Original Communication

IS SURVIVIN LEVEL IDENTICAL BETWEEN ADENOMAS OF PROXIMAL AND DISTAL COLON?

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ABSTRACT

Objectives: Considerable differences are known between proximal and distal colon, these include embryological, anatomical, histological, biochemical, and physiological characteristics. Above mentioned distinctions may influence development of variable clinico-morphological entities. Multifunctional anti-apoptotic protein survivin participates in regulation of cell cycle, apoptotic cascades, and stimulates angiogenesis. Material and methods: We immunohistochemically assessed expression pattern of anti-apoptotic protein survivin in a panel of 243 colon adenomas to determine its association with colon localization. In each section, subcellular compartment-alization of survivin and intensity of immunoreaction were evaluated. Results: Survivin was expressed in 190 cases (78.2%). Statistical analysis confirmed a significant correlation of subcellular survivin compartmentalization and intensity of immunoreaction with colon localization of adenomas. Conclusions: Taking into account unique features of survivin, its expression pattern in proximally sided adenomas, and distinctions between left and right colon, we suppose that survivin level may contribute to higher proliferative phenotype of proximal adenomas.

Key words: *proximal and distal colon; adenomas; survivin*

RESUMEN

Objetivos: Se conocen diferencias considerables entre el colon proximal y el distal, estas incluyen características embriológicas, anatómicas, histológicas, bioquímicas y fisiológicas. Las distinciones antes mencionadas pueden influir en el desarrollo de entidades clínico-morfológicas variables. La proteína antiapoptótica multifuncional survivina participa en la regulación del ciclo celular, las cascadas apoptóticas y estimula la angiogénesis. Material y métodos: Se evaluó inmunohistoquímicamente el patrón de expresión de la proteína antiapoptótica survivina en un panel de 243 adenomas de colon para determinar su asociación con la localización colónica. En cada sección se evaluó la compartimentación subcelular de la survivina y la intensidad de la inmunorreacción. Resultados: La survivina se expresó en 190 casos (78,2%). El análisis estadístico confirmó una correlación significativa de la compartimentación subcelular de survivina y la intensidad de la inmunorreacción con la localización de los adenomas en el colon. Conclusiones: Teniendo en cuenta las características únicas de la survivina, su patrón de expresión en los adenomas del lado proximal y las distinciones entre el colon derecho e izquierdo, suponemos que el nivel de survivina puede contribuir a un mayor fenotipo proliferativo de los adenomas proximales.

Palabras clave: *colon proximal; colon distal; adenomas; survivin*

INTRODUCTION

The colon represents the terminal segment of gastrointestinal tube in length approximately 1.5 meter in adult humans. Embryologically, colon is derived from two regionally different parts of primitive gut, which are the midgut and the hindgut. Midgut gives rise to proximal or right colon (cecum, appendix, ascending colon, and 1/3 up to 2/3 of transverse colon). Hindgut gives rise to distal or left colon (left part of transverse colon, descending and sigmoid colon, and rectum) (Lim et al., 2017; Baran et al., 2018).

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There are considerable differences between proximal and distal colon in anatomical, histological, biochemical, and physiological characteristics. These include blood supply, innervation, crypt histomorphology, capillary network of mucosa, fat and bile metabolites, apoptotic activity, differences in bacterial flora and variations of luminal content (Missiaglia et al., 2014; Pohl et al., 2016). Above mentioned distinctions between the proximal and distal parts of colon may influence the development of various clinico-morphological conditions with specific features, such as inflammatory processes, benign, premalignant, and malignant lesions as well (Pohl et al., 2016).

Survivin is a member of IAP (inhibitor of apoptosis) protein family along with C-IAP1, C-IAP2, IAP–like protein-2, XIAP (X-linked mammalian inhibitor of apoptosis protein), livin (melanoma inhibitor of apoptosis protein), neuronal apoptosis inhibitory protein and apollon. Survivin represents the shortest IAP protein consisting of 142 amino acids, only possessing a single BIR (baculovirus IAP repeat) domain which is related to antiapoptotic function (Li, 2005; Li and Brattain, 2006). Survivin is unique multifunctional protein involved in regulation of cell division, suppressing apoptotic cell death, and also enhancing angiogenesis. Survivin is expressed in wide spectrum of cancers, however it is usually absent in adult tissues. This protein is known by its cell compartmentalization, being present in cytoplasm, nucleus or in both (Wheatley and Altieri, 2019). Due to significant quantitative differences in the level of survivin expression and its intracellular pattern between cancers and corresponding normal tissues, this protein may represent promising tumor biomarker. Survivin is considered as a protein playing one of the key roles in carcinogenesis (Chen et al., 2016; Wheatley and Altieri, 2019). Its molecular features are associated with increased cancers aggressiveness and poor prognosis (Chen et al., 2016; Gil-Kulik et al., 2019). Furthermore, survivin overexpression is often responsible for radiotherapy and chemo-therapy resistance (Silke and Vucic, 2014; Warrier et al., 2020).

There is a lot of knowledge about proximal versus distal colon differences (Missiaglia et al., 2014). Survivin is described in detail by numerous scientific groups and undoubtedly plays one of the key roles in development of premalignant conditions and malignant tumors (Chen et al., 2016; Li et al., 2019;Wheatley and Altieri, 2019). Recently, many papers draw attention to the transition normal mucosa – low grade colon adenoma – high grade colon adenoma – carcinoma sequence with respect to survivin (Yang et al., 2013; Adamkov et al., 2015; Chen et al., 2016; Adamkov et al., 2018).

However, majority of papers study survivin mainly from different immunohistochemical, molecular, and prognostic aspects in cancers (Chen et al, 2016; Lim et al., 2017; Wang et al., 2017; Bustamante-Lopez et al., 2019; Gil-Kulik et al., 2019; Warrier et al., 2020; Zhou et al., 2020; Chen et al., 2021; Lucchesi et al., 2021). Despite of much discussion, the most research groups believe that right located tumors compared to tumors with left presentation have worse prognosis and higher mortality rate (Benedix et al., 2010; Weiss et al., 2011; Lim et al., 2017; Bustamante-Lopez et al., 2019). Furthermore, there are studies that also highlight a markedly different response to treatment modalities between left – and right – sided tumors (Lim et al., 2017; Baran et al., 2018). Other studies evaluate this antiapoptotic protein in colon adenomas which are considered as clinico-morphological precursors to develop cancer (Hernandez et al., 2011; Adamkov et al., 2015; Kováčová and Hodorová, 2021).

Considering salient features of protein in question and distinctions between right and left colon in all above mentioned aspects, we hypothesized that survivin expression level and its subcellular location may contribute to higher proliferative phenotype of proximally sided adenomas along with antiapoptotic function.

MATERIAL AND METHODS

Archival blocks of formalin-fixed paraffin-embedded tissue samples from 243 sporadic adenomas were included in present study. The archival paraffin blocks from diagnostically closed cases were obtained from Department of Pathology, St. Elisabeth Oncology Institute in Bratislava, Slovakia. All clinical data were obtained from the pathological reports. There was a group of 82 females (33.74%) and 161 males (66.26%). The mean age was 67.1 ± 9.4 years for females and 62.3 ± 10.2 years for males. In female / male patients, adenomatous polyps were situated in 21/53 cases (28.38% / 71.62%) in the proximal part of colon and in 31/85 cases (26.72% / 73.28%) in the distal part of colon. Each representative paraffin block was cut into 3 µm – thick sections. Two sections from each block were subjected to immuno-histochemical staining for survivin protein. To achieve a better adherence of the tissue sections to the glass slides, we used silanized slides (DAKO, Glostrup, Denmark), which were baked for two hours in an oven at 59°C. Then, the slides

were treated in PT Link System (DAKO). Activity of the endogenous peroxidase was quenched with 3% hydrogen peroxide for ten minutes. Immunohistochemical reaction was performed using polyclonal rabbit anti-survivin antibody (Abcam ab 469, dilution 1:700). After 30 minutes incubation by primary antibody, survivin was visualized by means of the EnVision Flex/HRP System using 3.3´-diaminobenzidine (DAB) chromogen as substrate, according to the manufacturer´s instructions. All sections were counterstained with Mayer´s hematoxylin. Negative controls were obtained by ommiting the primary antibody.

In each case, the subcellular localization of survivin and staining intensity were assessed, these two parameters were evaluated semi-quantitatively by two observers independently (MA, DV).

Analyzed data

Subcellular survivin compartmentalization and its staining intensity in 243 cases of sporadic colon adenomas.

Compared parameters

Subcellular survivin location and its intensity of staining vs. adenoma localization.

Statistical analysis

X^2 test was used for the statistical analysis whether the survivin subcellular localization and its staining intensity correlates with adenoma localization.

	survivin expression		**subcellular localization**		**intensity of immunoreactivity**	
	negative	**positive**	**C**	**N / NC**	**+**	**++ / +++**
localization						
proximal	18	74	20	54	53	21
distal	35	116	78	38	107	9
χ^2 test	**χ^2=0.438 p=0.508**		**χ^2=29.254p=6.35E-08**		**χ^2=14.447 p=0.0001**	

Table 1- Relationship between expression of survivin and colon adenomas localization. C – cytoplasmic immunoreaction of survivin, N – nuclear immunoreaction of survivin, NC – combined nuclear and cytoplasmic immunoreaction of survivin. + weak intensity, ++ / +++ moderate / strong intensity.

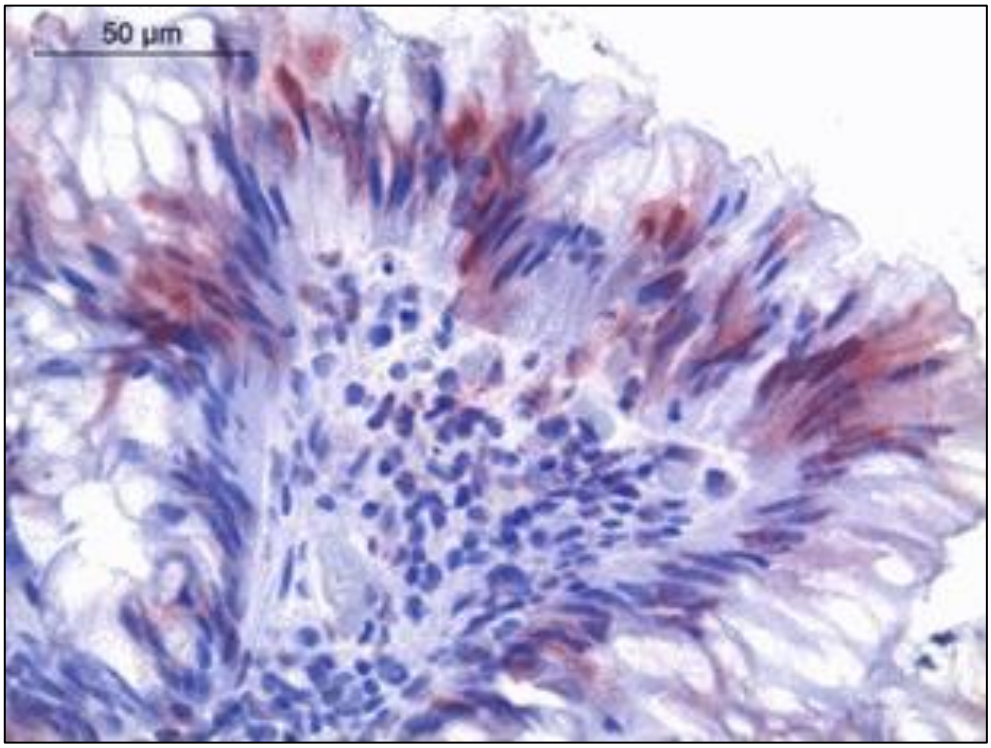

Figure 1- Cytoplasmic survivin immunoreaction in cells of distally located colon adenomas.

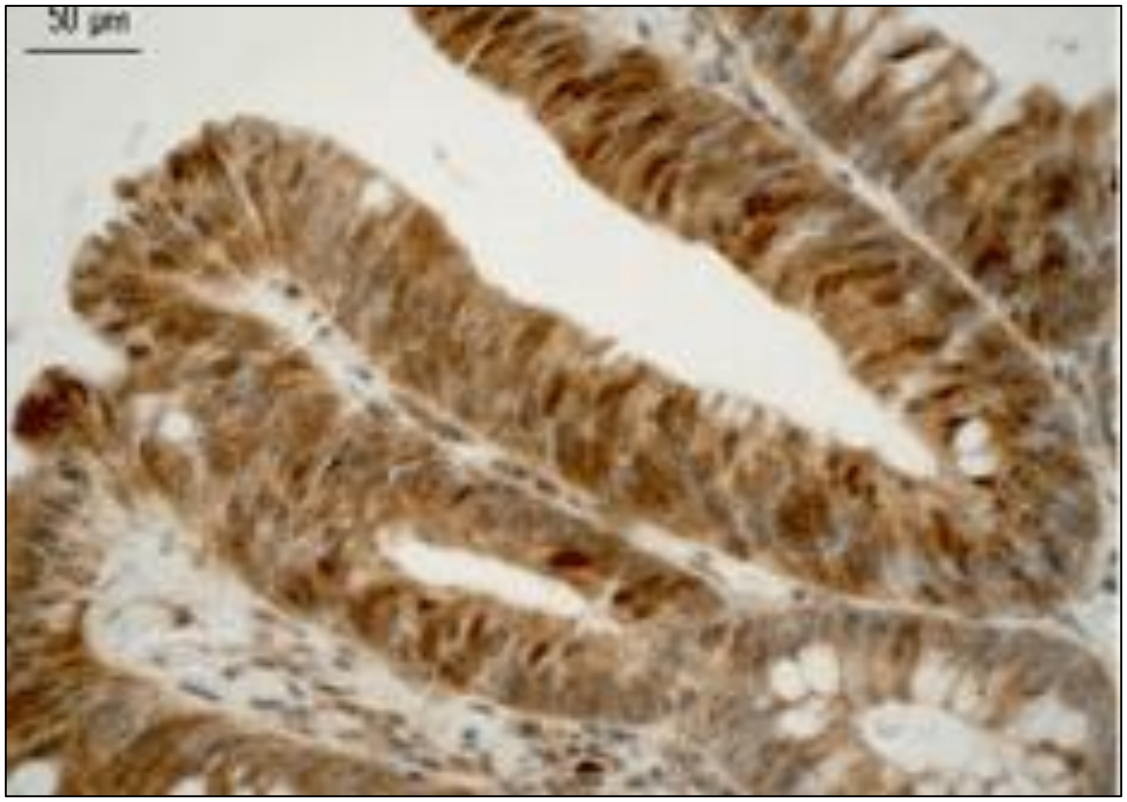

Figure 2- Combined N and NC survivin immunoreaction in cells of proximally located adenoma.

RESULTS

In our group of 243 adenomas, survivin was expressed in 190 cases (78.2%). In panel of 190 positive cases, 74 cases (38.9%) were localized in proximal part of colon (caecum, ascending colon and 2/3 of transverse colon) and 116 (61.1%) cases in distal part of colon (1/3 of transverse colon, descending colon, sigmoid colon and rectum). Expression pattern of immunohistochemical survivin reactions in respect to colon localization is shown in Table 1.
As for survivin subcellular compartmentalization, our results confirmed that protein in question significantly correlates with adenoma localization (p=6.35, E-08). Our findings indicate that cytoplasmic survivin immunoreaction dominates in the distal colon (Fig. 1), whereas NC and N reaction in proximal colon (Fig. 2). We found also statistically significant correlation between intensity of survivin immunoreactivity and adenoma localization (p=0.0001).

DISCUSSION

Based on our results, there are significant differences in immunohistochemical survivin expression profile between adenomas in proximal and distal colon. For instance, we have found nuclear (N) and combined nuclear and cytoplasmic (NC) subcellular survivin location was significantly associated with proximally sided adenomas and higher intensity of immuno-reaction as well. We consider the intensity of survivin immunoreaction as a valuable parameter because it reflects the amount of intracellular survivin. It may be an important indicator for both progression of dysplastic abnormalities and growth of adenoma. Severe dysplastic epithelial changes are characteristic features for larger and growing adenomatous lesions. Summarily, our findings demonstrate that N and NC survivin positivity is related to high grade adenomas with worse histomorphological features (Adamkov et al., 2015, 2018). Brennan et al. (2008) indicated that NC and C survivin expression is poor prognostic parameter and its increased nuclear level significantly correlated with proliferative phenotype. Similar results were obtained by Jakubowska et al. (2016).
The majority of papers deal with antiapoptotic role of survivin in apoptotic cascade. Survivin protects cells against apoptotic demise. Cytoplasmic survivin localization is fundamental for its antiapoptotic functions. Numerous studies describe that survivin is able to inhibit caspase

cascade activities (Chen et al., 2016; Wheatley and Altieri, 2019) in extrinsic and intrinsic apoptosis (Warrier et al., 2020). Survivin does not directly bind to and inactivate caspases. In cytoplasm, there are important adaptors and cofactors which may cooperate with survivin. For instance, it interacts with XIAP or HBXIP (hepatitis B virus X – interacting protein). This complex may interact with caspases through stabilization of XIAP (Jaiswal et al., 2015; Wheatley and Altieri, 2019). Link between survivin and XIAP may also activate other IAP proteins, such as c-IAP1 and c-IAP2 to suppress caspases. Moreover, survivin is involved in caspase-independent cell death by inhibition of AIF (apoptosis inducing factor) (Jaiswal et al., 2015).

On the other hand, survivin plays one of the fundamental roles in mitotic cell division. Some authors consider this role of survivin as more important than its antiapoptotic function (Yang et al., 2004). Survivin acts as active element of CPC (chromosomal passenger complex) apart from Aurora B, INCENP (inner centromere proteins), and Borealin/Dasra. During mitotic division, protein in question is dynamically localized in different parts of chromosomes (Gil-Kulik et al., 2019; Wheatley and Altieri, 2019). It is involved in stabilization of mitotic spindle and precise separation of sister chromatids (Yong-Gang et al., 2010; Kelly et al., 2011).

In proliferating adenomas, antiapoptotic survivin function and its role in mitotic cell division act simultaneously and complement each other.

More research groups described Wnt (Wingless / Integrated) / β-catenin signaling pathway in initiation of colorectal lesions in respect to survivin. In general, the Wnt / β-catenin participates in proliferation and differentiation of cells, in cellular invasion and migration, as well (Clevers, 2006; Muzny et al., 2012). β-catenin does not accumulate in the absence of Wnt signaling due to degradation by “destructive complex” which consists of APC (adenomatous polyposis coli), GSK3β (glycogen synthase kinase-3 beta), Axin (axis inhibitor), CK 1 (casein kinase 1), and proteinphosphatase 2A (Cheng et al., 2019).Survivin expression is down-regulated in colon crypts by wild type APC. In case of APC mutation and additional Axin and β-catenin stabilizing mutations, β-catenin accumulates in cytoplasm and subsequently enters nucleus interacting with transcription co-factor TCF (T-cell factor) / LEF (lymphoid enhancer-binding factor). TCF / β-catenin induce increased survivin expression in intestinal crypt cells via binding of three TCF elements in survivin promoter (Kim et al., 2003; Cheng et al., 2019). This might elucidate survivin overexpression with increased mitotic activity and decreased apoptotic index by which normal cellular homeostasis of colonic crypt is disturbed. Furthermore, also abnormally increased β-catenin was found during the onset and early developmental stages of colon adenomas (Shao et al., 2018).

Taken together, it is not surprising that increased survivin expression in cells of proximally sided adenomas may be critical for progression to malignant counterparts.

Conflicts of Interests

None

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Ethical Approval

Presented study was approved by local Ethics Committee of Jessenius Faculty of Medicine in Martin, registred in Office for Human Research Protection, U.S., Department of Health and Human Services under N°: IORG0004721

Informed Consent

Not necessary as the presented study was performed on the archival paraffin blocks.

Contributions:

M.A.: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing / original draft. S.H.C.: Methodology, Investigation, visualization. V.M.: Methodology, Investigation. D.V.: Investigation, Validation. B.K.: Data curation.

All authors have read and approved the final version of the manuscript, and all authors listed as co-workers met the criteria for authorship.

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