Hunter College of the City University of New York
Department of Biological Sciences
Fall 2023 Inga Richter Seminar Series

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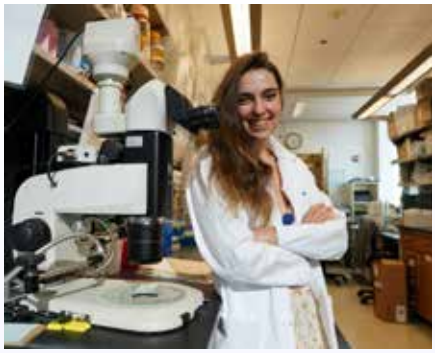

A transposase-derived gene required for human brain development

DNA transposable elements and transposase-derived genes are present in most living organisms, including vertebrates, but their function is largely unknown. PiggyBac Transposable Element Derived 5 (PGBD5) is an evolutionarily conserved vertebrate DNA transposase-derived gene with retained nuclease activity in cells. Vertebrate brain development is known to be associated with prominent neuronal cell death and DNA breaks, but their causes and functions are not well understood. We identified two unrelated consanguineous families with PGBD5 mutations using GeneMatcher. Affected individuals presented with disorder of intellectual disability, movement and seizures. We modeled the impaired human brain development phenotype using a knock-out PGBD5-deficient and putative catalytically inactive Pgbd5 mice. We observed phenocopy of the two mutants, indicating that Pgbd5 nuclease activity is required for its function in normal brain development. Using γH2AX, a surrogate marker for double-strand breaks, we found that Pgbd5 is necessary for the developmental induction of post-mitotic DNA breaks in neurons. Crossing Pgbd5 knock-out mice with Xrcc4 knock-out mice demonstrated epistasis between Pgbd5 and end-joining DNA repair, indicating that developmental neuronal DNA break repair is in part Pgbd5-dependent. We used high-coverage whole-genome sequencing and found that Pgbd5 is responsible for recurrent somatic genome rearrangements in developing neurons. Together, these studies nominate PGBD5 as the long-hypothesized neuronal DNA nuclease required for brain function in mammals. These findings have important implications for the evolution of other domesticated transposase derived genes in vertebrates.

Monday, Oct. 2, 2023 @12:30pm
Hunter North Room 926
Host: Hualin Zhong