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Extended insights into the pathophysiological role of UBR5: a commentary

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Dear Editor,

The recently published article by Wang *et al*.[1] in the *International Journal of Surgery* has captured our attention. The authors have attempted to extensively discuss the structure and domain-specific functions of ubiquitin-protein ligase E3 component n-recognition 5 (UBR5). Besides, the authors discussed the pathophysiological role of UBR5, a histone ubiquitylation regulator and a pivotal guard of DNA replication, in various diseases, including multiple cancers and neurological and viral diseases. However, their article falls short of exploring the pathological role of UBR5 in several critical diseases, including various cancers [e.g. urinary bladder cancer, testicular cancer, head and neck squamous cell carcinoma (HNSCC), Burkitt's lymphoma, Hodgkin's lymphoma], Alzheimer's disease (AD), and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

UBR5 has been reported to play an oncogenic role in the development of bladder cancer[2]. Mutations in the UBR5 gene and the subsequent dysfunction of UBR5 have been reported to increase the sensitivity of tumor cells to chemotherapy and enhance survival in limited-stage small-cell bladder cancer patients[2]. In an exciting study, Wang *et al*.[3] found that UBR5 gene expression has a reciprocal effect on the infiltration of cancer-associated fibroblasts in the tumor microenvironment of a testicular germ cell tumor.

Recently, Zhu *et al*.[4] demonstrated that the virus-like m6A methyltransferase-associated (VIRMA) protein elicits the oncogenic effect of UBR5 via N6-methyladenosine (m6A) and increases the proliferation, invasion, and migration of cancer cells in HNSCC. Furthermore, they showed that hypermethylation of UBR5, a characteristic feature of the tumor tissues in HNSCC, could be down-regulated through VIRMA knockdown.

UBR5 is one of the top 10 critical genes linked to Epstein–Barr virus (EBV; a well-known oncogenic virus)-associated carcinomas, including gastric and nasopharyngeal cancers, Burkitt's lymphoma, and Hodgkin's lymphoma[5]. Although the authors have discussed gastric and nasopharyngeal cancers, the triadic relationship between EBV, UBR5, and the development of Burkitt's lymphoma and Hodgkin's lymphoma has not been discussed.

UBR5 has been identified as one of the novel genetic loci linked to the progression of AD, one of the predominant neurodegenerative diseases affecting memory and other cognitive abilities[6]. Moreover, the upregulation of UBR5 in post-mortem AD brains indicates the critical role of UBR5 in AD progression.

Although the authors have discussed the antiviral effects of UBR5 in the pathogenesis of Middle East respiratory syndrome coronavirus (MERS-CoV), the role of UBR5 against SARS-CoV-2 has not been discussed. UBR5 exhibits its antiviral effects against SARS-CoV-2 via ubiquitination and degradation of open reading frame 9b (ORF9b) at its K40 site[7] and not via ORF4b[8].

Taken together, this communication deepens our knowledge about the pathological repercussions of UBR5 in certain cancers, AD, and SARS-CoV-2 infection. Furthermore, elucidating the molecular signaling mechanisms of specific UBR5 domains and their interactions with various proteins/substrates in several diseases is warranted, and UBR5-targeted strategies need to be explored in drug discovery.

Ethical approval

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A.M.: conceptualization, data curation, writing – original draft preparation, and supervision; S.T.S.: conceptualization, data curation, writing – reviewing and editing; M.R.I.: validation, writing – original draft preparation, and writing – reviewing and editing. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The author(s) of this work have nothing to disclose.

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