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Polycomb repressive complex 1 regulators of early ectodermal differentiation

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Pluripotent stem cells have the capacity to self-renew and differentiate into multiple cell lineages- ectoderm, mesoderm, and endoderm. Progression from undifferentiated to differentiated state needs stable restricted chromatin compaction which enables the cell to retain memory without altering the DNA sequence. Epigenetics modulators like DNMTs, NuRFs and histone modifiers are critical for establishing and maintaining heritable genetic changes and maintain cellular memory during development. Polycomb group (PcGs) proteins are one of the histone modifiers which regulate transcription by forming large protein complexes, notable amongst these complexes are Polycomb Repressive Complex 1 (PRC1) and 2 (PRC2) which add ubiquitin and methyl molecules respectively on specific histone proteins. PRC1 has two core components-RING1B and BMI1, where RING1B is the catalytic unit which performs monoubiquitylation of lysine 119 on Histone H2A. Earlier studies have highlighted the function of PcG proteins using mouse models of mammalian development and these were found to play an essential role in determining the fate of neuronal development. We used human pluripotent stem cells as an *in vitro* model to study the role of these PcG proteins during early human neural development. The stem cells were differentiated by forming embryoid bodies (EBs) via the hanging drop technique and later they were plated on gelatin-coated dishes; these EBs were observed to display cells of varied morphologies. The *RING1B* and *BMI1* expression were checked over a span of two weeks, it was seen that the *RING1B* and *BMI1* expression was upregulated in differentiated cells compared to undifferentiated cells. Subsequently, these PcG proteins were inhibited to determine the fate of differentiation and for this, we used two commercially available inhibitors. PRT-4165 was used to inhibit *RING1B* expression and PTC-209 was used to inhibit *BMI1* expression, acute treatment of inhibitors was given to EBs for 24 hours. It was observed that with inhibition of *RING1B* and *BMI1*, EBs showed a higher expression of neuroectodermal markers such as *NESTIN, PAX6*, and *SOX1* compared to its control. We also checked for expression of endoderm and mesoderm specific markers such as *SOX17, BRACHYURY, TBX5*, and *HAND1*, but there was no significant change in expression of endoderm and mesoderm markers compared to the control. Thus, our results indicate that PcG proteins are crucial for neuronal differentiation of human pluripotent stem cells and the inhibition of RING1B and BMI1 leads to the generation of more neural lineage cells. Thus, our results show the importance of PRC1 components in neurogenesis and understanding the functioning of RING1B and BMI1 proteins may be important in the context of neurodevelopmental diseases.

Biography

Divya Desai is a PhD Research Scholar, 2nd year, from SDSOS, NMIMS University from Mumbai, India. She is currently working on stem cell biology and epigenetics.

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