Controlling gene activity in human development

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Researchers at the Babraham Institute have revealed a new understanding of the molecular switches that control gene activity in human embryonic stem cells. This insight provides new avenues for improving the efficiency of being able to drive stem cells to create a desired cell type - an essential requirement to fulfil their promise in regenerative medicine.

In the developing embryo and during the specialisation of stem cells, the activity of genes must be tightly controlled (by a process called epigenetics) so that the correct genes are switched on and off at the right time and in the right cells. One of the main ways that this process is regulated is by a protein complex called Polycomb Repressive Complex 2 (PRC2), which keeps genes switched off until they are needed. We know from previous studies that PRC2 is necessary for controlling gene activity during the development of the fruit fly and the mouse, but we know very little about its role in human development or in the specialisation of stem cells.

As described in the journal *Cell Reports*, the researchers used the CRISPR gene editing technique to delete PRC2 from human embryonic stem cells. Loss of PRC2 caused the cells to switch on many genes that are not normally active in these cells. Interestingly, the set of genes that were switched on have important roles in the formation of specialised cell types in the developing embryo. This exciting finding reveals that one of the main functions of PRC2 is to keep these identity-specifying genes switched off during the very early stages of human development

until they are required. The researchers also discovered that the quality and stability of the embryonic stem cells were compromised when the set of genes was aberrantly switched on. These changes led to the inability of embryonic stem cells lacking PRC2 to specialise correctly into mature cell types.

Dr Peter Rugg-Gunn, senior author on the research paper and research group leader at the Babraham Institute explained: "This work is exciting because it reveals that gene activity is controlled by similar molecular switches in human development as in other species such as the fly and mouse. We have also uncovered human-specific differences in the way that embryonic stem cells respond to genes being misregulated. These findings provide new insights into the development of our own species, and might enable new ways to turn embryonic stem cells into useful cell types, such as heart and pancreas, which can be used for cell-replacement therapies."

More information: Collinson et al., (2016) Deletion of the Polycomb-group protein EZH2 leads to compromised self-renewal and differentiation defects in human embryonic stem cells. *Cell Reports*, DOI: 10.1016/j.celrep.2016.11.032 , www.cell.com/cell-reports/full … 2211-1247(16)31590-X

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