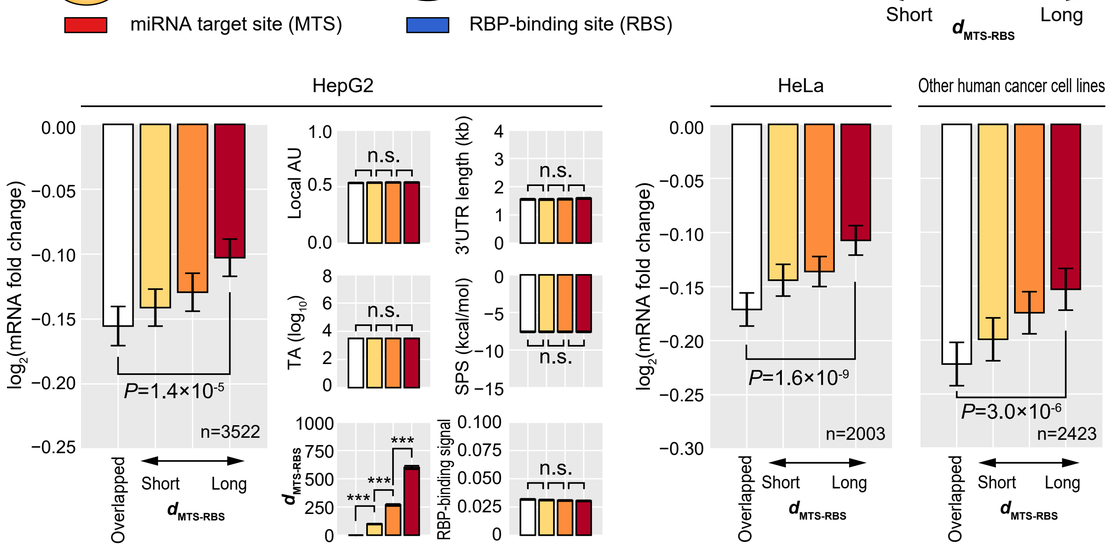
Argonaute is the primary mediator of metazoan miRNA targeting (MT). Among the currently identified >1,500 human RNA-binding proteins (RBPs), there are only a handful of RBPs known to enhance MT and several others reported to suppress MT, leaving the global impact of RBPs on MT elusive. In this study, we have systematically analyzed transcriptome-wide binding sites for 150 human RBPs and evaluated the quantitative effect of individual RBPs on MT efficacy. In contrast to previous studies, we show that most RBPs significantly affect MT and that all of those MT-regulating RBPs function as MT enhancers rather than suppressors, by making the local secondary structure of the target site accessible to Argonaute. Our findings illuminate the unappreciated regulatory impact of human RBPs on MT, and as these RBPs may play key roles in the gene regulatory network governed by metazoan miRNAs, MT should be understood in the context of co-regulating RBPs.

RBP binding opens up mRNA secondary structures

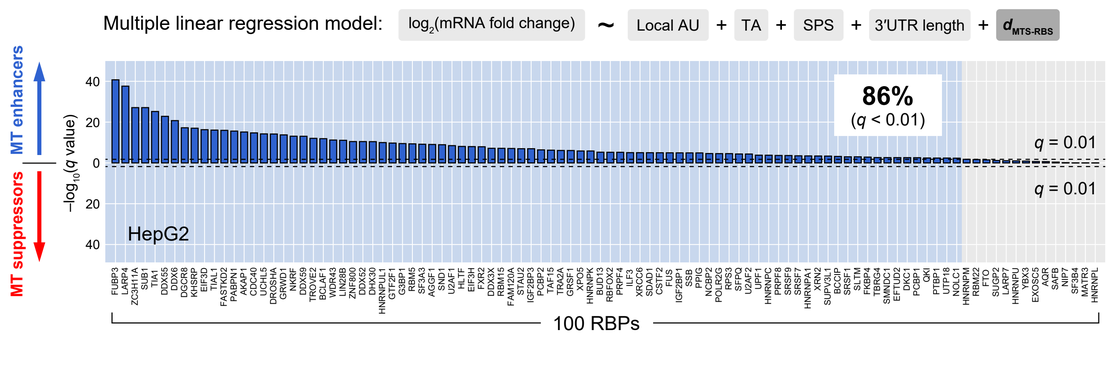


RBP binding close to a miRNA target site is associated with enhanced miRNA targeting (MT)

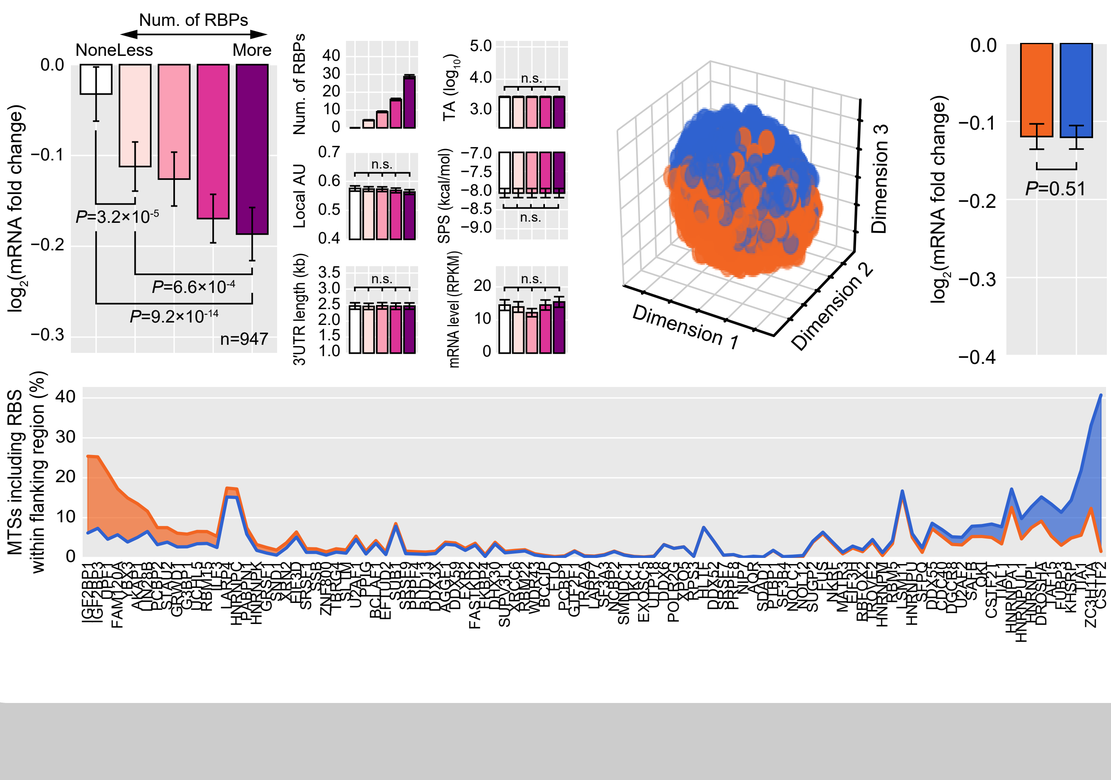




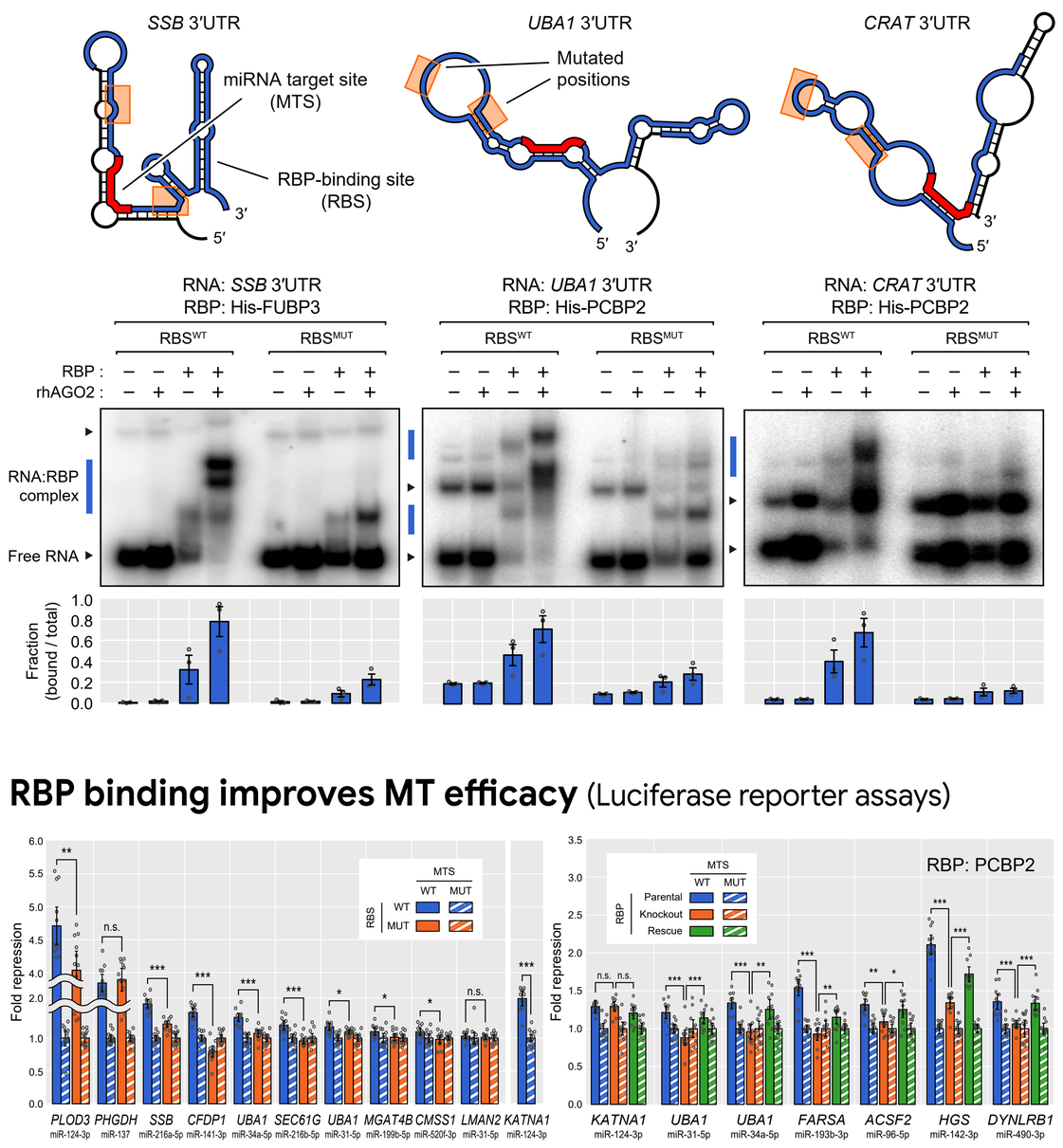
Most RBPs are associated with enhanced MT



Combined effect of RBPs on MT

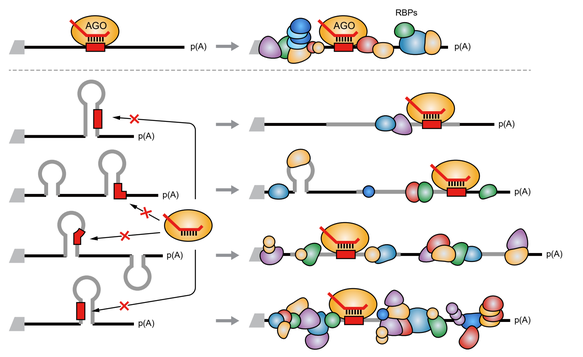


RBP binding enhances AGO accessibility (Gel mobility-shift assays)



RBP binding improves MT efficacy (Luciferase reporter assays)

Conclusions



- Based on massive-scale analyses of binding sites for 150 human RBPs and on extensive validation experiments, we report that most RBPs enhance MT instead of suppressing it on a global scale, by making the local secondary structure of the MTS more readily accessible to AGO.

- The study proposes a largely revised model that takes a much broader context of >1,500 co-regulating RBPs into additional consideration and unravels the complex nature of the gene regulatory network governed by metazoan miRNAs and their co-regulating RBPs.

- The RBP-binding information, if carefully combined with known determinants of MT, will help more accurately identify functional miRNA targets.

Acknowledgments

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