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SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Loss of Telomerase Makes Cells Immediately Vulnerable to Replication Stress

Telomeres protect chromosome ends from degradation that can lead to genomic instability. With prolonged loss of telomerase activity, telomeres become critically short, leading to permanent cell cycle arrest (senescence). Jay et al. (p. 1908–1919) show that even a short period of telomerase inactivation renders yeast cells completely dependent on DNA damage response (DDR) adaptor proteins. Serious defects found in telomerase DDR mutants cannot be accounted for by slow erosion of telomeres due to senescence. It is proposed that normally occurring telomeric DNA replication stress is resolved through telomerase activity and the DDR in two parallel pathways.

AMPK Facilitates Nuclear Accumulation of Nrf2 by Phosphorylating at Ser550

Nrf2 increases antioxidant capacity. AMP-activated protein kinase (AMPK) is activated by energy deficiency, frequently prior to oxidative stress. Nrf2 should therefore be coordinated with cell survival pathways controlled by AMPK, but the mechanistic connections remain undefined. Joo et al. (p. 1931–1942) reveal that AMPK phosphorylates Nrf2 at Ser550, located in the nuclear export signal sequence, causing nuclear accumulation of Nrf2 and increased antioxidant response element-mediated gene transcription. This event occurs in association with AMPK-mediated inhibition of glycogen synthase kinase 3β, which catalyzes Nrf2 nuclear exclusion. The study provides key information on the coherent "on-off" signaling loop for Nrf2, by which the status of energy deficiency promotes an increase in antioxidant capacity.

AMPK Phosphorylates Desnutrin/ATGL and Hormone-Sensitive Lipase To Regulate Lipolysis and Fatty Acid Oxidation within Adipose Tissue

AMP-activated protein kinase (AMPK) is known to promote fatty acid (FA) oxidation. However, the role of AMPK in lipolysis and FA metabolism in adipose tissue is controversial. Kim et al. (p. 1961–1976) generated adipose tissue-specific double knockout mouse models for α1 and α2 AMPK catalytic subunits. AMPK deficiency prevents phosphorylation of desnutrin/ATGL at Ser406 to decrease its lipase activity, lowering basal lipolysis. AMPK deficiency also decreases hormone-sensitive lipase phosphorylation at Ser565, allowing higher phosphorylation by protein kinase A, increasing its hydrolase activity in isoproterenol-stimulated conditions. With higher overall lipolysis, knockout mice are lean, with lower adipose triacylglycerol but higher free FA, which activates peroxisome proliferator-activated receptor delta to induce FA oxidation and energy expenditure. Thus, AMPK lowers FA oxidation in adipose tissue.

Novel MicroRNA Regulators of Atrial Natriuretic Peptide Production

Atrial natriuretic peptide (ANP) has a central role in regulating blood pressure in humans. Using computational, genomic, and cellular tools, Wu et al. (p. 1977–1987) identified two microRNAs (miRNAs) that modulate ANP production by cardiomyocytes and target *NPPA* 3′ untranslated region sequences containing genetic variants whose minor alleles are associated with higher human plasma ANP levels. Both miRNA 155 (miR-155) and miR-105 repressed *NPPA* mRNA in an allele-specific manner, with the minor allele of each variant conferring resistance to the miRNA. These findings suggest the potential for miRNA-targeted therapies to increase ANP levels, which could represent a new strategy for the treatment of hypertension/heart failure.

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