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HMGB2 orchestrates the chromatin landscape of senescence-associated secretory phenotype gene loci

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Abstract

Cellular senescence is a stable cell growth arrest that is characterized by the silencing of proliferation-promoting genes through compaction of chromosomes into senescence-associated heterochromatin foci (SAHF). Paradoxically, senescence is also accompanied by increased transcription of certain genes encoding for secreted factors such as cytokines and chemokines, known as the senescence-associated secretory phenotype (SASP). How SASP genes are excluded from SAHF-mediated global gene silencing remains unclear. In this study, we report that high mobility group box 2 (HMGB2) orchestrates the chromatin landscape of SASP gene loci. HMGB2 preferentially localizes to SASP gene loci during senescence. Loss of HMGB2 during senescence blunts SASP gene expression by allowing for spreading of repressive heterochromatin into SASP gene loci. This correlates with incorporation of SASP gene loci into SAHF. Our results establish HMGB2 as a novel master regulator that orchestrates SASP through prevention of heterochromatin spreading to allow for exclusion of SASP gene loci from a global heterochromatin environment during senescence.

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