Discovery of Exon Splicing Relationships Across Cancer Cell Lines

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Outline

- MDM4
  - Role in cancer
  - Alternative splicing regulation
  - Copy number effects

- Gene dependency models
  - Known confounding effects
  - Relation with exon splicing

- Future plans
MDM4 and p53


RNA splicing

MDM4 lacking exon 6 fails to suppress p53 activity

Bardot et al. 2015, *Oncogene* 34, 2943-2948
Copy number variation - exon splicing relationships
MDM4 exon 6 splicing is partly driven by a copy number variation
Confounding variables in gene dependency models


Only differential dependency genes have exon-correlated guides

Tumor drivers/essential genes

Tumor suppressors

Non-differential dependency
Does exon splicing confound shRNA gene dependency?

- Differential dependencies
- Non-differential dependencies

Difference in same-exon vs. different-exon correlations
Same-exon - different-exon correlation distribution is right-skewed

Difference in same-exon vs. different-exon correlations
PSMC2 exon-shRNA correlations
PSMC2 exon-shRNA correlations

PSMC2 same exon correlations

PSMC2 different exon correlations
Future plans

- **MDM4**
  - Investigate link between copy number variation and exon 6 splicing

- **Gene dependencies**
  - Could same-exon correlations be due to other factors (similar target sequences, RNA folding regions)?
  - Transform exon splice levels to discrete isoform-level expression levels
  - Are differences in sgRNA/shRNA-level dependencies explained by differential exon splicing?

- **Exon splicing**
  - Look for other predictors of exon splicing in the CCLE (methylation, chromatin profiling, mutations)
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