EXPRESSION OF DIFFERENT PROTEINS AS PROGNOSTIC MARKERS OF COLORECTAL CANCER: AN OVERVIEW

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ABSTRACT

Background: Colorectal cancer (CRC) is one of the most common cancers worldwide, about one to two million new cases being diagnosed every year, thus making CRC the third most common cancer and the fourth most common cause of cancer-related death with 700,000 death per year. Epithelial-mesenchymal transition (EMT) is a biologic process in which cells lose their epithelial characteristics and acquire mesenchymal features, which enable them to migrate more efficiently and invade the underlying mesenchyme. EMT plays a crucial role enabling cells of epithelial origin to migrate long distances to contribute to the formation of different tissues and organs. Recent studies have demonstrated that both SATB (Special AT-rich binding protein) family proteins including SATB1, SATB 2 are instrumental in cancer progression. β-Catenin is a 92 kDa protein that is found at cellular junctions bounded to E-cadherin, in the cytoplasmic compartment and in the nuclear compartment. SATB1 regulates critical players of Wnt signaling and is required for Wnt-dependent stimulation of β-catenin. E-cadherin plays an important role in epithelial cell adhesion and acts as tumor suppressor protein. Loss or decrease of E-cadherin expression has recurrently been associated with poor prognosis and poor overall survival of colorectal cancers

Key words: Colorectal cancer (CRC), Epithelial-mesenchymal transition (EMT), Special AT-rich binding protein (SATB).

I. COLORECTAL CANCER:

Colorectal cancer (CRC) is one of the most common cancers worldwide, about one to two million new cases being diagnosed every year, thus making CRC the third most common cancer and the fourth most common cause of cancer-related death with 700,000 death per year. By gender, CRC is the second most common cancer in women (9.2%) and the third in men (10%) (1).

The regional incidence of CRC is variable. The highest colon cancer incidence rates are found in parts of Europe (e.g. in Hungary, Slovenia, Sand Norway), Australia/New Zealand, Northern America, and Eastern Asia (Japan and the Republic of Korea, Singapore among females), with Hungary and Norway ranking first among males and females, respectively. Rates also are elevated in Uruguay among both men and women. Rectal cancer incidence rates have a similar regional distribution, although the highest rates are seen in the Republic of Korea among males and in Macedonia among females (2).

Pathology of Colorectal Carcinoma

Table (1): WHO Classification of malignant Epithelial Tumors of the Colon and Rectum (3)

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**Morphology of Colorectal Carcinoma (CRC)**

The gross appearance of CRC is usually infiltrative or annular, polypoid or ulcerated. The tumor may cause puckering if muscularis propria is involved. Right sided tumors tend to be polypoid and exophytic, while left sided tumors tend to be annular and encircling lesions (3).

**I-Conventional Colorectal adenocarcinoma**

Microscopically, Conventional colorectal adenocarcinoma appears usually well to moderately differentiated gland (often filled with necrotic debris (dirty necrosis) with marked desmoplasia in stroma especially in periphery. Inflammatory cells and scattered neuroendocrine cells are common (3).

The histologic appearance of well-differentiated adenocarcinomas (grade I) appears as ‘adenoma-like’ composition that show glandular structures in more than 95% of the tumor. The moderately differentiated adenocarcinomas (grade II) show more irregularity and disfigurement of the glands compromising 50-95% of them. Poorly differentiated adenocarcinomas (grade III) show marked more irregularity and disfigurement of the glands (< 5% formed of glandular component) with highly cellular pleomorphism (4).

The invasion through the muscularis mucosa into the submucosa is a defining character for CRC especially depending on demoplasia, however; a limited carcinoma within the mucosa is called “intramucosal adenocarcinoma” that does not constitute a risk for metastasis after complete removal (5).

**Fig. (1):** Conventional colorectal adenocarcinoma. The prototypic colorectal cancer is a well to moderately differentiated adenocarcinoma consisting of tubular, anastomosing and branching glands in a desmoplastic stroma (6).

**II. HISTOPATHOLOGICAL VARIANTS OF COLORECTAL CARCINOMA**

Many histological variants of Adenocarcinoma, NOS have been settled in WHO classification
1. Adenoma-like adenocarcinoma:

Adenoma-like adenocarcinoma is a low-grade adenocarcinoma that can be extremely challenging to diagnose on biopsy due to the overlapping features with villous adenomas (3).

Microscopically the tumor demonstrated villous projections at the surface. Desmoplasia was focally present around few isolated glands which can be helpful finding. The cells displayed low-grade dysplasia. Its early recognition might be beneficial due to its probable association with good prognosis and low metastatic potential (7).

![Histopathology of adenoma-like adenocarcinoma (3).](image)

Fig. (2): Histopathology of adenoma-like adenocarcinoma (3).

2. Micropapillary adenocarcinoma:

Micropapillary adenocarcinoma is a rare subtype of colorectal adenocarcinoma. Histological features consist of small round to-oval micropapillary clusters surrounded by clear spaces and there is no fibrovascular cores. The cells show reversed polarity (apical surfaces facing the periphery rather than the center of the tumor cluster), eosinophilic cytoplasm, and retraction artefacts forming lacunae-like spaces around the micropapillae (8).

Micropapillary adenocarcinoma is associated with increased rate of TP53 alterations and low rate of microsatellite instability. It bears a high malignancy potential and poor prognosis (9).

![Invasive micropapillary adenocarcinoma, colon. This lesion was composed mainly of polygonal cells arranged in clusters surrounded by lacunar-like clear spaces (8).](image)

Fig. (3): Invasive micropapillary adenocarcinoma, colon. This lesion was composed mainly of polygonal cells arranged in clusters surrounded by lacunar-like clear spaces (8).

3. Mucinous adenocarcinoma:

Mucinous colorectal adenocarcinoma accounts for 5-15% and is the second most frequent (after conventional adenocarcinoma). It was found more frequently in the proximal colon than distal colon or rectum. It may affect female and younger patients than non-mucinous colorectal adenocarcinoma (10).
Microscopically, Mucinous adenocarcinoma is defined as presence of > 50% of the tumor volume composed of pools of extracellular mucin (11).

Tumors with mucinous component >10% but <50% are usually termed adenocarcinoma with mucinous features or mucinous differentiation. (12).

Molecular assessments have revealed differences from non-mucinous colorectal adenocarcinoma, suggesting a different oncogenic mechanism. Overexpression of the MUC2 protein most characteristic molecular alternation in mucinous colorectal adenocarcinoma from other types (13).

Mucinous colorectal adenocarcinoma is also associated with a high frequency microsatellite instability (MSI-H) correlates mainly with Lynch syndrome and mutations that pass through RAS/MAPK pathway, and to be of the CPG island methylator phenotype (CIMP) (10).

Mucinous adenocarcinoma of the colon has been associated with an increased risk of metastasis, poor survival and resistance to chemotherapy (10).

**Fig. (4):** Histopathology of mucinous colorectal adenocarcinoma. HandE stained tissue section showing abundant extracellular mucin (red arrows) within the tumor (11).

4. **Signet ring cell adenocarcinoma:**

It is a rare variant of CRC accounts about < 1% of the cases of CRC. However, it is more common in young adults and common in female. Signet ring cell carcinoma (SRCC) is defined by presence of > 50% of the cells contain intracellular mucin that pushes the nucleus to the periphery (14).

**Fig. (5):** Signet ring cell adenocarcinoma (a) Invasive colonic signet ring carcinoma with extracellular mucin pools (b) Signet ring cell morphology, higher magnification (15).
5. Medullary carcinoma:
Medullary carcinoma (MC) is extremely rare, accounting for about 0.03% of colorectal carcinoma. It is common in elderly females above the age of 70. It is formed of sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm and a heavy lymphocytic infiltrate in between and around the tumor cells. Morphologically similar to poorly differentiated and undifferentiated MC but has a more favorable prognosis compared to them (16).

It is a distinctive histologic subtype that is strongly associated with MSI-H (17).

It usually has a favorable prognosis despite its poorly differentiated or undifferentiated histology as it has tumor infiltrating T lymphocytes, indicating antitumor immunity (18).

Fig. (6): Medullary carcinoma of colon (19).

6. Adenosquamous carcinoma (ASC):
Colorectal adeno-squamous carcinoma (ASC) is very rare. Microscopically, adeno-squamous carcinoma (ASC) is composed of two malignant components: glandular with various grade of differentiation and squamous cell counterpart with horny pearls and intercellular bridges. The two components present either mixed or separate.

This variant has been associated with high histological grade and worse prognosis compared with adenocarcinoma alone (20).

Fig. (7): Adenosquamous carcinoma of colon (H and E. original magnification. A x 200, B x 400) (21).

7. Carcinoma, undifferentiated, NOS:
Undifferentiated carcinomas (UCs) are variant of colorectal tumors showing no gland formation, but still presenting features of epithelial differentiation. Some studies include in this variant, minimal (generally less than 5%) glandular architecture. Undifferentiated carcinomas (UCs) arise more frequently in the right colon.
Microscopically, it is composed of sheets of undifferentiated cells showing a variable grade of pleomorphism with minimal gland formation, mucin production or other lines of differentiation such as squamous component. As a result, extensive sampling is required for diagnosis. Undifferentiated carcinomas (UCs) are often characterized by an infiltrative pattern of growth and extensive necrosis (22).

Pure undifferentiated carcinomas (UCs) are very rare but adenocarcinomas containing an undifferentiated component are more often found. Undifferentiated carcinomas (UCs) are aggressive tumors with very low survival rate (22).

8. Carcinoma with sarcomatoid component:

Carcinoma with sarcomatoid component also known as spindle cell carcinoma (Sp CC), a rare entity with an obscure origin that includes a mixture of carcinomatous (epithelial) and sarcomatous (mesenchymal) component. The prognosis is very aggressive for that variant (22).

![Image](a) ![Image](b)

Fig. (8): Sarcomatoid carcinoma of colon showing the upper fig: malignant glandular epithelial component (HandE x 200) and lower fig: sarcomatous component. (HandE x 400) (23).

III. NEUROENDOCRINE NEOPLASM (NENS):

NENs encompass a wide spectrum of neoplasms range from well-differentiated and relatively slowly growing but potentially malignant tumors, to highly aggressive poorly differentiated neuroendocrine carcinomas. The most common primary gastrointestinal NEN are the in rectum and small intestine. About 20% of patients present with metastases at the time of diagnosis. Well differentiated neuroendocrine tumors known as carcinoid tumor formed of uniform cell, polygonal in shape with fine granular chromatin, indistinct nucleoli and abundant cytoplasm. They are arranged in cord, trabecular, and pseudo-glandular patterns with occasional rosette formation (24).

1. Neuroendocrine tumor, grade 1, Neuroendocrine tumor, grade 2, Neuroendocrine tumor, grade 3:

According to WHO classification, the grading of neuroendocrine tumors based on proliferation rates defines three grades (G1, G2, G3). Using the mitotic count and Ki67 proliferation index for grading as a follow: grade 1 when mitoses ≤ 2/2 mm² and Ki67 index < 3%, grade 2: mitoses 2 - 20/2 mm² or Ki67 index 3% - 20% and High grade or grade 3: mitoses > 20/2 mm² or Ki67 index > 20% (25).

2. L. Cell tumors:

Colorectal NETs are composed of colonic-predominant EC-cell (serotonin-producing) NETs and rectum-predominant L-cell–type (GLP- and PP/PYY-producing) NETs. L-cell–type NETs are classified as tumors with uncertain malignant potential although no specific diagnostic criteria of L-cell– type NETs exist. Therefore, pathologists are confused about assigning behavior coding for rectal NETs as NET G1 or L-cell–type NETs.

In general, rectal NETs usually manifest as a single, smooth submucosal nodule or polyp with normal-appearing mucosa. About 80% of rectal NETs are 1 cm or smaller. The L-cell NETs are detected in 50% to 80% of rectal NETs with various combinations of L-cell markers, including GLP1, GLP2, PYY, and PPY (24).
Histologically, L-cell–type NETs have predominantly trabecular patterns. L-cell–type NETs are tumors with uncertain malignant potential in the WHO scheme. Biologic behaviors of rectal NETs depend on the L-cell immune phenotype, tumor size (≤1 or >1 cm), tumor grade, extension, and lymph node metastasis. Small (<1 cm) rectal NETs tend to have no recurrence, even with incomplete resection. On the other hand, large rectal NETs (>1 cm) and non–L-cell phenotype tumors have an aggressive clinical behavior and worse prognosis (24).

3. **Glucagon-like peptide producing tumor:**

   Glucagon-like peptide-1 receptor (GLP1R) is a G-protein coupled receptor for glucagon-like peptide-1 (GLP1). The receptor is involved in the regulation of the secretion of insulin, and the enhancement of the insulin secretion from the pancreatic beta-cells by GLP1 is known as “incretin effect.” Dipeptidyl peptidase (DPP)-IV is a peptidase that cleaves two amino acids of N-terminal of proteins (26).

   At present, the expressions of GLP1R in gastrointestinal NEN (GI-NEN) are not known. These molecules may be involved in the neuroendocrine function or growth of the neoplasms. It is thus valuable to know the expression of these molecules for the understanding of pathophysiology of NEN and for the possible development of new diagnostic and therapeutic modalities (27).

4. **PP/PYY producing tumors:**

   Neuroendocrine tumors occasionally have secretory characteristics. The production of peptide YY (PYY), a gastrointestinal hormone, may decrease intestinal motility. PYY is presumably the main cause of the constipation in patients. On histopathologic examination, trabeculae and small nests of uniform tumor cells. They were immunoreactive for synaptophysin in carcinoid areas. The immunohistochemical staining for PYY was performed additionally and the result was strongly positive (28).

5. **Enterochromaffin cell carcinoid:**

   Enterochromaffin cell carcinoid is uncommon colon and rectum. Microscopically, predominantly insular pattern with frequent invasion muscularis propria and serosa and may elicit desmoplastic response. Immunohistochemically, Synaptophysin and chromogranin A positive (24).

6. **Serotonin producing carcinoid:**

   Serotonin-secreting neuroendocrine tumors (5-HT-secreting NETs) are very rare, and characterized by high urinary 5-hydroxyindole-acetic acid (5-HIAA) levels (or high serum 5-HT levels). Immunohistochemically, serotonin, synaptophysin and chromogranin A positive. This subset of NETs are not associated with a worse prognosis than other NETs reported (29).

IV. **NEUROENDOCRINE CARCINOMA, NOS**

   Neuroendocrine carcinoma (NEC) show poorly differentiated histological features, high proliferative properties (>20 mitotic figures per 10 high-power fields [HPF] or a Ki-67 index >20%) and associated poor prognosis. WHO classification of 2019, NEC has been divided into small-cell and large-cell types (30).

1. **Large cell neuroendocrine carcinoma:**

   Large cell type shows organoid arrangement of cells larger than those in small cell carcinoma, with nuclear pleomorphism and hyperchromasia, prominent nucleoli, numerous mitoses and tumor necrosis (3).

2. **Small cell neuroendocrine carcinoma:**

   Small cell type (as that of pulmonary small cell carcinoma) is formed of sheets and nests of small round cells with minimal cytoplasm, hyperchromatic nuclei with stippled chromatin. The tumor showed nuclear molding and peripheral palisading, high mitotic activity and apoptotic cells (31).
Fig. (9): Large cell neuroendocrine carcinoma (3).

V. MIXED NEUROENDOCRINE - NONNEUROENDOCRINE NEOPLASM (MiNEN):

Mixed neuroendocrine - nonneuroendocrine neoplasm (MiNENs) are a heterogeneous group of extremely rare tumors, characterized by the simultaneous finding of a NE component and a non-NE component which, by convention, must each represent at least 30% of the tumor (32).

With regards to pathogenesis various studies have demonstrated a monoclonal origin of both NE and non-NE components due to overlapping mutational profiles which may explain the amphicrine nature of the two high grade components (poorly differentiated neuroendocrine carcinoma (PD NEC) and adenocarcinomatous areas). Whatever the pathogenesis, MiNENs are most often, not exclusively, aggressive neoplasms which show short survival times; from a pathology point of view they require accurate description with identification and grading of all components, even those which do not reach 30% of the surface area (33).

Fig. (10): Mixed adenoendocrine carcinomas show mixed carcinomas containing both malignant glandular (left half) and small cell carcinoma (right half) components (24).

Epithelial-mesenchymal transition

EMT is a biologic process in which cells lose their epithelial characteristics and acquire mesenchymal features, which enable them to migrate more efficiently and invade the underlying mesenchyme. EMT is associated with tumorigenesis, invasion, metastasis, tumour stemness and resistance to therapy (34).

An EMT involves a functional transition of polarized epithelial cells into mobile and ECM component–secreting mesenchymal cells. EMT needs activation of transcription factors, expression of specific cell surface proteins, reorganization and expression of cytoskeletal proteins, production of ECM-degrading enzymes, and changes in the expression of specific microRNAs (35).

EMT plays a crucial role enabling cells of epithelial origin to migrate long distances to contribute to the formation of different tissues and organs. These cells are believed to be able to migrate individually or collectively in a coordinated manner. In this process, migratory cells harboring different degrees or combinations of epithelial and mesenchymal features display an array of migratory behaviors (Figure13). Single-cell migration usually requires a
more complete EMT with reduced cell adhesion, loss of apical-basal polarity, gain of front-rear polarity and increased individual motility (36).

In collective migration, multiple cells migrate in the same direction at a similar speed. Although it was previously believed that groups of cells migrate collectively as epithelial cells, more recent evidence suggest that a wide spectrum of cell adhesion strength and EMT states can be found in the migrating clusters (37).

Leader cells, localized at the front of the migrating group, undergo partial EMT and gain mesenchymal phenotype with altered polarity and dynamic actin-based protrusive structures to drive migration. At the same time, they retain some epithelial characteristics and remain attached to their neighbors (38).

EMT-induced signals arise from the tumor-associated stroma. Transforming growth factor-beta (TGF-β), Endothelial growth factor (EGF), Platelets derived growth factor (PDGF) and Hepatocyte growth factor (HGF) are responsible for the induction of EMT-induced transcription factors in cancer cells (39).

**Special AT-rich Binding Protein 1 (SATB1)**

SATB (Special AT-rich binding protein) family proteins including SATB1, SATB 2 are nuclear matrix-associated proteins that are important for growth and development. Recent studies have demonstrated that both SATB1 and SATB2 are instrumental in cancer progression. Both members of the SATB family chromatin organizers are involved in long-range enhancer function extension of chromatin modifications (40).

Over expression of SATB1 was observed in many types of human tumors, where it promotes cancer cell growth and metastasis by altering the gene expression profile (40). SATB1 activates many genes that have roles in carcinogenesis, including E-Cadherin, VEGFB, and TGFβ1. SATB1 expression in many cancers including CRC is associated with progression, poor prognosis and microsatellite instability (MSI) (41).

Special AT-rich sequence-binding protein 1 (SATB1) might promote the epithelial–mesenchymal transition by increasing the aberrant expression of β-catenin (42).

The immunohistochemical expression of SATB1 was negatively expressed in normal colorectal mucosa or only few scattered cells while in cancer was expressed in the nuclei of cancer cells. Some tissues exhibited combined nuclear and cytoplasmic expression. The positive expression ratio of SATB1 protein in lymph node metastases was significantly higher than in primary lesions and normal colorectal mucosa (43).

**β-Catenin**

β-Catenin is a 92 kDa protein that is found at cellular junctions bounded to E-cadherin, in the cytoplasmic compartment and in the nuclear compartment (44).

It is well established that Wnt signaling pathway possesses important roles in the embryonic development of adult stem cells and their preservation, also in evolving tumors and their expansion (45).

Wnt signaling pathway includes three sub-pathways: canonical, non-canonical planar cell polarity (PCP) pathway and non-canonical Wnt/calcium pathway. The canonical Wnt signaling pathway is dependent on β-Catenin, where it is transported to the nucleus, activates certain genes and with the help of some signaling receptors, it regulates their expression. The non-canonical Wnt pathway is not dependent on β-Catenin, there is no activation of β-Catenin, and however signal transduction affects the polarity and the migratory action of the cell (46).

If Wnt signaling pathway is not activated, a destructive complex will break down the cytoplasmic Beta-catenin, keeping it at low levels. This complex is composed of APC, glycogen synthase kinase 3-β (GSK3-β), Axin, and other elements. On the other hand, up-regulation of Wnt signaling pathway or the APC gene or the β-Catenin gene mutation results in its high-level expression in the cytoplasm and their translocation to the nucleus (47).

**E-Cadherin**

E-cadherin protein is a member of cadherin family transcribed from CDH1 gene, which is located in chromosome 16q22.1. The mature E-cadherin protein is a 120 kDa, Ca2+-dependent transmembrane glycoprotein which binds normal and polarized epithelial cells together at lateral surface via adherens junctions (AJs) (48).
The amino terminal of E-cadherin houses five extracellular cadherin domains between which Ca2+ ions bind and its adhesive activity lies. Ca2+ ions binding then induce the stiffening of the entire span of the extracellular domain and promote protease resistance. The stiffening of the extracellular domain provides a vital role for three-dimensional domain swapping which is at the core of E-cadherin’s homophilic trans dimer formation between apposed cells (49).

In normal epithelial tissues with high expression of E-cadherin, β-catenin is sequestered at the cell membrane, preventing it from being released into the cytoplasm and entering the nucleus. This prevents β-catenin from binding to a member of the DNA binding protein family LEF (Lymphoid enhancer factor)/TCF (T cell factor) in the nucleus. Hence, the Wnt signaling pathway is not activated and cancer initiation is prevented (50).

**Fig. (11):** The schematic illustration of E-cadherin production through the central dogma. The CDH1 gene is transcribed into a precursor polypeptide of E-cadherin carrying the prosequence which has a cleavage site of Arg-Arg-Gln-Lys-Arg (R-R-Q-K-R) for its subsequent removal in the Golgi apparatus. The mature E-cadherin is then transported to the plasma membrane. The E-cadherin-β-catenin complex is linked to the actin filaments via association with α-catenin. JMDcore: juxtamembrane core domain; EC1-EC5: Extracellular cadherin/EC subdomains of E-cadherin (49).

**Fig. (12):** The schematic representation of the E-cadherin-mediated homophilic cell–cell adhesion mechanism (49).

E-cadherin is a well-known tumor suppressor protein, and the loss of its expression in tumor cells, in association with the epithelial–mesenchymal transition (EMT), occurs frequently during tumor progression and metastasis (50).

E-cadherin plays an important role in epithelial cell adhesion and act as tumor suppressor protein. Their loss of its function is a major contributor to cancer progression. The resulting loss of cell–cell adhesion and cell junctions mediated by E-cadherin homophilic binding is believed to allow cells to dissociate from the primary tumor, invade surrounding tissues, and migrate to distant sites (52).
Loss or decrease of E-cadherin expression has recurrently been associated with poor prognosis and poor overall survival of colorectal cancers (49).

SATB1 depletion blocks the up-regulation of E-cadherin and extracellular matrix (ECM) protein vimentin. Many studies showed that SATB1 plays a pivotal role in epithelial to mesenchymal transition (EMT) process (51)

Conflict of Interest: No conflict of interest.

REFERENCES