Topologically associating domain boundaries serve as hitchhiking platforms for the Drosophila dosage compensation complex

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Abstract

Dosage compensation in flies, in contrast to mammals, increases gene expression from the single X chromosome in males. To achieve this the dosage compensation complex (DCC) in Drosophila melanogaster specifically recognizes the X chromosome and acetylates the histone H4 of active genes. A set of genomic regions known as high-affinity sites (HAS) had been identified as the X-specific binding locations of the dosage compensation complex. However, HAS are scattered throughout the X chromosome but no logic behind such disposition is currently known. Using Hi-C data we demonstrate that HAS are non-randomly distributed, appearing almost exclusively at the boundaries of topologically associating domains (TADs). To understand the significance of this localization we analyzed Hi-C and 4C-seq contact data and found that TAD boundaries display more contacts to each other as well a to other chromosomal regions as compared to any other genomic region. These features are sex-independent as Hi-C and 4C-seq contact maps remain comparable between male, female and DCC knockdowns. Further experiments allowed us to differentiate a two step process in which dosage compensation progresses: First, the DCC targets the X chromosome by binding HAS at TAD boundaries, then the DCC spreads from HAS to reach spatially nearby genes. Thus, once the DCC is bound to the chromosome X, it spreads, probably by diffusion, to nearby chromatin. Based on our Hi-C and 4C-seq data we argue that TAD boundaries offer the best location from which spatial spreading can reach most chromatin, this could explain why the high-affinity sites are almost exclusively found at boundaries.

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