Hypoxia increases methylated histones to prevent histone clipping

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Hypoxia increases histone methylation by inhibiting O2- and α-ketoglutarate-dependent histone lysine demethylases. This study is the first to demonstrate how the hypoxia-induced increase in methylated histone levels interacts with other epigenetic changes, such as histone clipping and heterochromatin redistribution (senescence-associated heterochromatin foci, SAHF) during oncogene-induced senescence (OIS). Raf activation in primary IMR90 human fibroblasts increased cathepsin L (CTSL)-mediated histone 3 (H3), H2B, and H4 clipping at H3 A21/T22, H2B T19/K20, and H4 G11/K12, respectively. Hypoxia protected H3 from CTSL by increasing histone methylation, especially at H3K23me3, without reducing CTSL activity. Maintaining methylated histones is sufficient for protecting histones from CTSL. However, these methylated histones are insufficient but necessary for inhibiting SAHFs. ATAC-seq analyses showed that Raf activation increased chromatin accessibility, which hypoxia prevented.