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Survivin in Cancer: A Spider in the Web

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It has not been attributed to the ignitable curiosity of the cancer researchers in propagating survivin-ism, it would have certainly be an impossibility to dissect the multifaceted role of survivin in tumour biology [1]. The predominant factorability of survivin in modulating cancer is envisaged in the realms of diagnostic and prognostic abilities, preferential modulation of intricate evolving cancer cell and stem cell signalling paradigms and pharmacological retaliation against prevailing therapeutic efficacies. Therefore, this column provides a snapshot of recent research and development pertaining to survivin biology in cancer [1,2].

Diagnostic and Prognostic Strategies

Multiplexed nanoflare devices comprising of gold nanoparticle conjugates hybridised with the reporter, quencher and flourophore molecules, had enabled to efficiently detect survivin messenger RNA (mRNA) at relative very low concentrations [3]. Combinatorial multimodal nanotheranostic agents comprising of silencing RNA (siRNA) conjugates, membrane translocation peptides and flourophores coupled to the magnetic nanoparticles, have concomitantly achieved survivin abrogation and therapeutic imaging by magnetic resonance imaging and fluorosenesce imaging [4]. Detection of exosomes with survivin as a cargo protein has invigorated a relative novel speculation, pertaining to the role of survivin in angiogenic propagation with excessive stabilisation and secretion of exosomes among the cancer cells [5]. Furthermore, in addition to the already existing debate about the dichotomic role of nuclear and cytoplasmic survivin, nuclear survivin was detected proportionately along with Phosphohistone-H3 (pHH3), prominent mitotic count biomarker [6]. Nevertheless, survivin is attributed in promoting drug resistant tumours. In accordance with the previous observations, nuclear and cytoplasmic counterparts showed a predominant role in stabilisation of drug resistance in cervical carcinoma, in response to the radiation therapy [7].

Cancer Cell Signalling Paradigms

Critical role of survivin in transcriptional inhibition of p21 gene, a crucial associate with p53 tumour suppression gene via p53 signalling mechanisms was noted [8]. Further, novel orphan nuclear receptor TR3 (NR41A) overexpression in lung carcinoma subjects, was promoted by survivin via p53 and mammalian target of rapamycin (mTOR) dependent fashion [9]. Furthermore, systemic modulation of the cell signalling mechanisms including sphingosine-1-phosphate receptor 1 (a G-protein-coupled receptor for lysophospholipid sphingosine-1-phosphate (S1P)) - Signal transducer and activator of transcription 3 (S1PR1-STAT3) signalling [10], modulation of DNA methylatory mechanisms [11], Yes-associated protein (YAP) modulation in conjucture with epidermal growth factor receptor (EGFR), and hippopotamus like phentotype tumour growth - Yes-associated protein (hippo – YAP) organogenesis developmental pathway [12], modulation of an array of microRNA's (miR-542-3p, miR-494, miR-320a, miR-218, miR-708 and miR-203) [13], intervention with tumour necrosis factor apoptosis inducing ligand (TRAIL) associated anticancer therapies [14], modulation of mitochondrial apoptosis in association with second mitochondrial-derived activator of caspase (Smac) in receptor activating protein 1 (RIP1)/caspase-8, and Nuclear Factor-Kappa Beta (NF-kB) signalling was noted [15].

Cancer Stem Cell Signalling Paradigms

Survivin was significantly associated with the novel stem cell signalling mechanisms, including cluster of differentiation 34^+ ($CD34^+$) and differentiation 38^- ($CD38^-$) leukemic stem/progenitor cell mechanisms associated with unfavourable clinical prognosis [16], regulation of human telomerase reverse transcriptase and survivin specific Cytotoxic T Lymphocytes (CTLs) signaling [17], survivin-DEx3, a survivin splice variant based modulation of cell cycle check point (Chk2) phosphorylation leading DNA damage promoting resistance to genotoxic therapies [18], modulation of sonic hedgehog (SHh) developmental signalling pathway to promoted epithelial mesenchymal transition in promoting pancreatic cancer stem growth [19], modulation of transforming growth factor (TGF)-β signalling in hepatic cancer cells, thereby affecting Histone Acetylation Transferases (HATs) and Histone Deacetylases (HDACs) mechanisms that promote chromatin remodeling, and fluxation of antiapoptotic products in hepatic stem cell growth [20]. Pertaining to immunological aspects, survivin was known to critically modulate Signal transducer and activator of transcription (STAT) signalling cascades, having a regulatory effect on Myeloid-Derived Suppressor Cell (MDSC) promoting stem cell progression in tumour environment [21].

Therapeutic Strategies Targeting Survivin

Novel nanoscale drug formulations have been formulated including bioreducible poly (b-amino esters) (PAEs), poly[bis(2-hydroxylethyl)-disulfide-diacrylate-b-tetraethylenepentamine] (PAP) nanoformulation, for the delivery of short hair pin RNA (shRNA) and siRNA for multidrug resistant protein (MDR) - P – glycoprotein protein (PgP)) and survivin - iMdr-1-shRNA and iSurvivin-shRNA in doxorubicin resistant human breast cancer cells (MCF7) [22], combinatorial formulation of b-cyclodextrin (b-CyD) and polyethylenimine (PEI) nanomicelle for codelivery of survivin shRNA and paclitaxel in ovarian cancer cells (SKOV-3) [23], fabrication of lipid (DOTAP/DOPE) and apolipoprotein (APOA-I) - cytochrome C for intracellular targeted drug delivery in *in vivo* lung cancer cell

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model (NCI-H460) [24], multifunctional HER2 monoclonal antibody conjugated RNase A-associated CdTe quantum dot cluster (HER2-RQDs) nanoprobe, for therapeutic imaging and targeted delivery in *in vivo* gastric cancer cell model (MCG803) [25], Magnetic resonance (MR) sensitive liposomal nanoformulation entrapped siRNA (LEsiRNA) specific to survivin, promoted enhanced down regulation of survivin *in vivo*, leading to remarkable tumour reduction [26].

Future Directions and Challenges of Survivin-ism: Where do we go?

Needless to say, there is an incessant necessity to fabricate ecofriendly natural product derived multifunctional nanotheranostics that can offer lucrative advantages and ulterior therapeutic possibilities, in comparison with conventional drugs [4]. Novel anticancer nanotherapeutics devised at our laboratory yielded remarkable *in vivo* anticancer efficacy, in both breast and colon cancer models, parameterized by restoration of a myriad of critical apoptotic signalling cascades [27]. Furthermore, from a futuristic point of view, synergism of the evolving research platforms such as cancer systems biology, bioinformatics, computational chemistry, molecular nanotechnology, quantum medicine, enables the scientific community to concretely understand the evolving cancer growth mechanisms and also designing of drugs at atomic precise, to aptly target the spider – survivin in the web of cancer signalling mechanisms [2].

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