Important find shows how gene regulators select different partners to form different organs

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Scientists at the Agency for Science, Technology and Research's (A*STAR) Genome Institute of Singapore (GIS) have discovered that key gene regulators work in pairs to trigger stem cells to differentiate into specific cell types. Furthermore, they showed that selective partnering of the regulators result in uniquely specified developmental outcomes.

An embryo develops from a single cell to a complex, interconnected assemblage of multiple cell types in the adult organism, such as the muscles, nerves, lungs and heart. The fates of embryonic cells as they differentiate into specialized adult cells require tightly regulated expression of hundreds of genes; each cell type being regulated by a unique and specific pattern of gene expression. Transcription factors are master regulators of gene expression and have been implicated as key players in the appropriate specification embryo development. They do this by binding to DNA thereby "turning on" or "turning off" nearby genes. What is less clear is how these transcription factors select specific sets of genes for activation and repression.

A recent study by scientists from GIS has discovered that it takes a pair of transcription factors, working tightly together, to orchestrate key decisions in embryo development. The discovery was published in the prestigious *EMBO Journal*.

The study, a multidisciplinary collaborative effort, established that the transcription factor Oct4 alternatively partners with two related factors, Sox2 or Sox17. This paper, together with a related paper published in the journal *Stem Cells* in 2011 ("Conversion of Sox17 into a reprogramming factor by re-engineering its association with Oct4 on DNA."), makes a key discovery about how the selective partnering of the two transcription factors can lead to very different developmental outcomes.

Lead author Dr. Lawrence Stanton said, "This work was a unique collaboration between scientists hailing from different areas of expertise – computational biology, cell biology, developmental biology and biochemistry. The unique line of research was only possible by the interdisciplinary efforts of these scientists."

Co-lead author Dr. Prasanna Kolatkar said, "Our previous work described how re-engineering of developmental proteins through a single site change results in functions of proteins Sox2 and Sox17 becoming inter-converted – thus the decision to stay as a stem cell or differentiate is flipped through a single amino acid change. This study uses a genome-wide approach to validate this concept, and moreover leads to novel genes potentially involved in primitive endoderm formation."

"This work identified a novel regulatory switch from pluripotency to cell-lineage specific differentiation. It is remarkable that a single pluripotency factor, Oct4, was found to influence diverse cellular processes. This key discovery illustrates the complexity in the regulation of pluripotency programme in embryonic stem cells," said GIS Executive Director Prof Ng Huck Hui.

More information: Aksoy, I. et al. Oct4 switches partnering from Sox2 to Sox17 to reinterpret the enhancer code and specify endoderm, *The EMBO Journal*, 8 March 2013.

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