Polycomb proteins and 3D genome folding in transgenerational epigenetic inheritance

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Transgenerational Epigenetic Inheritance (TEI) studies the transmission of alternative functional states through multiple generations in the presence of the same genomic DNA sequence. Very little is known on the principles and the molecular mechanisms governing this type of inheritance. Here, I address the possibility that Polycomb Group (PcG) proteins might convey TEI in *Drosophila*. PcG proteins form multimeric protein complexes that regulate chromatin via histone modifications, modulation of nucleosome remodeling activities and regulation of 3D chromosome architecture. These proteins can dynamically bind to some of their target genes and affect cell proliferation and differentiation in a wide variety of biological processes. PcG proteins form two main complexes, PRC2 and PRC1, which coregulate a subset of their target genes, whereas others are regulated only by one of the complexes. We have previously described the 3D architecture of the genome and identified the Polycomb system as one of the fundamental folding and regulatory principles. More recently, we established stable and isogenic *Drosophila* epilines that carry alternative epialleles, defined by differential levels of the Polycomb-dependent H3K27me3 mark, by transiently enhancing 3D chromatin interactions. Once established, epialleles can be dominantly transmitted to naïve flies and induce paramutation. Importantly, epilines can be reset to a naïve state by disrupting chromatin interactions. Finally, environmental changes can modulate the expressivity of the epialleles and we extend our paradigm to naturally occurring phenotypes. Our work sheds light on how nuclear organization and Polycomb group proteins contribute to epigenetically inheritable phenotypic variability.

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