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Genome Reprogramming Over Eons and Embryogenes: Insights from the Sea Lamprey

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Abstract

The lamprey genome provides unique insights into both the deep evolutionary history of vertebrate genome/ developmental biology and the maintenance of genome structure/integrity over development. The lamprey lineage diverged from all other vertebrates approximately 500 million years ago. As such, comparisons between lamprey and other vertebrates permit reconstruction of ancient duplications and rearrangement events that defined the fundamental genome architecture, gene content and developmental biology of all extant vertebrate genomes. Lamprey also undergoes programmatic changes genome structure that result in the physical elimination of ~20% of its genomic DNA (~0.5Gb from a ~2 Gb genome) from all somatic cell lineages during early embryonic development. Here, we outline recent progress in assembly and analysis of the lamprey germline genome, and progress in the development of methods for characterizing the cellular events that mediate DNA elimination and epigenetic reprogramming. We have integrated information from several sampling approaches and sequencing technologies to achieve a highly contiguous assembly of lamprey genome. This genome assembly has dramatically improved our ability to dissect the molecular basis and genetic outcomes of programmed genome rearrangements (PGRs) and has improved our understanding of the tempo and mode of large-scale duplications and translocations within the ancestral vertebrate lineage. Analysis of the germline genome identifies several genes that are physically eliminated from all somatic tissues. These eliminated genes correspond to several known oncogenes that are somatically silenced by Polycomb Repressive Complex during early embryogenesis and reveal several novel oncogene candidates. Cas9-midiated knockout of Polycomb proteins indicates that these genes play a functional role in DNA elimination during lamprey PGR, and functional analyses in human cells provide more direct support for the hypothesis that lamprey uses PGR to eliminate a specific subset of “germline” genes that act as oncogenes in somatic tissues. These functional analyses are complemented by the development of approaches for in situ analysis of 3D preserved cells, which have revealed that PGR unfolds through a series of dramatic cellular events that involve the programmatic alteration of several fundamental mechanisms of mitosis and epigenetic silencing, including: chromatid cohesion, nuclear envelope formation, and covalent modifications of DNA and histones.