
miR-125b Promotes Early Germ Layer Specification through Lin28/let-7d and Preferential Differentiation of Mesoderm in Human Embryonic Stem Cells.

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Public Summary:

Unlike other essential organs, the heart does not undergo tissue repair following injury. Human embryonic stem cells (hESCs) grow indefinitely in culture while maintaining the ability to differentiate into many tissues of the body. As such, they provide a unique opportunity to explore the mechanisms that control human tissue development, as well as treat diseases characterized by tissue loss, including heart failure. MicroRNAs are small, non-coding RNAs that are known to play critical roles in the regulation of gene expression. We profiled the expression of microRNAs during hESC differentiation into myocardial precursors and cardiomyocytes (CMs), and determined clusters of human microRNAs that are specifically regulated during this process. We determined that miR-125b overexpression results in upregulation of the early cardiac transcription factors, GATA4 and Nkx2-5, and accelerated progression of hESC-derived myocardial precursors to an embryonic CM phenotype. We used an in silico approach to identify Lin28 as a target of miR-125b, and validated this interaction using miR-125b knockdown. Anti-miR-125b inhibitor experiments also showed that miR-125b controls the expression of miRNA let-7d, likely through the negative regulatory effects of Lin28 on let-7. We then determined that miR-125b overexpression inhibits the expression of Nanog and Oct4 and promotes the onset of Brachyury expression, suggesting that miR-125b controls the early events of human CM differentiation by inhibiting hESC pluripotency and promoting mesodermal differentiation. These studies identified miR-125b as an important regulator of hESC differentiation in general, and the development of hESC-derived mesoderm and cardiac muscle in particular. Manipulation of miR-125b-mediated pathways may provide a novel approach to directing the differentiation of hESC-derived CMs for cell therapy applications.

Scientific Abstract:

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