Reviews

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N.O. Kulyaba[1]*, A.V. Bdzhola[2]*,
A.R. Stasyshyn[1], V.V. Filonenko[2], D.M. Bidyuk[1]

[1] University Hospital of Danylo Halytskyi Lviv National Medical University
69, Pekarska Str., Lviv, Ukraine, 79000
[2] Institute of Molecular Biology and Genetics, NAS of Ukraine
150, Akademika Zabolotnoho Str., Kyiv, Ukraine, 03143
filonenko@edu.imbg.org.ua

CLASSICAL MARKERS FOR COLORECTAL CANCER DIAGNOSTICS AND BEYOND: EMERGING ROLES OF COA METABOLISM AND PROTEIN COALATION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide. Early diagnosis is essential for the effective treatment selection. Alongside standard clinical and instrumental methods, tumor markers are widely used in CRC diagnostics. The most common serum biomarkers are carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), although their limited sensitivity and specificity at early stages reduce their value for primary screening. Instead, they are mainly used for the disease monitoring. KRAS mutations are important genetic markers in CRC, while profiling of small non-coding RNAs in liquid biopsy is emerging as a promising non-invasive approach for diagnosis and patient stratification. However, most currently available biomarkers are more informative for prognosis and therapy selection than for early detection, emphasizing the need for additional molecular indicators. The recent evidence highlights oxidative stress and redox-dependent protein modifications as key contributors to CRC progression. Reactive oxygen species (ROS) promote genomic instability and regulate signaling pathways and post-translational protein modifications, including recently characterized Coenzyme A-dependent protein modification (CoAlation). This review integrates classical CRC biomarkers with redox biology and discusses the potential of CoA metabolism and protein CoAlation as novel CRC biomarkers, with particular emphasis on CoA synthase (CoASY) as a possible determinant of therapy resistance.

Keywords: *colorectal cancer, carcinoembryonic antigen (CEA), CA19-9, oxidative stress, protein CoAlation.*

* These authors contributed equally to this work

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Introduction

Cancer remains a major challenge for modern healthcare systems worldwide, with colorectal cancer representing one of the most prevalent malignancies [1]. Each year, more than 1.85 million new cases of colorectal cancer are diagnosed globally, with approximately 850,000 deaths reported annually.

European regions exhibit the highest incidence rates of colorectal cancer, a trend associated with socio-economic development, as well as adverse lifestyle factors and dietary shifts, including reduced physical activity and increased consumption of animal-based products [2]. Together with obesity, excessive alcohol consumption, and smoking, these factors are independently linked to an elevated risk of developing colorectal cancer [3]. Notably, the increasing incidence of early-onset colorectal cancer among individuals under 50 years of age observed in many countries is of particular concern, underscoring the urgent need for improved early detection, accurate prognostic assessment, and more effective treatment strategies.

The majority of colorectal cancer cases (about 75%) are sporadic, while the remaining 20—30% are associated with hereditary or familial predisposition, shared environment, or lifestyle-related risks [4]. At the time of diagnosis, metastatic disease involving the liver, lungs, peritoneum, and lymph nodes is detected in approximately 15—30% of patients [5].

The progression of the disease from benign adenomas to malignant adenocarcinomas is a rather slow process, which theoretically provides a window of opportunity for early detection. Therefore, identifying new molecular biomarkers that can serve as diagnostic and prognostic tools, as well as potential therapeutic targets represents a clinically important direction of research [6].

Military actions on the territory of Ukraine have significantly affected all aspects of the public life, including the availability and quality of healthcare services. In particular, the functioning of the national cancer registry system has been disrupted, complicating the systematic collection and reporting of data on diagnosed and treated cancer patients to regional registries. In many cases, such territorial documentation remains the only available source of patient-related oncological data. According to the most reliable data from 2022—2023, malignant neoplasms of the colon (27.5%), rectum, and anus (24.4%) constitute the most prevalent gastrointestinal cancers in Ukraine [7]. At the same time, there has been a statistically significant increase in the incidence of malignant neoplasms of the colon — 1.6% annually in men and 0.4% in women.

Analysis of the diagnostic stage distribution showed that the disease was detected at an advanced stage in approximately 20—25% of patients with colon or rectal cancer [8]. Early-onset colorectal cancer, defined as diagnosis before the age of 50, is becoming increasingly prevalent worldwide, although the underlying causes of this trend remain unclear. Projections indicate that within the next decade, up to 10% of colon cancer cases and 25% of rectal cancer cases will be diagnosed in patients younger than 50 years [8].

Recurrences and metastases of colorectal cancer are characteristic features of the disease. Early detection of metastatic processes at the preclinical stage remains a significant clinical challenge [8]. The liver represents the primary target organ for hematogenous metastases in intermediate and advanced stages, and hematogenous liver metastases are the leading cause of poor prognosis or cancer-related mortality [9, 10].

Tumor markers are biological molecules whose expression or release is associated with malignant transformation or, in some cases, with precancerous conditions. These markers can be detected in blood, urine, cerebrospinal fluid, tissues, or other body fluids. Tumor markers are molecules with intrinsic biological functions, whose altered levels or states are interpreted as indicators of cancer presence or progression. In clinical practice, tumor markers are used to support early cancer detection, monitor treatment efficacy, assess prognosis, and identify disease recurrence or metastatic progression following therapy.

However, not all tumor markers are sufficiently specific to cancer, which can sometimes complicate diagnostic accuracy. Nonetheless, they can still be considered as part of a comprehensive diagnostic approach. Elevated levels of some markers can also indicate other pathological processes, such as infections and chronic diseases. Given this, the search for new, more specific and sensitive tumor markers remains one of the primary goals of modern clinical oncology.

In this review we discuss several aspects of the discovery and establishment of tumor markers in colorectal oncology.

Classical tumor markers in CRC: limitations and clinical value

The possibilities for a comprehensive diagnosis of colorectal cancer, including the study of tumor markers, are outlined in two directions. The first one is based on the use of tumor markers whose diagnostic significance has been confirmed and which are standard predictors included in diagnostic algorithms. These include carcinoembryonic antigen (CEA) and CA19-9. The second direction involves identifying tumor markers that still require further investigation — from understanding their expression in tissues to assessing their diagnostic significance.

Carcinoembryonic antigen (CEA)

Carcinoembryonic antigen was first isolated by Gold and Freedman in 1965 from adenocarcinoma of the intestine and embryonic mucosa of the colon [11]. At that time, it was believed to be a unique antigen expressed only in tumors of the human digestive system.

The elevated level of CEA in the serum of cancer patients compared to the healthy individuals laid the foundation for its clinical use as a diagnostic biomarker more than 50 years ago. A healthy adult human colon produces at least 50—70 mg of CEA daily [12].

An increase of CEA level was also observed in other malignant conditions. The conditions predisposing to cancer include smoking, peptic ulcer disease, inflammatory bowel diseases, pancreatitis, hypothyroidism, bile duct obstruction, and cirrhosis. Serum CEA levels exceeding 10 ng/mL are rarely associated with benign conditions [13]. Thus, the CEA level in serum does not have sufficient diagnostic specificity and sensitivity.

At the same time, the serum CEA level is used for detecting recurrences after surgical intervention and for monitoring treatment effectiveness prior the clinical manifestation of metastatic complications [12].

CEA levels are elevated in approximately 50% of patients with lymph node involvement and in 75% of patients with distant metastases. The highest values (above 100 ng/mL) are observed in cases of metastasis, although poorly differentiated tumors are less likely to produce CEA [14, 15].

CA19-9

In 1979, Koprowski discovered a cancer carbohydrate antigen, now known as CA19-9. Elevated level of this marker was observed in tumors of the pancreas, liver, bile ducts, esophagus, and also in the colon [16].

One important aspect regarding CA19-9 is its genetic dependency. Individuals lacking the specific Lewis gene cannot produce CA19-9, which means that this marker may be absent in such patients even if cancer is present [17].

Serum levels of CA19-9 may also be affected by various neoplastic diseases of the gastrointestinal tract and benign conditions of the bile ducts, such as primary sclerosing cholangitis or bile duct obstruction due to common bile duct stones. Consequently, CA19-9 may not be an ideal marker for the patients with colorectal cancer [18].

Carbohydrate antigen 19-9 (CA19-9) is a widely used serum biomarker for early diagnosis, assessment of treatment response, monitoring of recurrences, and prognosis in various gastrointestinal tumors [19].

Some studies have shown that elevated levels of CA19-9 are associated with worse prognosis in

patients with colorectal cancer, independent of well-established prognostic factors such as TNM staging and carcinoembryonic antigen (CEA) levels [20—24]. However, other studies have not confirmed this correlation [25,26].

Combination of tumour markers CEA and CA19-9

The combined assessment of CA19-9 and CEA in predicting post-surgical outcomes in colorectal cancer is of clinical interest. Several studies have noted that patients with elevated levels of both CA19-9 and CEA have worse survival than those with elevated only one of these markers [23, 27]. The authors believe that the combination of preoperative CEA and CA19-9 levels may be useful for predicting outcomes after radical resection.

In a study by Stiksma *et al.*, it was found that patients with elevated preoperative CA19-9 levels had lower 5-year survival compared to those with elevated CEA levels, and the authors recommended using CA19-9 for monitoring disease progression in patients without elevated CEA [28]. Lin *et al.* concluded that elevated CA19-9 levels are associated with worse survival only in patients with normal preoperative CEA levels [29]. These results suggest that the combined use of CA19-9 and CEA has prognostic value in the colorectal cancer patients [23, 24, 27—29].

Additionally, Grotowski *et al.* reported that CA19-9 levels increase in the late stages of colon cancer. Despite its lower sensitivity compared to CEA in the early stages of colon cancer, the combination of both antigens may provide more information for predicting recurrence and survival than CEA alone [30].

Thus, despite the widespread use of CA19-9 in clinical practice, its prognostic value in colorectal cancer progression remains unclear and requires further investigation [31—33].

Taken together, these limitations highlight the need for biomarkers that not only reflect tumor burden but also provide insight into the underlying biological mechanisms driving colorectal cancer progression.

Genetic and post-transcriptional biomarkers

In recent years, the investigation of genetic alterations associated with colorectal cancer has become one of the key areas in molecular oncology. Among the most significant targets are oncogene mutations and microRNAs (miRNAs) dysregulation, which have emerged as potential prognostic and predictive biomarkers [34—36]. The analysis of these alterations provides deeper understanding of the mechanisms of carcinogenesis and supports the advancement of personalized medicine, particularly regarding early diagnosis, disease prognosis, and the selection of targeted therapy.

KRAS and related mutations

One of the most frequent and clinically significant genetic alterations in colorectal cancer is observed in *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*). *KRAS* mutations are detected in approximately 30—40% of cases and act as key oncogenic drivers by inducing constitutive activation of downstream signaling cascades, most notably the MAPK/ERK and PI3K/AKT pathways [37]. Persistent signaling through these pathways promotes uncontrolled proliferation, resistance to apoptosis, impaired differentiation, and enhanced tumor progression.

The majority of *KRAS* mutations in colorectal cancer occur at hotspot codons 12 and 13 within exon 2, with less frequent alterations affecting codons 61 (exon 3) and codons 117 and 146 (exon 4). Among these, substitutions such as G12D, G12V, G13D, and G12C account for most oncogenic activity, although individual mutations differ in biological aggressiveness and therapeutic sensitivity [38]. Rare *KRAS* variants have been described in other codons, but their functional and clinical relevance remains less well defined.

Clinically, *KRAS* mutation status is a predictive and prognostic biomarker in CRC. Tumors

harboring *KRAS* mutations are consistently associated with poorer overall survival, higher recurrence rates, and reduced responsiveness to conventional chemotherapy. Most importantly, activating *KRAS* mutations are associated with resistance to epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies, such as cetuximab and panitumumab. Consequently, *KRAS* genotyping is now a standard component of molecular diagnostics in metastatic cancers and is essential for the patient stratification and treatment selection [38—40].

The accurate detection of *KRAS* mutations is critical for precision oncology in colorectal cancer. The currently employed methodologies include real-time PCR-based assays, allele-specific PCR, Sanger sequencing, and next-generation sequencing (NGS), with NGS increasingly favored due to its ability to detect low-frequency variants and co-occurring mutations in parallel. Liquid biopsy approaches using circulating tumor DNA (ctDNA) have further expanded the clinical utility of *KRAS* testing, enabling non-invasive monitoring of tumor dynamics, therapeutic response, and resistance evolution [41].

MicroRNAs (miRNAs)

In parallel with the study of the *KRAS* mutational profile, small non-coding RNAs, particularly miRNAs involved in regulation of gene expression, have also become a subject of intense research as novel biomarkers for colorectal cancer [35, 36].

To date, approximately 50 miRNAs have been found up- or downregulated in CRC cells as compared to their normal counterparts [42]. Their clinical utility arises from their high stability in body fluids (protected by exosomes or protein complexes) and their differential expression at various stages of the adenoma-carcinoma sequence [43].

Circulating in blood, miRNAs allow for minimally invasive screening and real-time monitoring of tumor dynamics. Among the most extensively validated circulating miRNAs is miR-21, whose elevated serum levels are strongly associated with CRC presence, advanced TNM stage, and poor prognosis. Another key biomarker is miR-92a, a member of the miR-17—92 cluster, which exhibits high sensitivity for detecting early-stage CRC as well as precancerous adenomas [44].

Fecal-based tests of miR provide a direct look at the colonic environment, often showing changes before systemic markers rise. Particularly, upregulation of miR-135b indicates the transition from adenoma to carcinoma, making it a prime candidate for early detection [45]. The miR-143/145 cluster is one of the most studied tumor suppressors in the context of colorectal cancer. Unlike miR-135b, the levels of these miRNAs are usually dramatically reduced in colon cancer, making them negative markers of progression [46].

Exosomal microRNAs are the most studied exosomal cargo for «liquid biopsy» due to their role in tumor initiation and metastasis. They represent a highly stable and specific category of biomarkers for colorectal cancer, acting as «messengers» within the tumor microenvironment (TME). Unlike freely circulating RNAs, exosomal RNAs are encapsulated in lipid bilayers (30—150 nm), protecting them from RNase degradation and reflecting the physiological state of the parent tumor cell.

Recent studies confirm that exosomal miR-21—5p is propagated from CRC cells to endothelial cells, activating β-catenin signaling and promoting angiogenesis. In clinical cohorts, it shows high accuracy for describing advanced stages and predicting chemoresistance to 5-FU [47]. miR-1229, elevated in serum exosomes, may target HIPK proteins and activates the VEGF pathway, facilitating tumor vascularization. Its high expression in CRC patients correlates with the tumor size and lymphatic invasion [48]. A combination of miRs in panels like miR-15b, miR-16, and miR-21 has shown sensitivity and specificity rates exceeding 95% and 94%, respectively, outperforming traditional markers like CEA [49].

Despite their clinical relevance, the genetic and post-transcriptional biomarkers primarily capture static alterations in tumor genomes and

transcriptomes, while dynamic cellular processes that critically influence tumor behavior remain less well represented.

Oxidative stress in the context of colorectal cancer

Among metabolic reprogramming, mitochondrial dysfunction, and redox imbalance, oxidative stress represents an important feature of colorectal cancer biology, reflecting a dynamic imbalance between reactive oxygen species production and antioxidant defense systems. So another vital direction in molecular oncology is the evaluation of oxidative stress markers in tumor tissues for diagnostic purposes and prediction therapeutic response [50—52].

ROS in tumor initiation and progression

Colorectal cancer is consistently associated with a sustained imbalance in cellular redox homeostasis, characterized by elevated levels of reactive oxygen species (ROS) and impaired antioxidant defense systems. Multiple clinical and experimental studies demonstrate that CRC tissues and patient-derived samples exhibit increased oxidative damage [53, 54], including higher levels of DNA oxidation markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), as well as elevated lipid peroxidation products. In parallel, ROS activate redox-sensitive signaling pathways, including NF-κB, STAT3, MAPK, and PI3K/AKT, which collectively support proliferation, survival, angiogenesis, and inflammatory responses within the tumor microenvironment [55].

Importantly, the CRC cells exhibit a finely tuned adaptation to oxidative stress: while maintaining elevated ROS levels that sustain oncogenic signaling, they upregulate antioxidant systems — such as glutathione, thioredoxin, and enzymatic scavengers — to prevent excessive oxidative damage and cell death. This redox adaptation is critical for tumor maintenance and contributes to the disease progression [56, 57].

The increase in ROS production leads to DNA damage and the accumulation of further mutations. ROS directly attack nucleic acids, causing base oxidation, DNA strand breaks, and other damage. If unrepaired, this damage leads to mutations in proto-oncogenes (such as *KRAS*) and tumor suppressor genes (such as *p53*), which lead to malignant transformation. Persistent DNA damage also contributes to overall genomic instability, accelerating clonal selection of cancer cells [50].

While classical antioxidant systems such as glutathione and thioredoxin have been extensively studied in this context, additional redox-regulatory mechanisms are increasingly being recognized. In this regard, coenzyme A (CoA) has recently attracted attention as a multifunctional molecule that links cellular metabolism with redox regulation.

Coenzyme A and redox regulation in CRC

Within the cellular antioxidant network, coenzyme A (CoA) has emerged as an important, yet underexplored, component of redox regulation. In addition to its well-established metabolic roles, CoA contributes to cellular defense against oxidative stress alongside glutathione. The recent studies conducted in collaboration with the Institute of Molecular Biology and Genetics NASU have identified a novel redox-regulated post-translational modification termed protein CoAlation, in which CoA is covalently attached to cysteine residues of target proteins under conditions of oxidative or metabolic stress [58—60].

Protein CoAlation is proposed to function as a protective mechanism that shields reactive thiols from irreversible overoxidation while simultaneously modulating protein activity [61—65]. This positions CoAlation as both a sensor and effector of redox imbalance, linking metabolic state to stress response pathways. Given that CRC as well as other tumor types are characterized by persistent oxidative stress, CoAlation may represent a

previously unrecognized layer of regulation relevant to tumor adaptation that can be important for cancer diagnostic. Among the proteins CoAlated under conditions of oxidative stress, several involved in the regulation of cancer cell growth, such as Aurora A kinase [66], tumor suppressor NME1 [64] and the ribosomal protein S6 Kinase (S6K1) [63] were identified. In addition, an overall elevation of protein CoAlation was found in cancer cells of different tissue origion [67].

CoASY as a CRC-relevant biomarker

The relevance of CoA metabolism to CRC is further supported by the emerging role of CoA synthase (COASY), the enzyme catalyzing the final steps of CoA biosynthesis. Notably, COASY has been identified as a clinically relevant biomarker in rectal cancer, particularly in the context of radiotherapy response.

Ferrandon *et al.* demonstrated that COASY expression is significantly elevated in radioresistant rectal tumors [68]. The functional studies further showed that downregulation of COASY sensitizes cancer cells to ionizing radiation, indicating a direct role in mediating resistance. Mechanistically, COASY directly binds to the PI3K regulatory subunit p85α, leading to the increased phosphorylation of AKT and mTOR and thereby promoting cell survival. Additionally, COASY enhances the efficiency of DNA damage repair, particularly by promoting the resolution of DNA double-strand breaks, thereby supporting cell survival. These findings suggest that COASY contributes to the cellular adaptation under oxidative and genotoxic stress, conditions that are central to radiotherapy response.

From a biomarker perspective, COASY expression may therefore serve as a predictive indicator of radioresistance in CRC, particularly in rectal cancer patients undergoing neoadjuvant treatment. Moreover, given its central role in CoA biosynthesis, COASY may reflect broader metabolic-redox adaptations within the tumor.

The relationship of CoA metabolism with antioxidant and epigenetic pathways

Beyond its direct involvement in CoAlation, CoA metabolism intersects with multiple antioxidant and regulatory pathways. Through its derivative acetyl-CoA, CoA supports the synthesis and function of key antioxidant systems, including glutathione and coenzyme Q_{10} (CoQ_{10}).

Acetyl-CoA is frequently elevated in cancer and supports cell growth by driving lipid production and the mevalonate-CoQ_{10} pathway [69, 70]. In pancreatic tumours, CoA also supports ferroptosis resistance by promoting CoQ_{10} synthesis through the mevalonate pathway [69]. The enzymes that generate acetyl-CoA, such as ACLY and ACSS2, are often overexpressed or hyperactivated in tumors, further increasing its availability. High acetyl-CoA availability enhances antioxidant defenses and mitigates radiation-induced lipid peroxidation, contributing to radioresistance [70]. Acetyl-CoA also drives histone acetylation, opening chromatin and promoting transcriptional programs that support tumour growth and adaptation [71, 72].

Together, CoA metabolism, CoAlation and acetyl-CoA-dependent signaling enable cancer cells to remodel metabolism, resist ferroptosis and reprogram epigenetics, highlighting the therapeutic potential of targeting CoA biosynthetic enzymes and redox-regulated CoAlation pathways as well as applying it for cancer diagnostics, particularly for colorectal cancer. In CRC, where both oxidative stress and metabolic reprogramming are prominent, the CoA-dependent processes may therefore play a dual role in tumor progression and therapy resistance.

Conclusions

In conclusion, the detection of established tumor-specific markers in colorectal cancer has substantial diagnostic and prognostic value. Nevertheless, further research should focus on the clinical implementation of novel, more specific

laboratory methodologies for colorectal cancer diagnosis. This, in turn, necessitates the identification and validation of new biochemical markers of oncogenesis.

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Н.О. Куляба[1]*, *А.В. Бджола*[2]*, *А.Р. Стасишин*[1], *В.В. Філоненко*[2], *Д.М. Бідюк*[1]

[1] Університетська лікарня Львівського національного медичного університету імені Данила Галицького
вул. Пекарська, 69, Львів, Україна, 79000
[2] Інститут молекулярної біології і генетики НАН України
вул. Академіка Заболотного, 150, Київ, Україна, 03143
filonenko@edu.imbg.org.ua

КЛАСИЧНІ МАРКЕРИ ДІАГНОСТИКИ КОЛОРЕКТАЛЬНОГО РАКУ ТА НОВІ ПЕРСПЕКТИВИ: РОЛЬ МЕТАБОЛІЗМУ КОА І БІЛКОВОГО КОАЛЮВАННЯ

Колоректальний рак (CRC) залишається однією з провідних причин смертності від онкологічних захворювань у світі. Рання діагностика є критично важливою для вибору ефективної терапії. Поряд зі стандартними клінічними та інструментальними методами, у діагностиці CRC застосовують пухлинні маркери — молекули, рівень або структура яких змінюються під час онкогенезу. У клінічній практиці найчастіше використовують карциноембріональний антиген (CEA) та антиген 19-9 (CA19-9). Однак через низьку чутливість і специфічність на ранніх стадіях вони переважно придатні для моніторингу перебігу хвороби. Важливими генетичними маркерами CRC є також мутації гена *KRAS*, а профілювання малих некодуючих РНК у рідинній біопсії розглядається як перспективний неінвазивний підхід для діагностики та стратифікації пацієнтів. Попри значний прогрес, більшість сучасних біомаркерів залишаються більш інформативними для прогнозування та вибору терапії, ніж для раннього виявлення захворювання. Останніми роками зростає кількість даних про роль оксидативного стресу та редокс-залежних модифікацій білків у прогресуванні CRC. Активні форми кисню (ROS) сприяють геномній нестабільності та регулюють сигнальні шляхи й посттрансляційні модифікації білків, зокрема нещодавно описану модифікацію з залученням Коензиму А — КоАлювання. Даний огляд присвячений інтеграції класичних біомаркерів CRC з аспектами редокс-біології та потенціалу метаболізму КоА і КоАлювання як нових маркерів CRC.

***Ключові слова*:** колоректальний рак, раковоембріональний антиген (РЕА), CA19-9, оксидативний стрес, КоАлювання протеїнів.

* Автори, що мають рівний внесок.