UBR5, a novel and pivotal regulator of tumorigenesis and cancer immunity

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Abstract
The traditional cancer therapy is organ- and tissue-based, which has been ineffective in terms of cure rate, and which also frequently leads to therapy resistance and disease relapse. Recently, more common genetic features across cancer types are beginning to come to light by extensive genomic information now available on tumors. A new paradigm is thus emerging that combinations of a few key mutations in critical biological pathways may underlie broad arrays of malignant development and aggression. Targeting these common and vital points of tumorigenic regulation may yield much greater impact on cancer therapy across the spectrum than aiming at narrowly focused, individual cancer specific targets, if systemic toxicity can be avoided.

Our recent clinical and laboratory investigations have for the first time identified UBR5, a novel HECT-domain E3 ubiquitin ligase of potentially fundamental importance, as an essential master player and cross-cancer regulator of tumor growth, metastasis, and anti-tumor immunity. UBR5 gene alterations (predominantly amplifications) occur in 45% of prostate cancer, 25-35% of breast and ovarian cancers, close to 20% of bladder, liver, uterine, and stomach cancers, and in 10% of many other types of solid tumors. In addition, abnormal UBR5 expression is strongly associated with reduced survival rates in breast, ovarian, prostate and colon cancer patients. Our studies in experimental mouse models of ovarian and mammary carcinomas via CRISPR-mediated UBR5 gene deletion in tumor cells have demonstrated a profound role of UBR5 in cancer growth, metastasis and survival.

Moreover, we have also established that UBR5 promotes tumor growth in vivo through its strong immunoregulatory activities in a manner completely dependent on lymphocytes, which is manifested in increased infiltration of activated CD4+ and CD8+ T cells into UBR5-deficient tumor as well as enhanced maturation of dendritic cells. Additionally, we observed that targeting UBR5 in the tumor may result in the induction of potential neoantigens that trigger strong T cell-mediated immune responses. Further elucidation of UBR5’s pathophysiological and immunological properties will open up many new avenues for future scientific and clinical explorations that will have long and lasting repercussions in the field.

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