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Wiggly microRNA binding implies a more complex genome regulation

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MicroRNAs (miRNAs) regulate protein-coding gene abundance levels by interacting with the 3´ end of various messenger RNAs. Each target site matches the first few nucleotides of the targeting miRNA, the so called "seed" region, and this interaction leads to the degradation of the target or prevents its translation into amino acids. This dogma has led researchers to largely look for perfect base-pair matching of the "seed" region among candidate targets.

New research published today (August 8th) in Nature's open access journal *Scientific Reports* suggests that non-canonical binding may be much more prevalent than previously expected, revealing a much broader array of targets for miRNAs that includes both regions that code for proteins and others that do not.

"The findings may help explain why the microRNA field has run into difficulty when translating these powerful molecules into therapies for diseases ranging from cancer to diabetes," says senior author Isidore Rigoutsos, Ph.D., Director of the Computational Medicine Center in the Sidney Kimmel Medical College at Thomas Jefferson University. "There is still so much we don't know about how miRNAs work in the body."

The research add to previous reports by the Jefferson group and by others demonstrating that the miRNA "targetome" – the spectrum of RNAs that miRNAs attack – is much more complex than previously anticipated. "Our study shows that even conserved miRNAs that we share with animals and insects can have very different behavior across

organisms and even across different tissues in our bodies," says Rigoutsos.

For example, the team's analysis showed that one miRNA that's been implicated in cancer and is expressed by all vertebrates appears to bind to over 900 distinct sites in mouse embryonic stem cells, but does not bind to any sites in mouse brain cells, and only 25 sites in human pancreatic cells, suggesting that this one molecule likely has a variety of different and non-overlapping functions in mouse and human, and across different cell types.

Through an unbiased investigation of all possible combinations of miRNAs and experimentally-identified targets across seven tissue types and two organisms (human and mouse), the researchers found that the most likely pairings contained many instances of rogue binding in the seed region: instead of contiguous, well-formed base pairings, the nucleic acids of the seed region bulged and wobbled. In addition, the best target partners of miRNAs were often found in unexpected locations, such as in the 5´ untranslated region of messenger RNAs transcripts or in RNA transcripts that do not code for proteins.

Given that most miRNA studied to date have focused on exploring perfect matches of the miRNA's seed region to the messenger RNAs' 3´ untranslated regions, the abundance of alternatives binding sites suggests that many additional regulatory events may be at play in these previously unexplored areas. The apparent organism-dependence of these events may also help explain why studies showing effective miRNA approaches in animals do not translate so easily into humans. "If the repertoire of targets for one miRNA can be so different between cells of the same organism it is likely to also be different from one organism to the other," says Rigoutsos.