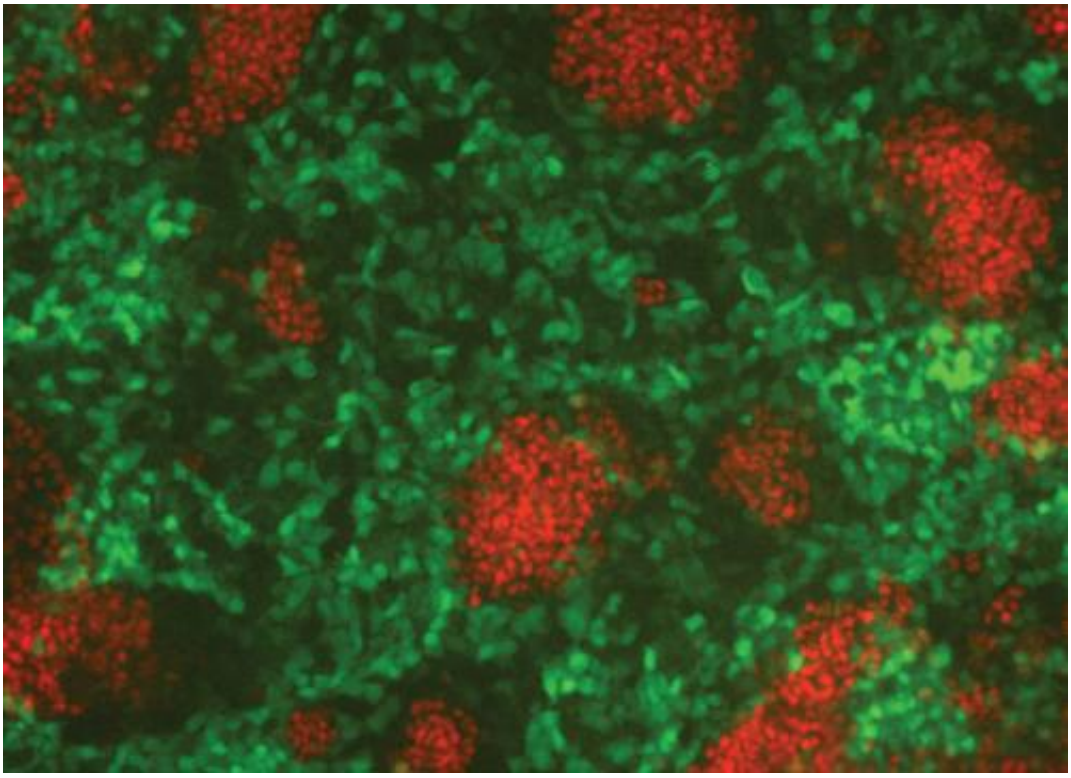
Medical Xpress

'Junk DNA' drives embryonic development

December 3 2012



These are differentiating mouse embryonic stem cells (green = mesoderm progenitor cells, red = endoderm progenitor cells). The microRNAs identified in this study block endoderm formation, while enhancing mesoderm formation. Credit: Sanford-Burnham Medical Research Institute

An embryo is an amazing thing. From just one initial cell, an entire living, breathing body emerges, full of working cells and organs. It comes as no surprise that embryonic development is a very carefully orchestrated process—everything has to fall into the right place at the

right time. Developmental and cell biologists study this very thing, unraveling the molecular cues that determine how we become human.

"One of the first, and arguably most important, steps in development is the allocation of cells into three germ layers—ectoderm, mesoderm, and endoderm—that give rise to all tissues and organs in the body," explains Mark Mercola, Ph.D., professor and director of Sanford-Burnham's Muscle Development and Regeneration Program in the Sanford Children's Health Research Center.

In a study published in the journal Genes *& Development*, Mercola and his team, including postdoctoral researcher Alexandre Colas, Ph.D., and Wesley McKeithan, discovered that microRNAs play an important role in this cell- and germ layer-directing process during development.

MicroRNA: one man's junk is another's treasure

MicroRNAs are small pieces of genetic material similar to the messenger RNA that carries protein-encoding recipes from a cell's genome out to the protein-building machinery in the cytoplasm. Only microRNAs don't encode proteins. So, for many years, scientists dismissed the regions of the genome that encode these small, non-protein coding RNAs as "junk."

We now know that microRNAs are far from junk. They may not encode their own proteins, but they do bind messenger RNA, preventing their encoded proteins from being constructed. In this way, microRNAs play important roles in determining which proteins are produced (or not produced) at a given time.

MicroRNAs are increasingly recognized as an important part of both normal cellular function and the development of human disease.

So, why not embryonic development, too?

Directing cellular traffic

To pinpoint which—if any—microRNAs influence germ layer formation in early embryonic development, Mercola and his team individually studied most (about 900) of the microRNAs from the human genome. They tested each microRNA's ability to direct formation of mesoderm and endoderm from embryonic stem cells. In doing so, they discovered that two microRNA families—called let-7 and miR-18—block endoderm formation, while enhancing mesoderm and ectoderm formation.

The researchers confirmed their finding by artificially blocking let-7 function and checking to see what happened. That move dramatically altered embryonic cell fate, diverting would-be mesoderm and ectoderm into endoderm and underscoring the microRNA's crucial role in development.

But they still wanted to know more…how do let-7 and miR-18 work? Mercola's team went on to determine that these microRNAs direct mesoderm and ectoderm formation by dampening the TGFβ signaling pathway. TGFβ is a molecule that influences many cellular behaviors, including proliferation and differentiation. When these microRNAs tinker with TGFβ activity, they send cells on a certain course—some go on to become bone, others brain.

"We've now shown that microRNAs are powerful regulators of embryonic cell fate," Mercola says. "But our study also demonstrates that screening techniques, combined with systems biology, provide a paradigm for whole-genome screening and its use in identifying molecular signals that control complex biological processes."

More information: Colas AR, McKeithan WL, Cunningham TJ, Bushway PJ, Garmire LX, Duester G, Subramaniam S, & Mercola M (2012). Whole-genome microRNA screening identifies let-7 and mir-18 as regulators of germ layer formation during early embryogenesis. *Genes & development* PMID: 23152446

Provided by Sanford-Burnham Medical Research Institute