ABSTRACT

Sarcomas are mesenchymal-derived malignant neoplasms that are characterized by early metastatic spread, and poor prognosis. YB-1 is a member of the highly conserved cold shock domain (CSD) containing family of proteins known to regulate transcription and translation of a multitude of genes. Importantly, YB-1 promotes an epithelial-to-mesenchymal transition (EMT) in non invasive breast epithelial cells. In spite of its role in EMT, comprehensive investigations into the role of YB-1 in the progression of childhood sarcomas are currently lacking.

To study the potential role of YB-1 in childhood sarcomagenesis, we used MNNG and MG63 (osteosarcoma), TC32 and TC71 (Ewing sarcoma), and Rh30 and Rh18 (rhabdomyosarcoma) tumour cell lines, and performed transient and stable YB-1 knockdown (kd) in each cell line. Then, cells were subjected to different assays.

Using *in vitro* cell motility, invasion, and proliferation assays, we found that YB-1 kd significantly reduced migration and invasion of each of these cell lines and this was associated with enhanced proliferative capacity of childhood sarcoma cells. YB-1 kd also profoundly inhibited migration and metastasis of human sarcoma cell lines xenotransplanted into either the yolk sacs of zebrafish embryos or under the kidney capsule of NOD/SCID mice, a model previously utilized for epithelial-derived tumours.

We then assessed potential mechanisms, and found that YB-1 directly bound and robustly activated the translation of HIF1α mRNAs, while it had no effect upon HIF1α transcription. YB-1 itself was robustly induced by hypoxia, and blocking this induction blocked HIF1α protein levels. HIF1α kd blocked YB-1 mediated induction of sarcoma cell migration and invasion, and ectopic expression rescued the effects of this correlated significantly with reduced mean microvessel density and VEGF production.

Based on our study, we can conclude that YB-1 promotes childhood sarcoma cell metastasis through translational activation of HIF1α, underscoring the potential impact of YB-1 on sarcoma angiogenesis. Importantly, targeting YB-1 or its downstream effectors represents a promising strategy in the treatment of childhood sarcomas.