Scientists discover new RNA processing pathway important in human embryonic stem cells

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Scientists at A*STAR's Genome Institute of Singapore (GIS), in collaboration with their counterparts from Canada, Hong Kong and US, have discovered a protein mediator SON plays a critical role in the health and proper functioning of human embryonic stem cells (hESCs) . This finding was reported on 8th September 2013 in the advanced online issue of the prestigious science journal *Nature Cell Biology*.

Correct expression of genes is essential for a cell to stay alive and to perform other cellular and physiological functions. During gene expression, DNA is first converted into RNA transcript and then some parts of it are removed while others are joined before the trimmed RNA transcript can be translated into proteins. This process of cutting and joining different pieces of RNA is called splicing, and the proteins that mediate splicing are known as splicing factors. Mutations in splicing factors can cause diseases such as myotonic dystrophy and cancer. Even though hESCs have been studied extensively over the last decade due to their potential to differentiate into cell-types of potential clinical applications, little is known about the role that splicing plays in the regulation of pluripotency in these cells.

Scientists at the GIS followed their previous study on a genome-wide investigation of gene functions in hESCs, which was published in *Nature* [Chia et al. 2010. 468(7321):316-20], and found that splicing factors, such as the protein known as SON, are key regulators of hESC

maintenance.

SON was discovered to be essential for converting differentiated cells into pluripotent stem cells. In addition, SON promotes correct splicing of a particular group of RNAs, including those coding for essential hESC regulators, and thereby helps hESCs to survive in an undifferentiated state. Moreover, the authors showed that silencing of SON induced new transcript isoforms that seemed to be non-functional in hESCs.

The study, led by GIS Executive Director Prof Ng Huck Hui, establishes an initial connection between splicing and pluripotency in hESCs and contributes to the comprehensive understanding of the nature of hESCs. Besides its role in hESCs, SON was previously found to be involved in the development of leukemia and influenza virus infection.

Prof Ng Huck Hui said, "Maintenance and differentiation of human embryonic stem cells are governed by an intricate network that comprises diverse cellular processes. In the past, we had been focusing primarily on transcriptional regulation. In our new study, it is clear that splicing contributes to the unique cellular state of hESCs and this can be explained in part through the function of a protein known as SON. SON regulates the precise splicing of specific transcripts which are important for pluripotency. A systematic dissection of the different pathways required for maintenance of pluripotency can eventually guide us in engineering novel cellular states in the laboratory."

"In this new manuscript in *Nature Cell Biology*, Ng Huck Hui and his colleagues continue to cement their position at the forefront of pluripotency research worldwide," said Dr Alan Colman, the former Executive Director of the Singapore Stem Cell Consortium. "The distinctive feature of human embryonic stem cells is their ability to either self renew or alternatively, given the right conditions, to differentiate into all the cell types that comprise the adult body. In

previous work, the team had uncovered a number of unique transcription factors that mediate the maintenance of pluripotency via binding to genomic DNA. In this latest publication, they reveal a novel mechanism where SON, a protein localized to nuclear speckles, regulates the proper splicing of transcripts encoding pluripotency regulators such as OCT4, PRDM14, E4F1 and MED24, and ensures cell survival and maintenance of pluripotency in hESC (and by extrapolation, presumably human induced pluripotent stem cells also)."

Prof Eran Meshorer from the Department of Genetics at the Hebrew University of Jerusalem added, "In recent years, a growing number of papers focusing on the transcriptional regulators that control embryonic stem cell biology have been published. However, the link between RNA splicing and pluripotency has only very recently emerged and the factors that regulate splicing and alternative splicing in ES cells are unknown. The paper by Ng Huck Hui and colleagues now shows that the splicing regulator SON, previously identified in a screen conducted by the same group for novel pluripotency-related factors, regulates the splicing of several key pluripotency genes, linking splicing with stem cell biology and pluripotency. This paper provides a major step towards a more complete understanding of the mechanisms controlling pluripotency and self-renewal, and calls for the identification of additional splicing regulators in ES cells. It is also tempting to speculate that SON and other splicing-related proteins may assist in converting somatic cells into pluripotent cells in the process of reprogramming." Prof Meshorer is the winner of the 2013 Sir Zelman Cowen Universities Fund Prize for Medical Research for the extensive and groundbreaking work undertaken in his laboratory to shed light on pluripotency.

More information: Xinyi, L. et al. SON connects the splicing-regulatory network with pluripotency in human embryonic stem cells, *Nature Cell Biology*, September 8, 2013.