MCB
Journals.ASM.org

Articles of Significant Interest Selected from This Issue by the Editors

Full-Length RAG Complex Provides New Insights into Targeting during V(D)J Recombination

Shimazaki et al. (p. 365–375) used full-length purified RAG complexes to examine the discrimination of correct (optimal) and off-target sites in T cell lymphomas. DNA sequence discrimination relies on the RAG2 C terminus, which is a new role for this region, beyond its known role in histone tail interaction. Discrimination occurs at the nicking step rather than the hairpinning step and is due to stronger binding and a higher catalytic rate. The heptamer affects the catalytic rate, whereas the nonamer affects both binding and catalytic rate. Therefore, the basis for RAG discrimination is that the RAG complex falls off the suboptimal (off-target) sites before it can nick, relative to optimal sites.

Recognition of CpG Island Chromatin through Linker DNA

CpG islands are associated with 70% of human promoters, yet how these features are recognized and utilized in gene regulation remains poorly understood. Recently the zinc finger CXXC DNA binding domain was shown to target chromatin modifying activities to CpG islands. Zhou et al. (p. 479–489) now reveal that one of these enzymes, KDM2A, recognizes CpG islands through interrogation of linker DNA and demonstrate that both DNA methylation and nucleosome occupancy elsewhere in the genome restrict its binding to CpG islands. Therefore, DNA sequence, methylation status, and chromatin structure are defining factors that regulate how the CpG island signal is translated into chromatin modification at gene promoters.

Translational Regulation of the ARF Tumor Suppressor by mTORC1 Signals

The ARF tumor suppressor is a crucial checkpoint against hyperproliferative stimuli. Previous studies have elucidated the transcriptional mechanisms by which ARF can be induced from oncogenic signals, such as those emanating from oncogenic Ras. However, ARF's ability to respond to oncogenic stimuli in the absence of cooperating transcriptional cues is poorly defined. Miceli et al. (p. 348–364) report that the progrowth Ras/TSC/mTORC1 signaling pathway regulates ARF protein expression and triggers ARF-mediated cell cycle arrest through a novel translational mechanism. Thus, ARF tumor suppression safeguards the cell against additional hypergrowth signals that could aid in the mechanisms underlying tumorigenesis.

Androgen Receptor Collaborates with NKX3-1 To Promote Prostate Cancer Cell Survival

Androgen receptor (AR) orchestrates an intricate transcriptional regulatory network governing prostate cancer development. Tan et al. (p. 399–414) show that *NKX3-1,* an androgen-responsive homeobox gene, is integrated into the AR transcriptional network via two distinct pathways: (i) by directly upregulating the expression of AR and (ii) by collaborating with AR and the pioneering factor FoxA1. They also demonstrate that RAB3B GTPase, an AR and NKX3-1 direct target, contributes to prostate cancer development by promoting cell viability. Taken together, their findings highlight a novel hierarchical transcriptional network between AR, NKX3-1, and the RAB GTPase signaling pathway in prostate cancer progression.

Stabilization of Mitochondrial Respiratory Complexes by Low-Reactive-Oxygen-Species Conditions

The mechanisms that regulate mitochondrial respiratory complexes stability and their association into supercomplexes are unknown. Diaz et al. (p. 415–429) showed that the compromised stability of complex I (CI), CIV, and supercomplexes observed in Rieske iron sulfur protein (RISP) knockout cells was associated with increased levels of reactive oxygen species (ROS). Likewise, mitochondrial inhibitors that increased ROS caused CI and supercomplex instability. Exposure of RISP knockout cells to hypoxia or superoxide scavengers reverted CI and CIV instability and increased supercomplex formation. Stabilization of respiratory complexes and supercomplexes could constitute a regulatory mechanism to control cellular ROS levels.

doi:10.1128/MCB.06641-11