In This Issue

Cell

Telomerase Turns Back Time in Organismal Aging

PAGE 609

Telomerase can confer limitless proliferative potential to human cells through its ability to elongate telomeres. However, study of telomerase in organismal aging has been complicated by its cancer-promoting effects. To circumvent this issue, Tomas et al. use mice engineered to be cancer resistant through the enhanced expression of the tumor suppressors p53, p16, and p19ARF to study the effects of telomerase expression. In this context, telomerase overexpression improves organismal fitness and produces a systemic delay in aging accompanied by life-span extension. These results demonstrate that telomerase can provide antiaging activity in mammalian organisms.

The Silencing Effects of Pol V Transcription

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Although most of the nuclear genome is transcribed, only a small fraction of the resulting RNAs encode proteins or serve obvious functions. Wierzbicki et al. show that *Arabidopsis* nuclear RNA polymerase V (formerly know as Pol IVb) synthesizes noncoding transcripts that function in the silencing of overlapping SINE and LINE retroelements, most likely by serving as scaffolds for siRNA-mediated heterochromatin formation. In addition to providing a functional role for noncoding intergenic transcription, the study addresses one of the paradoxes of epigenetic control, namely the need for transcription in order to transcriptionally silence genes in the same region.

Histone Variant Pairs Up with Polycomb in ES Cells

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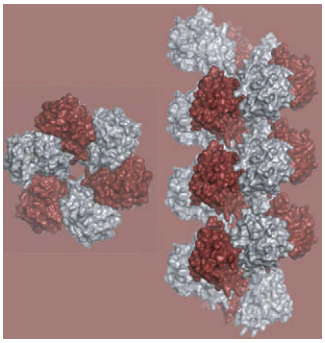
The replacement of histones with histone variants has emerged as a key epigenetic mechanism to regulate genome function in all eukaryotes. Here, Creyghton et al. find that the essential histone H2A variant H2AZ colocalizes with Polycomb group (PcG) proteins to a large cohort of developmentally important genes in embryonic stem (ES) cells, and that H2AZ is necessary for target gene regulation and for ES cell differentiation. In contrast, H2AZ and PcG proteins occupy different subsets of genes in lineage-committed cells. This work suggests that H2AZ and PcG proteins function together in ES cells as components of a regulatory switch that mediates the initial stages of lineage commitment.

DDK Ramps Up for Meiosis

PAGE 662

Meiosis generates haploid gametes from diploid germ cells through a single DNA replication phase that is followed by the sequential segregation of homologous chromosomes and sister chromatids. Matos et al. show that the Dbf4-dependent Cdc7 kinase (DDK), which has an established role in DNA replication, is also essential for the segregation of homologous chromosomes in meiosis. Activation of DDK during premeiotic DNA replication therefore commits cells to undergo a meiotic instead of a mitotic pattern of chromosome segregation. DNA replication and homolog segregation require different levels of DDK activity, suggesting a possible mechanism for how cells establish the order of meiotic events.

Spiraling into DNA Replication Initiation



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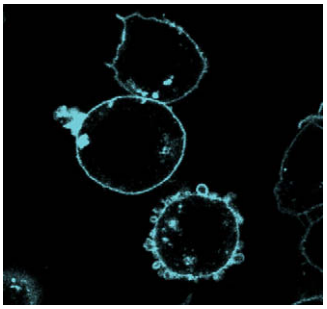
The appropriate loading of helicases onto replication origins is essential for DNA replication. A critical unexplained step in this process is the mechanism by which initiator and helicase loader ATPases of the AAA+ superfamily regulate helicase recruitment and deposition. In this issue, Mott et al. show that, like the initiator DnaA, the loader DnaC adopts a conformation of right-handed oligomers when bound to ATP. This architectural congruence facilitates ATP-dependent crosstalk between the factors. These results indicate that the helicase loader is a molecular adaptor that "plugs into" an activated initiator assembly to ensure the correct spatial deposition of replicative helicases on DNA.

Antibiotic Double Whammy Kills Bacteria

PAGE 679

Aminoglycosides are a powerful, broad-spectrum class of antibiotics with excellent activity against common infections involving Gram-negative bacteria. These antibiotics directly target the ribosome. Kohanski et al. now show that mistranslation and misfolding of membrane proteins are central to aminoglycoside-induced oxidative stress and cell death. Signaling mediated by the envelope stress response two-component system and the redox-responsive two-component system are also required. Importantly, these two-component systems are shown to play a general role in bactericidal antibiotic-mediated cell death, thus expanding our understanding of the common mechanism of killing induced by bactericidal antibiotics.

TCR Tyrosines Make Like an Ostrich



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Many immune receptors signal through cytoplasmic tyrosine-based motifs (ITAMs). Phosphorylation of tyrosines in the ITAM following receptor ligand binding initiates downstream signaling and lymphocyte activation. Most models predict that the cytoplasmic domains of the receptor complex float as unstructured chains in the cytosol, making the tyrosines accessible to kinases for modification. Xu et al. now demonstrate that the CD3ε cytoplasmic domain of the T cell receptor is membrane bound prior to binding of ligand to the receptor. In this inactive, membrane-bound state, the key tyrosines insert into the hydrophobic core of the lipid bilayer, rendering them inaccessible to kinases, thus suggesting a mechanism to prevent lymphocyte activation in the absence of ligand. Sequestration of this signaling motif into the lipid bilayer represents a new mechanism for the control of receptor activation.

Bacteria Beat Back Bleach

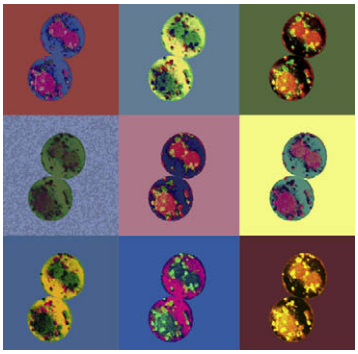
PAGE 691

Hypochlorous acid, the active ingredient of household bleach, is one of the most effective disinfectants known. As such, mammals produce it to fight bacterial infections. Winter et al. now report one mechanism by which bleach kills bacteria. The authors find that bleach causes large-scale oxidative unfolding and aggregation of cellular proteins. The authors also uncover a bacterial defense mechanism against bleach. The bacterial molecular chaperone Hsp33 is specifically activated by the protein-unfolding actions of bleach and prevents aggregation of the unfolded proteins, thus protecting bacteria from cell death.

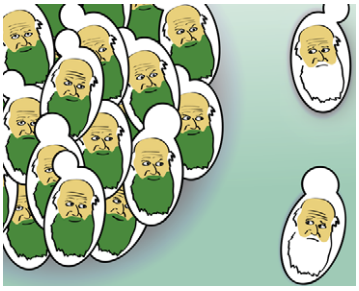
Artfully Cleaning Up the Cell Surface

PAGE 714

Cell-surface remodeling is a dynamic process affecting cell growth, differentiation, and homeostasis. Eukaryotic cells mediate remodeling through endocytosis, where specific surface proteins are targeted for internalization by ubiquitination. Lin et al. now report the identification of a family of ubiquitin ligase adaptors in yeast that exhibit similarity to mammalian arrestins and may contribute towards determining specifity in endocytic downregulation. The authors show that two of these ARTs (arrestin-related trafficking adaptors) regulate induced endocytosis of specific surface proteins by recruiting a yeast Nedd4 ubiquitin ligase. Their results provide insight into how cells remodel their surface during growth and development.



Yeast with Green Beards Battle Cheaters



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How does cooperative behavior evolve in the face of a selective advantage for cheating (that is, reaping the benefits of cooperation without investing in it)? Smukalla et al. show that flocculation in budding yeast, in which cells clump together to form multicellular aggregates, is a model for the evolution of cooperation. Flocculation is driven primarily by one gene, *FLO1*, and protects yeast from environmental stresses that are lethal to single cells. *FLO1*$^{+}$ cells avoid exploitation by *FLO1*$^{-}$ "cheater" cells by self/nonself-recognition mediated by the FLO1 protein. *FLO1* is therefore one of a few known so-called "green beard genes" that direct cooperation towards other carriers of the same gene.

Setting TRAPs for Neuronal Subtypes

PAGE 738 and PAGE 749

The brain is composed of many hundreds of distinct cell types, and this complexity has made it difficult to elucidate the biological properties of individual neuronal populations. Heiman et al. have now overcome this problem by developing a new methodology that permits identification of all translated mRNAs in specific populations of neurons. In an accompanying paper, Doyle et al. apply this methodology for large-scale comparative studies of multiple distinct neuronal and glial CNS cell populations. This approach, translating ribosome affinity purification or TRAP, provides a foundation for in-depth analysis of the molecular properties of specific cell types in complex tissues under various physiological, pharmacological, and pathological conditions.