Pathology

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ABSTRACT

Introduction: Colorectal adenocarcinomas contribute to a significant proportion of cancer related morbidity and mortality. Survivin is a novel member of the IAP family of proteins involved in apoptosis inhibition, being overexpressed in many cancers. This study was done to evaluate the expression of Survivin in colorectal adenomas and adenocarcinomas and its association with the clinicopathological tumor characteristics.

Materials and methods: Immunohistochemical analysis of Survivin expression was performed on 30 cases each of normal colorectal mucosa, adenomas and adenocarcinomas respectively.

Results: Survivin expression was absent in normal mucosa with increased expression in adenomas and maximal expression in adenocarcinomas. It also correlated with the degree of differentiation of adenocarcinomas.

Conclusion: The results indicate that dysregulation and over expression of Survivin is involved in colorectal tumorigenesis and malignant transformation of adenomas.

KEYWORDS
Survivin, Colorectum, Adenoma, Adenocarcinoma, Immunohistochemistry.
DISCUSSION:

Evasion of apoptosis is an important step in carcinogenesis. Dysregulation of apoptosis can occur by down regulation of pro apoptotic factors or an over expression of anti apoptotic factors. This confers increased longevity to the cell and makes it prone to accumulate transforming mutations. Thus dysregulated apoptosis is involved in various stages of cancer including the emergence of tumor, increased survival and growth of the tumor, evolution of an aggressive clone, metastasis and has also been shown to confer tumor resistance to anticancer therapy.

There are three important antiapoptotic family of proteins which include FLICE-inhibitory proteins (FLIPs), Bcl-2 family and Inhibitors of Apoptosis Proteins (IAPs). The Inhibitors of Apoptosis (IAP) family of proteins are a group of proteins which inhibit the intrinsic pathway of apoptosis. IAP has nine family members which are X-linked IAP, cIAP1, cIAP2, neuronal apoptosis inhibitor protein, melanoma IAP, IAP-like protein 2, livin, apollon, and survivin. Common to all the members of this family is the presence of BaculoVirus IAP repeats (BIR), a 70 amino acid motif, in one to three copies which is essential for their function.

Survivin the smallest member of the IAP family of proteins is a 142 aminoacid containing 16.5 kDa protein. It is encoded by the BIRC5 gene located at the telomeric position on chromosome 17q25. Two main functions of Survivin are inhibition of apoptosis and regulation of cell division. Unlike other members of the IAP family, which bind to and promote the degradation of active initiator and executioner caspases, Survivin lacks the structural motifs necessary for binding caspases. It has a more complex mechanism of action. It functions by targeting the multi molecular processes involved in caspase 9 activation, in cooperation with other molecules like Hepatitis B X-interacting protein, X-linked IAP and by binding to and inhibiting smac/DIABLO, a proapoptotic protein. Survivin is essential for mitosis and cytokinesis. It has a transcriptionally controlled expression at the G2/M phase and functions during a narrow window of time. With its expression during mitosis, survivin localises to various components of the mitotic apparatus including centrosomes, microtubules of metaphase, anaphase spindle and remnants of the mitotic apparatus suggesting that Survivin has an important role in microtubule dynamics and maintenance of normal bipolar mitotic apparatus.

What makes Survivin clinically intriguing is its differential distribution in cancers compared to its limited expression in normal, terminally differentiated tissues. Survivin is normally expressed in embryonic and fetal tissues but is undetectable in terminally differentiated normal adult tissues. In contrast most human cancers have been shown to overexpress Survivin. Genome-wide searches have confirmed the differential expression of Survivin in tumors compared to normal tissues. The overexpression of Survivin has been shown to be consistently associated with more aggressive tumors, increased rates of recurrence, resistance to therapy and poorer prognosis than tumors that are negative for Survivin.

The mechanisms by which survivin expression is deregulated in cancers include amplification of Survivin locus on chromosome 17q25, demethylation of survivin exons, increased promoter activity and increased upstream signalling in the PI3-kinase or MAP kinase pathways. In addition, upregulation of Survivin expression in cancers is cell cycle independent, unlike normal cells.

The role of Survivin in cancers is much more than simple inhibition of apoptosis. Its dysregulation causes abnormality in mitotic spindle formation resulting in multiple genetic defects in the affected cells and a pro-mutagenic state and such cells are not eliminated by apoptosis. In addition to its role in tumorigenesis, malignant transformation and tumor progression, Survivin is also implicated in tumor angiogenesis and resistance to anti cancer therapy.

In our study it was found that Survivin expression was practically absent in normal colorectal mucosa. Survivin localized to the nucleus of the cells of adenomas and adencarcinomas and its expression increased from normal mucosa to adenomas and was maximally expressed in adencarcinomas. The differences in mean Survivin expression between normal mucosa and adenomas and between adenomas and adencarcinomas was statistically significant (P value less than 0.001). This result of the present study correlates with that of Hiroshi Kawasaki et al who in their 2001 study of colorectal neoplasia noted that the immunoreactivity of Survivin significantly increased from hyperplastic polyps to adenomas with low grade dysplasia and adenomas with high grade dysplasia and carcinomas which showed that survivin played an important role in the malignant transformation of adenomas.

Similar findings were made by Lian-Jie Lin et al who in their 2003 study inferred that the positive rate of survivin expression increased in transition from normal epithelium to adenoma with low grade dysplasia to adenoma with high grade dysplasia and carcinoma concluding that survivin expression is related with the early stage of colorectal carcinogenesis and plays an important role in the adenoma-carcinoma sequence.

Ulrike Gerlach et al in their 2006 study reported that Survivin expression correlated with the degree of differentiation of adencarcinomas with similar conclusions drawn by the study of Hai Yan Tan et al. The present study showed similar results with Survivin expression increasing from well differentiated to moderately differentiated adencarcinomas with maximum expression seen in poorly differentiated adencarcinomas. However there are other studies which have concluded that no such correlation could be demonstrated.

In the present study no significant correlation was found between Survivin expression and patient age, gender and the stage of adencarcinoma. Other studies have shown a poor survival with over expression of Survivin. In conclusion:

Survivin expression was negligible to absent in normal colonic epithelium with a significant increase in expression from adenomas to adencarcinomas, suggesting that Survivin has an important role in early colorectal tumorigenesis and malignant transformation of adenomas( the adenoma-carcinoma sequence). This observation of minimal to absent Survivin expression in normal colonic epithelium and its significantly higher expression in adenomas and adencarcinomas makes Survivin a potentially exploitable target of anti-cancer therapy with maximal targeting of the tumor and minimal damage to the normal epithelium. Survivin expression also showed a significant correlation with the degree of differentiation of adencarcinomas. The results showed that dysregulation and over expression of Survivin expression is associated with an aggressive behaviour in colorectal adencarcinomas. Detection of Survivin expression by immunohistochemistry may be used as a prognostic marker to predict tumor behavior.
References: