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REVIEW PAPER OPEN ACCESS

Role of *hSRBC*, a putative TSG, in development of primary cancer: a review

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Abstract

Multistep progression into cancer involves inactivation of tumor suppressor genes (TSGs) by deletion, methylation and mutation. Chr 11p15 has been found to be deleted in primary carcinoma of many tissues, including breast, cervix, stomach, lung, bladder cancer, etc. *hSRBC*, a candidate TSG located in chr 15.4, and associated with many molecular pathways, like PKC-δ, p53 and caveolin pathway may well be responsible for tumirogenesis. hSRBC can induce cell cycle arrest and increase the apoptotic sensitivity of cells in stressed condition by stabilizing p53. hSRBC can also associate with caveolin when caveolae bud to form vesicles. hSRBC also effects localization of EGFR to caveolae through phosphorylation by PKC-δ. Thus, inactivation of hSRBC plays havoc inside the cell. Future hope may lie in restoring the function of hSRBC in cells and guiding the affected cells to apoptotic pathway instead of using radiation or chemotherapy.

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Introduction

The initiation and progression of tumor/cancer involves many complex, multi-stage processes comprising genetic alterations in different tumor suppressor genes (TSGs) and protooncogenes, as well as, infection by different carcinogenic viruses like human papilloma virus (HPV), Epstein-Barr virus (EBV), etc. Alterations of the TSGs may involve deletion, indicated by loss of heterozygosity (LOH) of a specific genetic loci, mutations and epigenetic alterations like methylation.

Deletion of chromosome 11p15 have been implicated in carcinoma of breast, lung, bladder, stomach, eosophagus, glial cells and cervix (Chunder *et al.*, 2004; Kozlowski *et al.*, 2006; Moskaluk *et al.*, 1998; Panani *et al.*, 2004; Pulido *et al.*, 2000; Rodriguez *et al.*, 1990; Roy *et al.*, 2003; Tran *et al.*, 1996; Zhao *et al.*, 2001).

The human *SRBC* gene [serum deprivation response factor-related gene product that binds to the c-kinase (*hSRBC*)] was mapped to the chromosomal region (11p15.4) (Xu *et al.*, 2001) and hence is considered as a putative TSG involving many molecular pathways.

hSRBC structure and function

The human SRBC gene (hSRBC), also known as Protein Kinase C Delta Binding Protein (PKCDBP)/ Cavin-3 was mapped to the chromosomal region 11p15.4 at 6.3Mb from p-ter (Xu *et al.*, 2001). It consists of two exons and codes for a 261 amino acids long protein (Fig. 1). The N-terminal end has a leucine zipper-like motif and a protein kinase C (PKC) phosphorylation site is present in the middle region (172–194 amino acids) of the protein (Xu *et al.*, 2001). PKC-δ binds and phosphorylates SRBC.

Although the role for *hSRBC* in tumor suppression has been suggested, the molecular basis of the hSRBC-mediated growth suppression has not been elucidated (Xu *et al.*, 2001; Zochbauer-Muller *et al.*, 2005). hSRBC was initially isolated as a BRCA1-interacting protein in a two-hybrid assay, raising the possibility that hSRBC may act in the BRCA1 tumor suppression pathway (Xu *et al.*, 2001). The possible involvement of hSRBC in cell cycle control has been also suggested by observations that mRNA and protein expression of hSRBC is induced on serum starvation and down-regulated during G_0-G_1 transition (Gustincich *et al.*, 1993).

The rat SRBC shares 81% amino acid identity to hSRBC binds to and is phosphorylated by PKC-δ that is involved in growth inhibition and tumor suppression (Xu *et al.*, 2001; Perletti *et al.*, 2005; Gschwendt, 1999). These findings also led to the conjecture that hSRBC might be engaged in the PKC signalling pathway.

Moreover, the ability of hSRBC to induce cell cycle arrest and apoptotic sensitivity of tumor cells to genotoxic stresses, and to suppress tumor cell growth by enhanced stability of p53 has also been reported (Lee *et al.*, 2008). Thus, p53 might play an important role for the hSRBC-mediated tumor suppression and dysregulation of hSRBC might result in attenuated p53 response to stress conditions, thus contributing to survival advantages of malignant cells.

hSRBC has also been implicated to be associated with caveolin when caveolae bud to form vesicles (cavicles) that travel on microtubules to different regions of the cell (McMahon *et al.*, 2009). The PKC adapter function of hSRBC may be linked to the targeting of Epidermal Growth Factor Receptor (EGFR) to caveolae in two ways. EGFR was the first receptor tyrosine kinase localized to isolated caveolae (Smart *et al.*, 1995). Subsequent work determined that under quiescent conditions EGFR is highly enriched (about 7- fold) in caveolae but rapidly departs this domain when the cells are exposed to EGF (Mineo *et al.*, 1999). EGFR migration from caveolae depends on EGF binding plus a functional tyrosine residue in the regulatory region of the cytoplasmic tail. PKC-dependent phosphorylation of S654 markedly reduces EGF stimulated migration of EGFR from caveolae. Therefore, one way that hSRBC might affect localization of EGFR to caveolae is by linking PKC-δ to the phosphorylation of EGFR. Secondly, hSRBC

may function to regulate the traffic of EGFR to and from caveolae membranes. This implies that hSRBC links ubiquitinated EGFR to caveolae, whereas unmodified EGFR, released from caveolae, moves to other membrane domains such as clathrin-coated pits (McMahon *et al*., 2009).

Alteration and inactivation of hSRBC in different primary tumors

The expression of hSRBC mRNA was greatly reduced in gastric carcinoma cancerous tissues compared to its adjacent normal counterparts (non-cancerous tissues).

The protein expression was also severely reduced in 11 out of 15 gastric cancer cell lines, in spite of the transcript level being normal in 2 of the cell lines, suggesting a post-transcriptional mechanism of inactivation in gastric cancer. The protein expression was concordant with the result of Northern blotting.

Fig. 1. Schematic representation of *hSRBC* protein.

Promoter hypermethylation is the major cause of no or low expression of hSRBC in the gastric cancer cell lines and tissues, as is also evidenced by increased expression after treatment with 5-aza-dC. There are 23 CpG sites in the promoter region of hSRBC. Almost all the CpG sites (20-23) were methylated in the cell lines with no expression of hSRBC. Most of the cancerous tissues had methylation at 9-14 sites, compared to only 1-4 methylation sites in paired normal tissues. However, deletion and mutation was not reported in gastric cancer cell lines and tissues.

Further analysis showed that hSRBC arrests cells in G_1, partly by stabilizing p53, and expression of its target genes $p21^{Waf1}$, *PUMA* and *NOXA* (Lee *et al*., 2008).

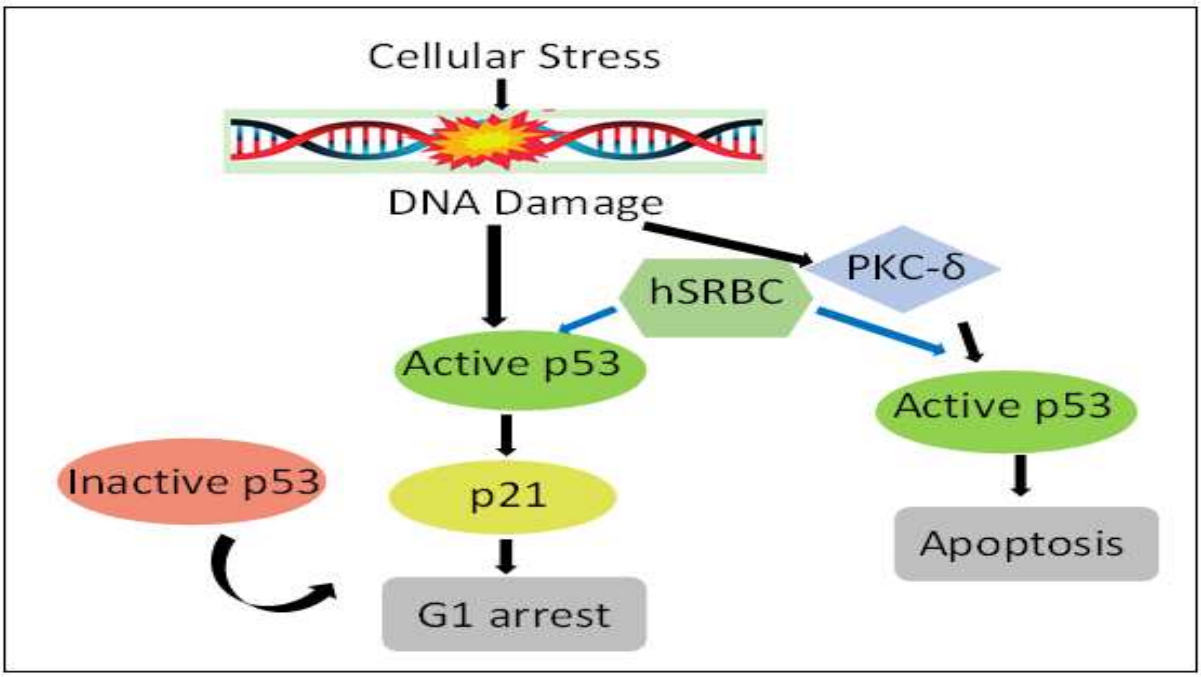

Fig. 2. Schematic flowchart with the blue arrows pointing towards the possible mechanism of interaction between hSRBC, PKC-δ and p53.

Methylation is the major cause of inactivation of *hSRBC* as reported for other various primary cancerous tissues; 41%-79% in non-small cell lung carcinoma (NSCLC), 80% in small cell lung carcinoma (SCLC) (Zöchbauer-Muller *et al.*, 2005; Xu *et al.*, 2001), 60% in breast cancer (Xu *et al.*, 2001), and 41% in ovarian cancer (Tong *et al.*, 2010).

The expression of hSRBC in the cell lines increased significantly on treatment with 5-aza-dC.

Molecular pathways involved

The possible involvement of hSRBC in cell cycle control is exerted by arresting cells in G_1 and enhancing the apoptotic sensitivity of tumor cells to genotoxic stress. hSRBC also stabilizes p53 and enhances expression of $p21^{Wafi}$, PUMA and NOXA, thus pointing to its anti-proliferative and pro-apoptotic activity.

Thus, inactivation of hSRBC may result in reduced response of p53 during stress and thus contribute to the survival and development of malignant cells.

Interestingly, PKC-δ can induce antiproliferative/apoptotic effects in cells, via the p53 and $p21^{Wafi}$ pathway. It is highly possible, that hSRBC plays a critical role in the PKC-δ signaling pathway, and the antiproliferative effects of PKC-δ might in part be mediated via hSRBC induced activation of p53 and $p21^{Wafi}$ (Fig. 2).

Conclusion

In conclusion, the various reports in primary cancerous tissues clearly show the high epigenetic inactivation of hSRBC due to promoter hypermethylation, associated with increasing tumor grade. Down regulation of hSRBC provides a growth and survival advantage to the neoplastic lesions by inhibiting the apoptotic response of p53. Thus, restoration of the function of hSRBC could provide a plausible therapeutic outcome, whereby, tumor cells can be induced or directed to apoptotic pathway, thus providing a safe alternative to radiations and chemotherapy.

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