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Articles of Significant Interest Selected from This Issue by the Editors

Inactivation of FBXO4 Contributes to Cyclin D1 Overexpression and Metastatic Melanoma

Cyclin D1 dysregulation is a major contributor to melanomagenesis. FBXO4, a specificity factor for the E3 ligase that directs phosphorylation- and ubiquitin-dependent cyclin D1 degradation, has not been evaluated in melanoma. Lee et al. (p. 4422–4433) demonstrate that *FBXO4* is subject to somatic, inactivating mutations in human melanoma and that these mutations selectively contribute to cyclin D1 dysregulation while maintaining activity toward another substrate, TRF1. Consistent with inactivating mutations in human melanoma, Fbxo4 knockout mice are susceptible to Braf-driven melanoma, underscoring the importance of this ubiquitin ligase in tumor suppression.

PIAS1, a Novel Regulator of Adipogenesis

C/EBPβ, a master transcription factor during adipogenesis, turns on series of adipocyte genes that give rise to the adipocyte phenotype. The function of C/EBPβ is regulated by SUMOylation, but the E3 ligase that is required for C/EBPβ SUMOylation has not been identified. Liu et al. (p. 4606–4617) demonstrate that PIAS1 acts as a SUMO E3 ligase for C/EBPβ. PIAS1 SUMOylates C/EBPβ and contributes to the ubiquitin-mediated degradation of C/EBPβ, thereby inhibiting adipogenesis. This observation provides new insight into the role of PIAS1 in adipogenesis and the regulation of C/EBPβ.

Uaf1, a Critical Player in DNA Repair and Embryonic Development

Deubiquitinating (DUB) enzymes are known to regulate DNA repair. DUB enzyme complex Usp1/Uaf1 regulates the Fanconi anemia (FA) DNA repair pathway. Usp1 deficiency in mice results in a FA-like phenotype and a defect in homologous recombination (HR) repair. Park et al. (p. 4360–4370) disrupted the murine Uaf1 gene and unraveled some of its novel functions. Surprisingly, homozygous deletion of Uaf1 resulted in murine embryonic lethality. Similar to Usp1 deficiency, however, inactivation of Uaf1 impaired the FA pathway function, caused defective HR repair, and inhibited tumorigenesis. These results suggest that some DUB complexes regulate other cellular functions beyond DNA repair.

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