MCB, vol.16, supplemental 2, pp.83, 2019

Histone Modification and Chromatin Reorganization Regulated by Mechanical Tension in Single Cell Mitosis

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Abstract: The dramatic re-organization of chromatin during mitosis is perhaps one of the most fundamental of all cell processes [1,2]. It remains unclear how epigenetic histone modifications, despite their crucial roles in regulating chromatin architectures, are dynamically coordinated with chromatin reorganization in controlling this process. Mechanical cues have also been shown to play important roles in modulating gene expressions and cellular functions [3,4]; however, it is still unclear about the mechanical regulations of epigenetics and chromatin organization. In this study, we have developed and characterized biosensors with high sensitivity and specificity based on fluorescence resonance energy transfer (FRET). These biosensors were incorporated into nucleosomes to visualize histone H3 Lys-9 tri-methylation (H3K9me3) and histone H3 Ser-10 phosphorylation (H3S10p) simultaneously in the same live cell. We observed an anti-correlated coupling in time between H3K9me3 and H3S10p in a single live cell during mitosis. A transient increase of H3S10p during mitosis is accompanied by a decrease of H3K9me3 that recovers prior to the restoration of H3S10p upon mitotic exit. We further showed that H3S10p is causatively critical for the decrease of H3K9me3 and the consequent reduction of heterochromatin structure, leading to the subsequent global chromatin reorganization and nuclear envelope dissolution as a cell enters mitosis. Moreover, we observed higher H3K9me3 level and slower cell mitosis process on harder PAA gel (21.5KPa), while lower H3K9me3 level and faster cell mitosis process on softer PAA gel (2.5KPa). These results suggest a tight coupling of H3S10p and H3K9me3 dynamics in the regulation of heterochromatin dissolution prior to global chromatin reorganization during mitosis, and also mechanical tension can affect epigenetic modifications via the same phosphorylation-methylation regulation mechanism.

Keywords: Histone modification; chromatin reorganization; mechanical tension; FRET biosensor

Acknowledgement: This work is supported by NIH Grants HL121365, GM125379 (to S.C. and Yingxiao Wang), CA204704, and CA209629 (to Yingxiao Wang); NSF Grants CBET1360341 and DMS1361421 (to Yingxiao Wang and S.L.); and the Beckman Laser Institute Foundation and is also funded by China Scholarship Council (to Q.P.).

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