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The role of catalytic activities within Polycomb and Trithorax regulatory systems

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Academic dissertation

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Abstract

Development in multicellular organisms starts with a single totipotent cell, the zygote, that gives rise to the full diversity of specialized cell types. Given that all the cells in an organism contain the same genetic material as the initial starting zygote, the difference between cell types lies in which genes are active and which genes are inactive. The gene expression patterns of critical developmental genes are established during early embryogenesis and need to be maintained through many rounds of cell division. Polycomb group (PcG) and Trithorax group (TrxG) proteins play a key role in preserving these transcriptional states, ensuring that the cell identity is faithfully maintained through successive cell divisions. While PcG proteins maintain gene repression, TrxG proteins ensure that active developmental genes remain active.

PcG proteins act in two main complexes: Polycomb Repressive Complex 1 (PRC1) and Polycomb Repressive Complex 2 (PRC2). One of the core subunits of PRC1, the Ring1 protein, has also been found in complex with other proteins that are not part of PRC1, such as Siesta protein. However, it is unclear whether the Siesta-Ring1 complex is part of the Polycomb system, or if it has a different function. In Manuscript I, we discovered that this complex works independently of the Polycomb system, as it does not epigenetically control developmental genes. Instead, it regulates locomotion independently of Ring1 catalytic activity. The study further shows that PRC1 and Siesta complexes deposit H2AK118ub at different genomic locations and that it is unlikely that H2AK118ub has a repressive role on transcription.

Ash1 and Trx are two TrxG lysine methyltransferases that play a central role in counteracting erroneous PcG-mediated repression. In addition to methylating histones, both proteins are thought to methylate as-yet-unknown non-histone substrates. Furthermore, Ash1 and Trx depend on each other for recruitment to chromatin, but it is unclear whether this process requires their catalytic activity. In Manuscript II, we improved a previously published method to identify lysine-methylated non-histone proteins and established the draft *Drosophila* nuclear lysine-methyl-proteome. In Manuscript III, we identified several candidate non-histone substrates of Ash1 and Trx. Moreover, we showed that the catalytic activities of Ash1 and Trx are not required for their mutual recruitment to chromatin.

Keywords: Drosophila melanogaster, Polycomb group proteins, Trithorax group proteins, Siesta, lysine methylation

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