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Optogenetic control of endogenous neuronal commitment and differentiation through epigenetic amendments of Ascl1 (Mash1) promoter

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Achaete-scute homolog 1 (Ascl1 or Mash1 in mammal) is an important candidate of proneural genes, known to promote cell cycle exit and neuronal differentiation. Mash1 initiates the neuroblast differentiation from neuroepithelial cells and also protect the neuroblasts from damages through 'delta' protein mediated lateral inhibition machinery during nervous system development. Aberrant methylation status at the proneural gene promoters however may lead to their ectopic expressions which have been recognized in conjunction with impaired nervous growth, increase of excitatory neurons or acute neuralgia. Herein, we have targeted intelligently engineered light inducible (optogenetic) fusion protein tools to demethylate the Mash1 promoter with spatiotemporal precision, which otherwise identified hyper methylated with reduced expression in a few murine neural stem cell (NSC) lineages. The promoter targeting construct contained blue light inducible protein CIB1 (cryptochrome-interacting basic helix loop helix) fused to the Ascl1 promoter specific transcription activator-like effectors (TAL-TFs), while the CIB1 interacting protein partner CRY2 was fused to the ten-eleven translocation proteins (TET). Light induced association of these optogenetic fusion proteins resulted in significant selective demethylation at the target CpGs of Mash1 promoter with increased gene expression. The overall outcome of these light induced epigenetic changes was then analyzed in regard to the altered phenotype and fashion of differentiation amongst the NSCs. We also introduced several single molecule fluorescence tools like FLIM-FRET or FCS to monitor intra-nuclear association rate and binding dynamics of the optogenetic proteins. This system hence, allows direct and non-invasive probing of the critical stages of NSC morphogenesis through light induced epigenetic alterations and transcriptional activation.

Biography

Samrat Roy Choudhury has graduated in Nanobiotechnology from the Biological Sciences Division of Indian Statistical Institute, India. He is currently pursuing his Postdoctoral Research at the Purdue University, USA. He has received several prestigious Doctoral and Postdoctoral Fellowships from the Indian Government. He has more that 20 peer reviewed publications in the international journals, patients, books and book chapters to his credit.

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