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Landes Highlights

Nuclear co-import of functionally and topologically linked cargo

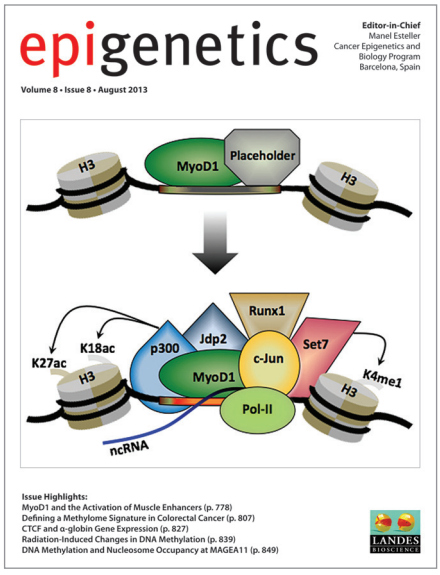
Ribosomes are the macromolecular machines that synthesize all cellular proteins from mRNA templates. In eukaryotes, ribosomes, which are composed of ribosomal proteins and rRNA, are mainly assembled in the nucleus. Thus, ribosomal proteins require a nuclear transport step from their place of synthesis in the cytoplasm to their site of assembly in the nucleus. Recognition of import substrates is mediated by different types of nuclear localization signals, which are either directly recognized by import receptors or recruited to these via adaptor proteins. The novel transport adaptor Syo1 (Symportin), which is dedicated to the synchronous import of two functionally related ribosomal proteins, has recently been described. In a novel review, Dr Dieter Kressler and colleagues highlight and discuss these findings in the context of current knowledge of ribosome assembly and nucleocytoplasmic transport. They propose that nuclear co-import of functionally and topologically linked cargo could be a widespread strategy to streamline assembly of macromolecular complexes in the nucleus.

Reference

Bange G, Murat G, Sinning I, Hurt E, Kressler D. New twist to nuclear import: When two travel together. Commun Integr Biol 2013; 6:e24792; http://dx.doi.org/10.4161/cib.24792; PMID:23940825

DNA methylation and nucleosome occupancy regulate cancer germline gene *MAGEA11*

MAGEA11 is a cancer germline (CG) antigen and androgen receptor (AR) co-activator. It was previously reported that the *MAGEA11* promoter island is hypermethylated in benign prostatic intraepithelial neoplasia but can become hypomethylated in prostate cancer, particularly in castration-recurrent disease, and that this occurs in conjunction with gene activation. MAGEA11 appears to make a specific contribution to prostate cancer via its myriad of effects on AR signaling. A research team led by Dr Adam Karpf set out to clarify two questions: (1) Is *MAGEA11* activation a specifically selected event or associated with activation of other CG genes as a result of a global epigenetic alteration, such as DNA hypomethylation? (2) Is *MAGEA11* activated in human cancers other than prostate, and if so, does this result from epigenetic alterations? In silico analyses revealed that *MAGEA11* is frequently expressed in human cancers, is increased during tumor progression and correlates with poor prognosis and survival. In prostate and epithelial ovarian cancers (EOC), *MAGEA11* expression was associated with promoter and global DNA hypomethylation and with activation of other CG genes. Inhibition of DNA methyltransferases and/or histone deacetylases activated *MAGEA11* in a cell line specific manner. As for the mechanism of *MAGEA11* activation, the authors found that DNA methylation regulated nucleosome occupancy specifically at the –1 positioned nucleosome of *MAGEA11*. Methylation of a single Ets (E-20 six, a family of transcription factors) site near the transcriptional start site correlated with –1 nucleosome occupancy and, by itself, strongly repressed *MAGEA11* promoter activity. Thus, DNA methylation regulates nucleosome occupancy at *MAGEA11*, and this appears to function cooperatively with sequence-specific transcription factors to regulate gene expression. *MAGEA11* regulation is highly instructive for understanding mechanisms regulating CG antigen genes in human cancer.



Reference

James SR, Cedeno CD, Sharma A, Zhang W, Mohler JL, Odunsi K, Wilson EM, Karpf AR. DNA methylation and nucleosome occupancy regulate the cancer germline antigen gene MAGEA11. Epigenetics 2013; 8:849-63; http://dx.doi.org/10.4161/epi.25500; PMID:23839233

Novel role for septin 9 in nucleocytoplasmic transport

Mammalian septins are a family of evolutionarily conserved GTP-binding proteins with roles in multiple core cellular functions. Previous studies suggest that heteromeric septin complexes provide higher-order structures that can act as scaffolds or docking sites for other proteins important in key cellular processes. There are 13 genes encoding both ubiquitous and tissue-specific septins. Septin 9 has been identified as a potential oncogene, and its overexpression has been observed in several carcinomas. Septin 9 isoform 1 (SEPT9_i1) protein associates with hypoxia-inducible factor (HIF)-1α, and this interaction increases HIF-1α protein stability as well as HIF-1 transcriptional activity, leading to enhanced proliferation, tumor growth and angiogenesis. The first 25 amino acids of SEPT9_i1 (N_{25}) are unique compared with other members of the mammalian septin family. This N_{25} domain is critical for HIF-1 activation by SEPT9_i1 but not essential for the protein-protein interaction. A recent study by Drs Golan and Mabjeesh describes a novel mechanism by which SEPT9_i1 promotes HIF-1 transcriptional activation. The authors found that SEPT9_i1 binds to both importin-α and HIF-1α to facilitate HIF-1α translocation into the nucleus. The observation that SEPT9_i1 associated with HIF-1α through the GTPase domain and with importin-α through a bipartite nuclear localization sequence (NLS) in the N25 domain supports the hypothesis that SEPT9_i1 acts to facilitate the assembly of importin-α/HIF-1α complex to enable efficient nuclear translocation of HIF-1α. In conclusion, the results of the current study demonstrate a new and previously unrecognized role of a septin protein in the nucleocytoplasmic transport. This also represents a novel mechanism that regulates tumor growth and angiogenesis via affecting intracellular HIF-1α trafficking. The authors propose that disruption of HIF-1α-SEPT9_i1-importin-α interactions could therefore serve as a target for cancer therapeutics.

Reference

Golan M, Mabjeesh NJ. SEPT9_i1 is required for the association between HIF-1α and importin-α to promote efficient nuclear translocation. Cell Cycle 2013; 12:2297-308; http://dx.doi.org/10.4161/cc.25379

Rad4p regulates heterochromatin structure and gene silencing in yeast

DNA in eukaryotes is packed into chromatin, which exists in two different forms, euchromatin and heterochromatin. The transcriptionally silent mating HM loci of the *Saccharomyces cerevisiae* genome represent the yeast equivalent of metazoan heterochromatin. In contrast to euchromatin structure that is permissive for gene expression, heterochromatin adopts a condensed higher order structure that silences gene transcription. The silent information regulator (SIR) complex mediates heterochromatin formation at the mating type loci. Rad4p is a DNA damage recognition protein essential for global genomic nucleotide excision repair in *S. cerevisiae*. A new study by Dr Feng Gong and colleagues showed that Rad4p binds to the heterochromatic HML locus (one of the silent mating cassettes). In a yeast mutant lacking Rad4p, an increased level of SIR complex binding at the HML locus was accompanied by an altered, more compact heterochromatin structure, as revealed by a topological analysis of chromatin circles released from the locus. In addition, gene silencing at the HML locus was enhanced in the rad4Δ mutant. Importantly, re-expression of Rad4p in the rad4Δ mutant restored the altered heterochromatin structure to a conformation similar to that detected in wild-type cells. Taken together, these findings reveal a novel role of Rad4p in the regulation of heterochromatin structure and gene silencing.

Reference

Zhang L, Chen H, Bi X, Gong F. Detection of an altered heterochromatin structure in the absence of the nucleotide excision repair protein Rad4 in Saccharomyces cerevisiae. Cell Cycle 2013; 12:2435-42; http://dx.doi.org/10.4161/cc.25457; PMID:23839037