【103-1 中國醫藥大學現代生物醫學講座】

Regulation of PML tumor suppressor in human cancers

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Abstract

Tumor suppressors are frequently downregulated in human cancers and understanding of the mechanisms through which tumor cells restrict the expression of tumor suppressors would be important for the prognosis and intervention of diseases. The promyelocytic leukemia (PML) protein plays a critical role in multiple tumor suppressive functions, such as growth inhibition, replicative senescence, suppression of oncogenic transformation, and inhibition of migration and angiogenesis. The expression of PML protein is frequently downregulated in diverse types of human tumors and is correlated with tumor progression. We have identified several mechanisms through which PML is downregulated in human cancers. The first mechanism involves the Cul3-KLHL20 ubiquitin ligase complex, which coordinates with the actions of CDK1/2 and Pin1 to mediate PML ubiquitination. Importantly, this pathway participates in a positive feedback loop to potentiate tumor hypoxia responses and is hyperactivated in human prostate cancer. However, in several types of human tumor tissues that display PML downregulation, an inverse correlation between PML and KLHL20 expression is not observed, suggesting the existence of additional layers of PML regulatory mechanism. We subsequently identified USP11 as a positive regulator of PML by siRNA screen. USP11 deubiquitinates and stabilizes PML, thereby counteracting the functions of PML ubiquitin ligases. In human glioma, USP11 is transcriptionally repressed through a Notch/Hey1-dependent mechanism, leading to PML downregulation. The Notch/Hey1-induced downregulation of USP11 and PML confers multiple malignant characters of aggressive glioma and potentiates the properties of patient-derived glioma-

initiating cells, indicating a key role of this pathway in glioma pathogenesis. To explore additional mechanism for PML downregulation in tumors, we identified SCP1/2/3 as PML phosphatases and SCPs-mediated PML dephosphorylation blocks PML ubiquitination by Cul3-KLHL20 complex. In human clear cell renal cell carcinoma (ccRCC), SCP1 and SCP3 are downregulated, leading to PML degradation. Restoration of SCP-mediated PML stabilization not only inhibits multiple malignant features of ccRCC but also suppresses mTOR/HIF pathway. Furthermore, blockage of PML degradation pathway by Pin1 inhibitor enhances the tumor suppressive effects of mTOR inhibitor, suggesting a rationale of combinatory therapy for ccRCC. In conclusion, our studies uncover several mechanisms that lead to PML downregulation in human malignancies, which underscores the importance of personalized strategies for cancer therapy.