Are isomiRs real or junk?

Making sense of miRNA variants

QIMR Berghofer Medical Research Institute

Variants of microRNAs (isomiRs), are commonly reported but their functional significance has been debated. Our study demonstrates that isomiRs are not junk, and that they function cooperatively with parental miRNAs.

Methods & Materials

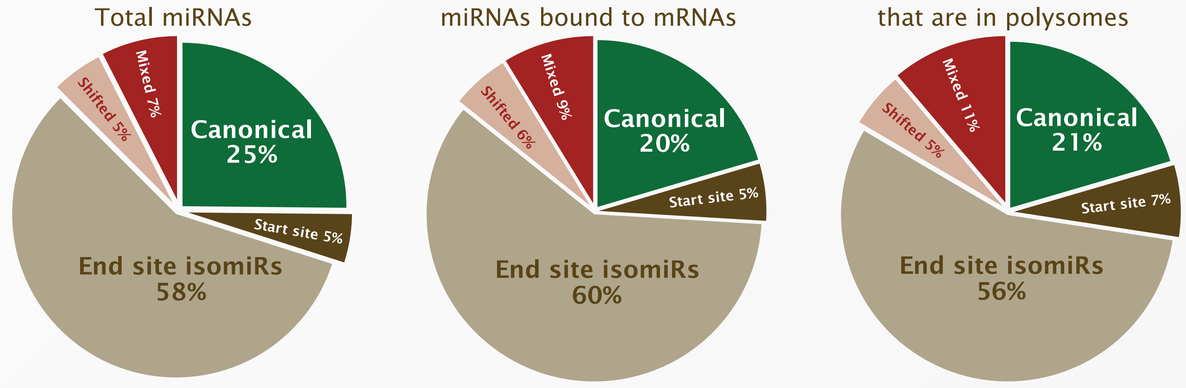
Ultra-deep miRNA-seq to study miRNA complexity

- 10 adult tissues
- multiple individuals
- multiple prep mehtods
- ~1/2 billion mapped tags

Biotin pull-downs to study miRNA-mRNA interactions

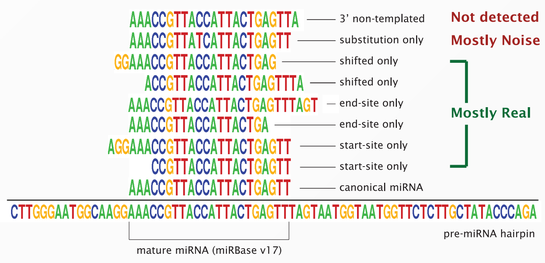
- assays direct interactions
- 10 miRNAs and isomiRs
- arrayed on HT-12 chips
- RNA-seq on targets

IsomiRs are biologically active



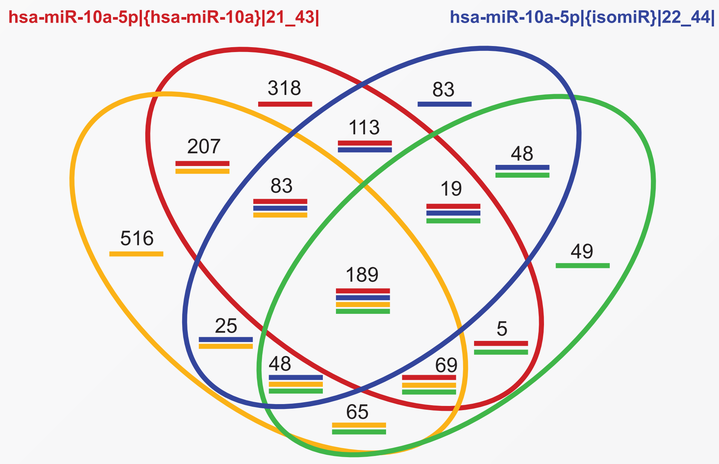
miRNA-seq of polysomes shows that there is no real difference between the number or type of 'active' isomiRs compared to all isomiRs *in vivo*.

Finding & classifying isomiRs



- stringent threshold
- conservative alignment
- most isomiRs are 3' variants
- most substitutions are noise
- isomiRs are strongly correlated with parent miRNAs

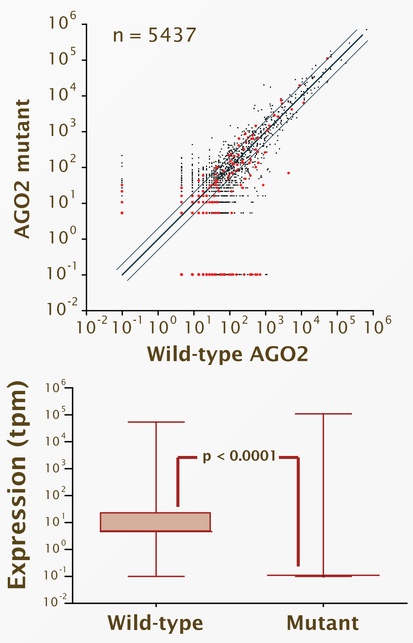
isomiRs target cooperatively



- more genes targeted by miRNAs and isomiRs than would be expected
- Same pathways are targeted even when the individual gene targets differ between miRNAs and isomiRs

Many isomiRs are AGO cleavage products

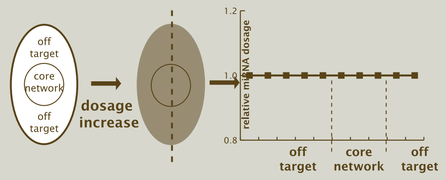
miRNA-seq data (Cifuentes et al., Science 2010, 328:1694-8) shows that miRNAs and isomiRs identified as AGO2 cleavage candidates are knocked out in AGO2 mutant cells.



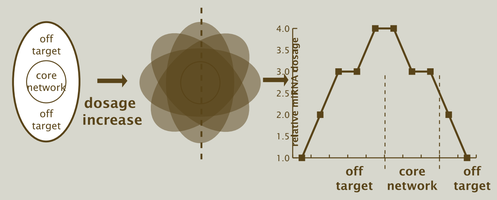
- AGO2 cleavage leaves isomiR footprint
- at least 13 other miRNAs have this footprint in our data
- 11 of these are absent in AGO mutant miRNA-seq
- accounts for ~50% of isomiRs

IsomiRs potentially reduce targeting noise

miRNAs acting along cannot increase dosage specifically to the core network of targets



miRNAs and isomiRs together can increase dosage specifically to the core network



Authors

Nicole Cloonan
Hilary C. Martin
Shivangi Wani
Anita L. Steptoe
Sean M. Grimmond

The University of Queensland
AUSTRALIA

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Genomic Biology Lab

300 Herston Rd, Herston, Q 4006 Australia
E: nicole.cloonan@qimrberghofer.edu.au
W: www.qimrberghofer.edu.au
Twitter: @ncloonan