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Chromatin Structural Proteins as Integrators of Metabolic, Hormonal and Biomechanical Stress

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Environmental stressors from the diet, toxin or drug exposure, and physical trauma interact with genetic susceptibility to impair human health. These factors impart durable change in gene expression and cellular phenotype through mechanisms that involve alterations in epigenetic processes. By studying classes of DNA binding proteins responsible for higher order genome organization, we have discovered that chromatin itself serves as a biosensor for metabolic processes, mechanical perturbation and potentially the actions of hormones and other drugs. As an archetype, we have recently shown that the linker histone H1 family of proteins is responsible for coupling various biomechanical behaviors of cells, including proliferation, production of extracellular matrix and passive contraction in the setting of wound healing in various organs. Histone H1 accomplishes these functions through coordination with specific post-translational modification of nucleosome histones and by the recruitment of reader proteins to target genes. Importantly, we demonstrate that the actions of histone H1 to regulate cellular biomechanical behaviors are directly linked with its actions to compact chromatin at the locus and whole genome level—actions that influence the overall deformability of the nucleus and cell. By characterizing the time course of these changes, we have identified how the stoichiometry of linker H1 to nucleosome histones is influenced by metabolism, hormones and changes to the extracellular environment, providing molecular insights into how cells remember experiences via chromatin. These findings have fundamental implications for how tissues respond to drugs, injury and the inflammatory responses engaged in disease.