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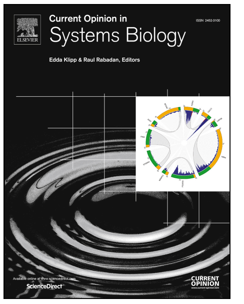

Insights into the role of somatic mosaicism in the brain

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Insights into the role of somatic mosaicism in the brain

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Abstract

Somatic mosaicism refers to the fact that cells within an organism have different genomes. It is now clear that somatic mosaicism occurs in all brains and that somatic mutations in a subset of cells can cause various rare neurodevelopmental disorders. However, for most individuals, the extent and consequences of somatic mosaicism are largely unknown. The complexity and unique features of the brain suggest that somatic mosaicism can play an important role in behavior and cognition. Here we review recent manuscripts showing instances of somatic mosaicism in the brain and estimating its extent and possible biological consequences. The consequences of somatic mosaicism span vast dimensions -from a single-locus variant, to genes and gene networks, to cells, to the interactions of the mosaic cells via neural networks affecting behavior and cognition. We highlight how systems biology approaches are particularly well suited for the complex emerging field of brain somatic mosaicism.

Introduction

Somatic mosaicism results from de novo DNA changes within cells of a body. Each individual cell within an organism has a history of growth, cell division, differentiation, exposure to chemical insults/metabolic stresses, DNA damage and repair that leads to the accumulation of mutations in its DNA. It is inevitable that genomic changes will accumulate within somatic cells during the life of an organism, but somatic mosaicism is of particular interest in the brain because of some of the brain's unique features. For the most part, once the mammalian brain is developed, the neuronal population is not replenished, with the exception of two regions harboring adult neurogenesis (the dentate gyrus of the hippocampus and the subventricular zone). Thus, individual somatic mutations persist throughout the lifetime of the neuron, which can coincide with the lifetime of the organism. Mosaic DNA mutations can potentially alter the physiological properties of each neuron, contributing to overall brain function. The importance of different circuits to the immediate behavior of the organism is modulated over time as the state of the brain changes. Thus, small groups of neurons or even single neurons can influence the behavior of the organism.

The multi-dimensional nature of somatic mosaicism and brain function presents multiple challenges and opportunities for understanding their relationship. In this article, we review the studies, techniques and data that underlie our current understanding of somatic mosaicism. We then explore multiple dimensions of somatic mosaicism data and discuss perspectives on holistic and data integrative approaches that shed light on the role of somatic mosaicism in the brain.

Variant types and mechanisms generating mosaicism

Surprising levels of genomic variation occur within the brain. Structural variations (SV), including copy number variations (CNV), LINE-1 retrotransposon insertions, deletions associated with LINE-1, along with single nucleotide variants (SNVs), create somatic genomic variation within neurons of the