HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight April 2014

☐ co-ordinated with the Director of the Institute / Research Unit

Institute of Diabetes and Regeneration Research

PSP-Element:
G-502300-001

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Title of the highlight:
miR-335 promotes mesendodermal lineage segregation and shapes a transcription factor gradient in the endoderm

Keywords:
Endoderm, Foxa2, Gastrulation, Mesendoderm, miR-335

Central statement of the highlight in one sentence:
miR-335 targets endoderm specific transcription factors to establish a spatio-temporal gradient formation in the endoderm and to stabilize lineage decisions during mesendoderm formation

Text of the highlight:
Transcription factors (TFs) pattern developing tissues and determine cell fates; however, how spatio-temporal TF gradients are generated is ill defined. Here we show that miR-335 fine-tunes TF gradients in the endoderm and promotes mesendodermal lineage segregation. Initially, we identified miR-335 as a regulated intronic miRNA in differentiating embryonic stem cells (ESCs). miR-335 is encoded in the mesoderm-specific transcript (*Mest*) and targets the 3′-UTRs of the endoderm-determining TFs *Foxa2* and *Sox17. Mest* and miR-335 are co-expressed and highly accumulate in the mesoderm, but are transiently expressed in endoderm progenitors. Overexpression of miR-335 does not affect initial mesendoderm induction, but blocks Foxa2- and Sox17-mediated endoderm differentiation in ESCs and ESC-derived embryos. Conversely, inhibition of miR-335 activity leads to increased Foxa2 and Sox17 protein accumulation and endoderm formation. Mathematical modeling predicts that transient miR-335 expression in endoderm progenitors shapes a TF gradient in the endoderm, which we confirm by functional studies *in vivo*. Taken together, our results suggest that miR-335 targets endoderm TFs for spatio-temporal gradient formation in the endoderm and to stabilize lineage decisions during mesendoderm formation.

Publication:
Yang D, Lutter, D, Burtscher I, Uetzmann L, Theis FJ., **Lickert H**
miR-335 promotes mesendodermal lineage segregation and shapes a transcription factor gradient in the endoderm. Development 2014 Feb; 141(3):514-25.

Taking account of the HMGU mission:
The Helmholtz Zentrum München develops the fundamental principles for medicine of the future and a personalized medicine, focused on the causes of the chronic complex diseases diabetes and lung diseases. We are also making important contributions to the mechanisms of neuropsychiatric diseases, cancer, cardiovascular diseases, allergies and infectious diseases. Additionally, we investigate ecological systems with essential significance for human health.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
Institute of Bioinformatics and Systems Biology, G-503800-001