INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Primary bone cancer is an uncommon malignant tumor of the bone, originating from primitive mesenchymal cells and are responsible for 3–5% of all pediatric cancers and accounts for approximately 0.2% of all malignant neoplasms. The propensity for early spread, lack of suitable biomarkers for early diagnosis, as well as prognosis and ineffective existing therapies, contribute to the poor survival rate of bone cancer. Therefore, there is an urgent need to develop novel biomarkers for early diagnosis and prognosis which in turn can facilitate newer therapeutic avenues for the management of this aggressive neoplasm. TIPE2 (tumor necrosis factor-α-induced protein 8-like 2), a recently identified cytoplasmic protein, possesses enormous potential in this regard. TIPE2 was strongly involved in the positive regulation of bone carcinogenesis and was found to be significantly overexpressed in both HOS and U2OS cell lines and overall bone cancer cases compared to normal HaCaT cell line and normal adjacent tissues, respectively. Moreover, TNF-α, TNF-β, and RANKL induced proliferation, colony formation, and migration potential of HOS and U2OS bone cancer cells and did not induce cell death in the cancer cells. Treatment of TNF-α, TNF-β, and RANKL enhanced the expression level of TIPE2 in bone cancer cells. Further, knockdown of TIPE2 resulted in significantly reduced proliferation, survival, EMT, invasion and migration; and increased autophagy of human bone cancer cells through modulation of the NF-κB signaling axis. In addition, knockdown of TIPE2 also caused arrest in the G1- and S-phase of the cell cycle of bone cancer cells. As cytokines are the most predominant factors in bone cancer, we therefore evaluated the effect of TIPE2 in cytokine-mediated bone carcinogenesis as well. Our results showed that TIPE2 was involved in TNF-α, TNF-β, and RANKL-mediated bone cancer through inhibited proliferation, survival, and migration via modulation of nuclear factor kappa B (NF-κB)- and NF-κB-regulated gene products, which are involved in the regulation of diverse processes in bone cancer cells. Taken together, TIPE2 possesses an important role in the development and progression of bone cancer, particularly in cytokines-promoted bone cancer, and hence, specific targeting of it holds an enormous prospect in newer therapeutic interventions in bone cancer. However, these findings need to be validated in the in vivo and clinical settings to fully establish the diagnostic and prognostic importance of TIPE2 against bone cancer.