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Short Communication

The Emerging Roles of the DEAD Box RNA Helicase p68 in Oncogenesis

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RNA helicase p68 belongs to the DEAD box family and is an important molecule responsible for RNA metabolism. Emanating evidences suggests it to be significantly implicated in oncogenesis apart from being a vital player of RNA metabolism. It is overexpressed in various cancers viz colon, breast and prostate tumors and acts as a transcriptional co-activator of several transcription factors viz β-catenin, p53, Estrogen Receptor α (ERα), Androgen Receptor (AR), nuclear factor-κB (NF-κB), Notch transcriptional activation complex and p53 and correlates with tumor progression [1-4]. Recent studies also suggest that p68 is significantly elevated in higher grade glioma and co-activates NF-κB for enhanced glioma cell growth and survival.

Overexpression of AKT is an early event in colorectal carcinogenesis; crucial for tumor growth and metastasis. Mounting evidences suggest AKT is overexpressed in colon cancer and highlights it as a crucial target for colorectal cancer prevention [4,5]. The expression of DEAD box RNA helicase p68 and AKT exhibits strong positive correlation in normal and colon carcinoma patient samples. It occupies AKT promoter with β-catenin as well as NF-κB and cooperates with these in potentiating AKT transcription. Indeed, p68 enhanced AKT promoter activity thus increased both AKT mRNA and protein in multiple colon cancer cell lines [6]. FoxO3a is the legitimate AKT target for its destruction and a cardinal tumor suppressor. The increase of active AKT results in enhanced phosphorylation of FoxO3a, leading to its nuclear exclusion and eventual degradation by the proteasomal system. p27Kip1, one of the key tumor suppressor which functions as a cell cycle checker is downregulated by 'p68-AKT-FoxO3a' signaling axis. p68 significantly reduced the levels of FoxO3a and its downstream target proteins in an AKT dependent manner. This is also supported by studies in primary tumors and metastatic lung nodules generated in mice colorectal allograft model, using syngeneic cells stably expressing p68.

Signal transducers and activators of transcription 3 (Stat3) is essential for various cellular processes like embryonic development, adult homeostasis, immune response, cell survival and proliferation. It also promotes immune-suppression, cellular migration, and mediates cancer through inflammation, obesity, cancer stem cells and the formation of pre-metastatic niche. Ever-increasing evidences suggest that Stat3 exhibits overexpression as well as hyperactivation and responsible for tumorigenesis. Specific inhibitions of Stat3 and modulations of IL-6/Jak/Stat3 pathway are currently been widely explored for therapeutic interventions [7]. It plays pivotal roles in oncogenesis through regulation of broad array of genes such as Cyclin D1, c-Myc, B-cell lymphoma 2 (Bcl-2), B-cell lymphoma extra-large (Bcl-xL), myeloid cell leukemia 1 (Mcl-1) and AKT for cellular proliferation, survival and evasion of apoptosis. It modulates matrix metalloproteinases (MMPs), Vimentin etc for invasion and metastasis; vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-α (HIFα) for angiogenesis. Stat3 is persistently activated in diverse cancers; majorly mediated by members of the Janus kinase (Jak) family of tyrosine-kinases as a result of hyper-stimulative signals in the tumor microenvironment. Aberrant Stat3 signaling is linked to various cancers, and Stat3 is one of the most potential targets in cancer therapy [8-10]. Stat3 is considered to be one of the most promising candidates for cancer therapy. The expression of RNA helicase p68 and Stat3 bears strong positive correlation and significant colocalization in normal and colon carcinoma patient samples. Enhanced expressions of Stat3 target genes observed in primary tumors and metastatic lung nodules, generated in mice colorectal allograft model using syngeneic cells stably expressing p68. It interacts with Stat3 and occupied the promoters of multiple Stat3 target genes in enhancing Stat3 dependent transcription. Increased expression of tumor promoters like Mcl-1, Bcl-xL, Cyclin D1, VEGF, MMP2 and MMP9 accounts for heightened cellular proliferation, survival, angiogenesis, invasion and metastasis; ultimately leading to tumorigenesis [11].

These strings of events triggered by p68, lead to heightened cellular proliferation and survival, culminating in tumorigenesis and highlighting it as a potential candidate for therapeutic interventions.

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