

Enhancer Regulation of WNT3A

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Upon traumatic brain injury, epigenome reprograms allowing gene expressions for injury response and regeneration. Using chromatin immunoprecipitation-sequencing of histone marks, we identify a novel enhancer region for induced *WNT3A* transcription during regeneration of injured cortical neurons. An increased mono-methylation of histone H3 at lysine 4 (H3K4me1) modification and a topological transformation of this enhancer and with promoter of *WNT3A* gene orchestrate the transcription of *WNT3A* gene during neuronal regeneration.

Keywords: epigenome ; *WNT3A* ; histone modification ; traumatic brain injury ; transcriptional regulation ; topological transformation

1. Introduction

There are approximately 70 million individuals suffering from traumatic brain injury (TBI) each year, which has been a major cause of morbidity and lifelong disability worldwide ^[1]. TBI is caused by external mechanical force, such as a blow to the brain, or by other mechanisms of displacement of the brain tissue that leads to focal (e.g., penetrating injuries) or diffuse brain damage (e.g., blast exposure) ^[2]. Following primary injury, secondary injury can evolve and sustain complexed pathophysiological cascades. Secondary injury-initiated cascades include hypoxia, ischemia, increased neurotransmitter excitotoxicity (e.g., increased release of glutamate), diffuse neuronal depolarization and an excessive cellular influx of calcium, leading to cellular/molecular/metabolic derangements and ultimate cellular dysfunction or cell death ^[3].

2. Discussion

In this regard, long-lasting and progressive nature of pathophysiology after TBI warrants secondary injury cascades a potential target for therapeutic intervention. Unfortunately, due to the heterogeneity of pathophysiology, severity, outcomes upon brain injury and the lack of knowledge about the underlying molecular mechanism, there is currently no therapy for TBI. Promising outcomes in preclinical studies did not lead to clinical efficacy. There are neither efficacy-proven neuroprotective nor neuroregenerative agents available to treat TBI in clinical trials ^[4]. Poor regeneration of the injured central nervous system in part due to inhibitory gliosis and an aging-related decline of intrinsic regenerative capacity ^{[5][6][7]}. However, inhibiting the non-permissive environment alone has not been a successful strategy to promote regeneration of injured brain neurons ^{[8][9][10]}. TBI was reported to reprogram epigenome ^{[11][12]}. Epigenomic profiling of mice hippocampus after TBI exposure revealed injury-induced inter-correlated transcriptomic and methylomic perturbations ^[12]. Significant epigenetic changes identified in the brain after TBI in animals and humans include DNA methylation, histone methylation/acetylation and microRNAs expression. Cognitive or functional recovery was assayed following administration of epigenetic modifying drugs in post-TBI animal models, demonstrating variable behavioral outcomes ^[11]. As more attention has been drawn on the epigenetic mechanism upon TBI, TBI-relevant epigenetic changes are found implicated in shaping neuronal functions and plasticity ^[13]. It is believed that better understating of the pathophysiology following brain injury in an epigenetic scale would gain insight into therapeutic development for TBI. To this point, we performed chromatin immunoprecipitation-sequencing (ChIP-seq) of histone marks, tri-methylation of histone H3 at lysine 4 (H3K4me3) and histone H3 lysine 27 acetylation (H3K27ac), to investigate transcriptional regulation of candidate regeneration-associated genes (RAGs). Our laboratory identified *WNT3A* gene as a promising RAG of which expression was up-regulated during regeneration of injured cortical neurons ^[14]. Nonetheless, the transcriptional regulation of *WNT3A* expression remains to be determined. This study predicted the novel enhancer for *WNT3A* expression and characterized the long range enhancer-promoter interaction that dynamically orchestrated the induced transcription of *WNT3A*.

Figure 1. H3K4me1 modifications, enhancer RNAs (eRNAs) and topological transformation at *WNT3A* enhancer/promoter regions during neuronal regeneration. **(A)** Schematic summary of histone H3K4me1- and eRNA-mediated enhancer regulation for *WNT3A* transcription during regeneration. Dark blue line depicts genomic DNA ranging from predicted enhancer, sub-regions e1 to e10. Relative position of the e2, e5, e7 enhancer regions are denoted. Pink hexagon represents H3K4me1. Brown circle represents H3K27ac. eRNAs derived from e5 and e7 are indicated as light blue and green lines, respectively. Red arrows point to the activation of eRNA transcription mediated by increased histone modification during regeneration. Black arrow marks the transcription of *WNT3A*. Promoter region for *WNT3A* is depicted by thick gray dashed line. The transcription start site (TSS) is denoted as “+1”. **(B)** Schematic model of topological transformation of enhancer-promoter looping mechanism for *WNT3A* regulation during neuronal regeneration. Green arrows point to HindIII cutting sites. Red arrows indicate the site and direction of primers designed for chromosome conformation capture analysis.

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