The methylation of histones is a fundamental epigenetic process regulating gene expression programs in mammalian cells, and dysregulated histone methylation patterns have been implicated in malignant transformation. Heparanase is an endo-β-glucuronidase that cleaves heparan sulfate and facilitates the passage of migrating cells through extra-cellular matrices (ECM), as well as releasing heparan sulfate-bound growth factors from the ECM, whereby the released growth factors also aid wound healing and angiogenesis. Recent studies suggest that heparanase has biological functions independent of its enzymatic activity, and a number of studies have reported the presence of heparanase in the nucleus of cells. Now, a new study found that heparanase enters the nucleus of activated human lymphocytes and regulates transcription of a cohort of inducible immune response genes by controlling histone H3 methylation patterns. Dr Sudha Rao and colleagues found that nuclear heparanase preferentially associates with euchromatin. Genome-wide ChIP-on-chip analyses showed that heparanase is recruited to both the promoter and transcribed regions of a distinct cohort of transcriptionally active genes. Knockdown and overexpression of heparanase confirmed that chromatin-bound heparanase is a prerequisite for the transcription of a subset of inducible immune response genes in activated T cells. Furthermore, the specific actions of heparanase seem to influence gene transcription by associating with the demethylase LSD1, preventing recruitment of the methylase MLL and thereby modifying histone H3 methylation patterns. Heparanase belongs to an emerging class of proteins that play an important role in regulating transcription in addition to their well-recognized extra-nuclear functions.

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Nucleo-cytoplasmic transport of cytoplasmic poly(A)-binding proteins

Cytoplasmic poly(A)-binding proteins (PABPs) regulate mRNA stability and translation. Although predominantly localized in the cytoplasm, PABP proteins also cycle through the nucleus. Recent work has shown that their steady-state localization can be altered by cellular stresses such as UV radiation or infection by several viruses, resulting in nuclear accumulation of PABPs. A recent report by Drs Burgess and Gray presents further evidence that the interaction of PABPs with and release from mRNA and translation complexes are important in determining the sub-cellular distribution of PABPs. The authors propose an integrated model for regulated nucleo-cytoplasmic transport of PABPs, in which RNA is a major determinant of the transport of PABP to and from the cytoplasm. Perturbations of the balance between PABP import and export, such as the introduction of viral endonucleases that destroy cytoplasmic mRNAs or the cessation of mRNA export result in a redistribution of predominantly cytoplasmic PABPs to the nucleus.

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Role of nucleolin in disease

The protein nucleolin is primarily localized in the nucleolus, but also found in the nucleoplasm, cytoplasm, and cell membrane. The multifunctional protein is involved in several aspects of DNA metabolism, and participates extensively in RNA regulatory mechanisms, including transcription, ribosome assembly, mRNA stability and translation, and microRNA processing. Nucleolin has also been implicated in disease. It can associate with target RNAs via its four RNA-binding domains and its arginine-glycin-rich domain. By modulating the post-transcriptional fate of target mRNAs, which typically bear AU-rich and/or G-rich elements, nucleolin has been linked to cellular events that influence disease, notably cell proliferation and protection against apoptotic death. Through its diverse RNA functions, nucleolin is increasingly implicated in pathological processes, particularly cancer and viral infection. A recent Review by Drs. Abdelmohsen and Gorospe focuses on the RNA-binding activities of nucleolin, its influence on gene expression patterns, and its impact upon diseases. The authors also discuss the rising interest in targeting nucleolin therapeutically.

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HP1 and PCNA
Components of a multiprotein DNA replication complex

Heterochromatin protein 1 (HP1) is a small non-histone chromosomal protein known as a dominant suppressor of position-effect variegation and a major component of heterochromatin. It is highly conserved and found in fungi, plants and animals (but not in prokaryotes or yeast). Posttranslationally modified HP1, through interaction with protein partners from different groups, can be involved in a number of nuclear processes, including gene activation, chromatin remodeling, replication, transcription and DNA repair. One such protein partner of HP1 is proliferating cell nuclear antigen (PCNA), a key player in DNA replication. In a new study, Drs. Trembecka-Lucas and Dobrucki demonstrated that HP1β (one of three HP1 isoforms existing in human cells) and PCNA are closely spaced components of a multiprotein complex involved in replication, both in S phase and during DNA repair, and that the functional complex requires formation of an HP1 dimer. The findings are based on bimolecular fluorescence complementation analysis (BFC), where two proteins suspected of forming an in-vivo complex are fused to complementary fragments of a fluorescent protein (FP). The nonfluorescent FP fragments form an active fluorescent molecule only when the complementary moieties of FP are brought together by the interaction of fusion proteins. The study results suggest that HP1β may be a component of a replication complex and a critical factor in DNA replication, both in S phase and in DNA repair.

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