Whole-genome microRNA screening identifies let-7 and mir-18 as regulators of germ layer formation during early embryogenesis.

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Public Summary:
The initiating event in heart formation is to distinguish cardiovascular precursors from endoderm. microRNAs are small, non-coding RNA molecules that regulate many biological processes. Here we describe high throughput functional screening of human microRNAs, identifying two families that control the cell fate choice between endoderm and mesoderm capable of forming heart tissue. The two microRNAs (miR-18 and let-7) act by blocking signaling from Nodal, a member of the Transforming Growth Factor family of signaling proteins. The study is important because it reveals an critical early step in heart formation, and also shows that functional screening of the whole genome collection of microRNAs can uncover signaling pathways that control phenomena as complex as stem cell differentiation.

Scientific Abstract:
Tight control over the segregation of endoderm, mesoderm, and ectoderm is essential for normal embryonic development of all species, yet how neighboring embryonic blastomeres can contribute to different germ layers has never been fully explained. We postulated that microRNAs, which fine-tune many biological processes, might modulate the response of embryonic blastomeres to growth factors and other signals that govern germ layer fate. A systematic screen of a whole-genome microRNA library revealed that the let-7 and miR-18 families increase mesoderm at the expense of endoderm in mouse embryonic stem cells. Both families are expressed in ectoderm and mesoderm, but not endoderm, as these tissues become distinct during mouse and frog embryogenesis. Blocking let-7 function in vivo dramatically affected cell fate, diverting presumptive mesoderm and ectoderm into endoderm. siRNA knockdown of computationally predicted targets followed by mutational analyses revealed that let-7 and miR-18 down-regulate Acvr1b and Smad2, respectively, to attenuate Nodal responsiveness and bias blastomeres to ectoderm and mesoderm fates. These findings suggest a crucial role for the let-7 and miR-18 families in germ layer specification and reveal a remarkable conservation of function from amphibians to mammals.