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Investigating epigenetic roles of repetitive elements in the developing brain

1. Running title

Investigating roles of repetitive genetic elements in brain development

2. Introduction

Neural progenitor cells (NPCs) proliferate, and give rise to neurons or glial cells. Balancing these processes is critical to properly develop our brain. Although various genes responsible for NPC regulation have been identified, gene coding regions in our genome compose only -2% of our genome, whereas repetitive elements (RE) compose more than half of the human genome, and their function in brain development are largely unknown. In the proposed project, we will explore physiological roles of RE in the brain development.

3. Project Description

The proliferation of neural progenitor cells (NPCs) is a key feature of brain development. The majority of NPCs proliferate substantially, and then give rise to neurons or glial cells. Proper regulation of these processes is critical to develop our brain. Furthermore, during evolution, the expansion of NPCs significantly contributes to the increase of brain size, which is one of fundamental features in higher mammals. Epigenetic mechanisms, which modulate cell type-specific gene expression, play critical roles in the development and evolution of the brain, and several genes have been identified. However, gene coding regions in our genome compose only -2% of our genome, whereas repetitive elements (RE) compose more than half of the human genome. Emerging evidence indicate possible roles of RE-derived transcripts as epigenetic factors. Nevertheless, physiological roles of RE in the brain development and evolution largely remained elusive.

Classically, RE were considered as junk DNA. One of the most abundant RE is the Long Interspersed Nuclear Element-1 (LINE-1), a retrotransposon that self-replicates and accounts for almost 20% of human and rodent genomes. Only a fraction of LINE-1s is transcribed and capable of active retrotransposition, but in doing so, they can create de novo mutations, induce genomic instability and reorganize the genome. Other RE are also known to be associated with cancer. Because of their deleterious effects on the genome, the expression of RE is tightly controlled in most cell types. Paradoxically, it has been shown that LINE-1s are highly expressed in neural progenitor cells (NPCs) as well as neurons, suggesting unexplored roles of RE in physiological neurodevelopment.

The proposed project aims to address how RE regulate NPCs, and which specific functions of NPCs are controlled by RE. Using a mouse model, we will address the underlying mechanisms about how RE regulates brain development. First, to identify RE that are expressed in NPCs, we will use deep-sequencing approaches. Second, using loss- and gain-of-function strategies, we will investigate mechanisms underlying RE-dependent epigenetic regulation. Finally, using epigenetic profiling with deep-sequencing and super-resolution imaging, we will address how manipulation of RE-derived RNA affects chromatin status and nuclear architecture of NPCs, which is the fundamental structure in nuclei to maintain cell type-specific epigenetic regulation. Based on the support from the Schram foundation, the project will provide new insights about physiological roles of RE in brain development and evolution.