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An Integrative Approach to Autophagy and Oxidative Stress Pathways for Clinical Prediction in Colorectal Cancer: A Narrative Review

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Abstract: Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide. Increasing evidence suggests that oxidative stress and autophagy are interconnected biological processes involved in tumor initiation, progression, therapeutic resistance, and patient survival. However, their combined role as an integrated prognostic biomarker panel has not been comprehensively reviewed. This narrative review aimed to summarize current evidence on the interaction between oxidative stress and autophagy pathways and to evaluate the clinical potential of their biomarkers for prognostic prediction in CRC. This review was based on peer-reviewed open access publications from major scientific databases between 2019 and 2025. Studies that have assessed oxidative stress biomarkers, such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), 4-hydroxynonenal (4-HNE), nuclear factor erythroid 2-related factor 2 (NRF2), Kelch-like ECH-associated protein 1 (KEAP1), and autophagy-related biomarkers, including microtubule-associated protein 1 light chain 3 beta (LC3B) and sequestosome 1 (p62/SQSTM1) were critically synthesized. Current evidence suggests a role for oxidative stress and autophagy dysregulation in the development of CRC. Increased expression of LC3B, p62/SQSTM1, NRF2, and 8-OHdG is always associated with advanced disease, treatment resistance, tumor recurrence, and poor overall survival. Integrating biomarkers from both pathways appears to improve prognostic accuracy compared with individual biomarkers. Combined assessment of oxidative stress and autophagy biomarkers represents a promising prognostic approach for CRC. Nevertheless, large prospective studies are required to validate their clinical utility before routine implementation in precision oncology.

Keywords: Autophagy, Biomarkers, Colorectal Cancer, Oxidative Stress, Prognosis.

INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide despite substantial advances in screening programmes, surgical management, systemic chemotherapy, targeted therapy, and immunotherapy. While these advances have increased survival in a significant number of patients, there is still a high heterogeneity in disease evolution, response to treatment and long-term outcomes even among patients with similar clinicopathological characteristics. This clinical heterogeneity underscores the need for better biomarkers to complement standard pathological assessment and to enable personalised therapeutic decisions (Carretero-Fernández et al., 2025; Damiano et al., 2025; Nordengen et al., 2024).

Oxidative stress and autophagy have emerged as important determinants of tumour behaviour in the biological processes involved in CRC progression. Both pathways contribute to tumour adaptation under cellular stress and have been implicated in disease progression, therapeutic response and patient prognosis. As a consequence, oxidative stress and autophagy-related biomarkers have attracted increasing interest as potential tools to improve prognostic evaluation and advance precision oncology. These pathways are however generally investigated independently, despite accumulating evidence supporting their close biological coordination (Carretero-Fernández et al., 2025; Hasan et al., 2022; Nickoloff et al., 2020; Xu et al., 2024).

Recent advances in molecular oncology indicate that tumour progression is driven by complex interactions among multiple adaptive pathways rather than by isolated molecular events. Within this context, the interplay between oxidative stress and autophagy has gained increasing interest because it may influence tumour survival, metabolic adaptation, therapeutic resistance, and ultimately clinical outcome. This biological interaction has led to current research focusing on integrated biomarker strategies that can better reflect tumor biology than single molecular markers alone (Dera & Al Fayi, 2025; Pan & Valapala, 2022; Prime et al., 2024; Shan et al., 2024).

Research in this area has grown rapidly, but the current evidence is scattered among molecular, pathological and clinical studies. Most previous reviews have discussed oxidative stress or autophagy separately, whereas relatively little attention has been given to their combined prognostic significance or their potential integration into clinically applicable biomarker panels. Consequently, the translational value of these interconnected pathways has not yet been comprehensively synthesised, limiting their potential application in routine pathology and precision oncology.

Accordingly, this narrative review aims to integrate current evidence regarding the relationship between oxidative stress and autophagy in CRC and to evaluate the potential clinical relevance of combining biomarkers from these pathways for prognostic assessment. By synthesising molecular mechanisms together with emerging pathological and clinical evidence, this review provides an integrated perspective that may facilitate future biomarker development, improve prognostic stratification, and support the implementation of precision oncology in CRC.

METHOD

The current work was performed as a narrative review to critically summarise the current evidence of the relationship between oxidative stress and autophagy in CRC, focusing

on the molecular mechanisms, prognostic importance, and clinical implications. A literature search was undertaken using PubMed, Scopus, ScienceDirect, and Google Scholar, with a focus on peer-reviewed studies published between 2020 and 2025. The search phrases included combinations of the following: CRC, oxidative stress, reactive oxygen species, autophagy, LC3B, p62/SQSTM1, NRF2, KEAP1, 8-OHdG, biomarkers, prognosis. High-quality original studies, systematic reviews, meta-analyses and review articles were included when they offered significant molecular, pathological or clinical data and were published as open-access publications. We removed conference abstracts, editorials, duplicate papers and research with insufficient methodological information. The collected literature was narratively synthesised and organised into theme sections on the CRC pathogenesis, oxidative stress, autophagy, their molecular interaction, and the clinical implications of integrated prognostic indicators.

RESULTS AND DISCUSSION

CRC is a multistep process, in which genetic, epigenetic and microenvironmental changes accumulate leading to transformation of normal colonic epithelium into invasive carcinoma. The classical adenoma–carcinoma sequence is the best characterised model of colorectal tumorigenesis, with sequential molecular events including mutation of the adenomatous polyposis coli (APC) gene, activation of KRAS and inactivation of TP53, as well as dysregulation of signalling pathways such as Wnt/β-catenin and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT). These molecular changes progressively inhibit cellular proliferation, differentiation, apoptosis and genomic stability, ultimately leading to malignant transformation (Caldecott, 2024; Hsu et al., 2022; Huang & Zhou, 2020).

Besides genetic aberrations, oxidative DNA damage and chronic inflammation are also playing a major role in colorectal carcinogenesis. Chronic inflammatory disorders, such as inflammatory bowel diseases (ulcerative colitis and Crohn's disease), result in an overproduction of ROS which leads to DNA damage and higher mutation rates in colonic epithelial cells. Continued oxidative stress further enhances genomic instability and produces a favourable microenvironment for cancer development and progression (Cabrera-Serrano et al., 2025; Nickoloff et al., 2020; Nordengen et al., 2024).

Environmental exposure is also a significant factor for pathogenesis of CRC. Increased risk of CRC has been linked to a diet high in processed meat and saturated fat, obesity, alcohol, smoking and physical inactivity. More recently, changes in the composition of the gut microbiota have been recognised as a key factor in colorectal carcinogenesis. Microbial dysbiosis contributes to the production of carcinogenic metabolites including secondary bile acids, hydrogen sulphide and N-nitroso compounds, which induce oxidative stress, DNA damage and chronic mucosal inflammation, and weaken the integrity of the intestinal barrier as well as the host's immune responses (Cintoni et al., 2025; Li et al., 2022; Paduraru et al., 2025).

The malignant epithelial cells are in continuous interaction with the tumour microenvironment, which is further impacting the cancer progression. Cancer-associated fibroblasts, infiltrating immune cells, endothelial cells, components of the extracellular matrix and inflammatory mediators orchestrate together the regulation of tumour growth, angiogenesis, local invasion and metastatic dissemination. These interactions form a dynamic biological ecosystem that enables cancer cells to adapt to metabolic stress and avoid host immune surveillance, hence facilitating disease development and resistance to therapy (Cabrera-Serrano et al., 2025; Xu et al., 2024).

Although there has been great progress in surgery, systemic chemotherapy, molecular targeted therapy, and immunotherapy, a large number of patients still arrive with advanced-stage cancer and suffer from recurrence after curative treatment. Such clinical heterogeneity underlines the need for robust molecular biomarkers to better stratify prognosis, predict therapy response, and enable precision oncology. Increasing lines of evidence suggest that oxidative stress and autophagy-associated pathways may provide useful prognostic information over and above traditional clinicopathological parameters, thus providing new opportunities for personalised management of CRC (Cabrera-Serrano et al., 2025; Hasan et al., 2022; Xu et al., 2024).

Oxidative stress pathway and its clinical relevance in CRC

Oxidative stress is a condition in which the production of ROS exceeds the antioxidant capacity of the cell, leading to disturbance of the intracellular redox balance. Under physiological conditions ROS are important signalling agents modulating cellular proliferation, differentiation, apoptosis and immunological responses. However, long-term oxidative stress results in overproduction of ROS which causes oxidative damage of DNA, proteins and membrane lipids. Such imbalance results in genomic instability, the acquisition of oncogenic mutations, and an environment conducive to colorectal carcinogenesis (Caldecott, 2024; Hsu et al., 2022; Nickoloff et al., 2020).

A number of endogenous and exogenous variables lead to the overproduction of ROS in CRC. Mitochondrial dysfunction, chronic inflammation, metabolic reprogramming, dietary carcinogens, alcohol intake and changes in intestinal flora lead to an overall increase in oxidative stress in the cancer microenvironment. Sustained exposure to ROS can lead to oxidative DNA lesions, in particular the creation of 8-OHdG that has been extensively acknowledged as a biomarker of oxidative DNA damage. Meanwhile, lipid peroxidation generates reactive aldehydes, including 4-HNE, which further amplifies pro-tumorigenic signalling and promotes cancer progression (Catalano et al., 2025; Damiano et al., 2025; Nordengen et al., 2024).

Furthermore, ROS induce direct molecular damage, but also affect the activity of several intracellular signalling cascades involved in tumour progression and metastatic behaviour. Oxidative stress activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and inhibits the phosphatase and tensin homolog (PTEN), which increases the stabilisation of hypoxia-inducible factor-1α (HIF-1α) and the release of vascular endothelial growth factor (VEGF). In addition, activation of the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-kB) pathways increases the expression of matrix metalloproteinases (MMPs), facilitating degradation of the extracellular matrix, endothelial cell migration, angiogenesis, tumour invasion and distant metastasis (Iqbal et al., 2024; Liang et al., 2025; Nigam et al., 2025). The major ROS-mediated signalling pathways involved in these processes are summarised in Figure 1.

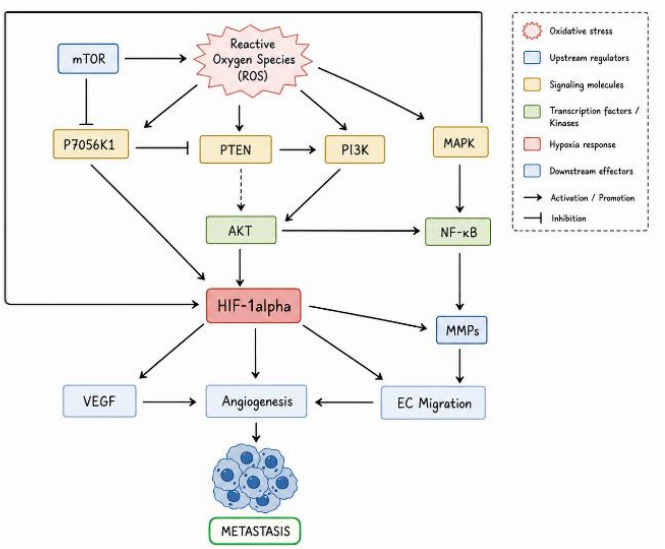


Figure 1. Schematic representation of ROS-mediated signalling pathways in CRC. Elevated ROS activate major oncogenic signalling pathways, including PI3K/AKT, MAPK, and NF-κB, thereby promoting angiogenesis, tumour invasion, and metastatic progression.

The nuclear factor erythroid 2–related factor 2 (NRF2)–KEAP1 pathway is one of the major adaptive responses to oxidative stress. In resting settings, NRF2 is retained in the cytoplasm by KEAP1 and is continuously degraded by ubiquitin-mediated proteolysis. In response to oxidative stress, KEAP1 undergoes conformational changes that lead to the release of NRF2. The released NRF2 translocates to the nucleus and activates antioxidant response element (ARE) dependent genes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione peroxidase (GPx) and other cytoprotective enzymes. Such responses restore redox homeostasis in the intracellular environment and protect against oxidative injury in normal cells (Cabrera-Serrano et al., 2025; Dera & Al Fayi, 2025; Hsu et al., 2022).

NRF2 activation is physiologically protective, yet, within malignant cells chronic activation might paradoxically boost cancer survival. Constitutive NRF2 signalling boosts antioxidant capacity and provides adaptability to oxidative stress, hence reducing vulnerability to chemotherapy and radiotherapy. Consequently, deregulation of the NRF2–KEAP1 axis has been widely identified as a crucial mechanism causing tumour growth, metabolic adaptability and treatment resistance in CRC (Dera & Al Fayi, 2025; Liang et al., 2025; Xu et al., 2024).

Thus, a number of biomarkers of oxidative stress have been gaining substantial attention as potential prognostic indicators in CRC. These are 8-OHdG as a marker of oxidative DNA damage and 4-HNE as a marker of lipid peroxidation. Furthermore, the levels of expression of NRF2 and KEAP1 are indicative of the activation of antioxidant defence systems in cells. Other antioxidant enzymes such as SOD, catalase (CAT) and GPx have been explored as surrogate markers of tumour adaptation to oxidative stress (Brandl et al., 2025; Catalano et al., 2025; Kang et al., 2023).

There is increasing clinical evidence that dysregulation of the markers of oxidative stress is associated with aggressive activity of tumours and poor prognosis in patients. Consistent upregulation of 8-OHdG and NRF2 has been linked to poorer overall survival, greater treatment resistance and risk of cancer recurrence. Moreover, the simultaneous assessment of multiple oxidative stress biomarkers seems to improve the prognostic accuracy compared to single markers, indicating that integrated biomarker profiling can enhance risk

stratification and support personalised therapeutic decision-making in CRC (Catalano et al., 2025; Kang et al., 2023; Yagishita et al., 2020).

Autophagy Pathway and Its Clinical Implications in CRC

Autophagy is a highly conserved intracellular degradation process that maintains cellular homeostasis by sequestering and degrading damaged organelles, protein aggregates, and other defective components of the cytoplasm with lysosomes. Autophagy recycles intracellular substrates to provide energy and biosynthetic precursors that enable cells to survive under conditions of nutritional restriction, hypoxia, oxidative damage, and other metabolic stresses. This process guarantees genomic stability and cellular integrity in normal tissues, thereby playing a key role in tissue homeostasis (Cabrera-Serrano et al., 2025; Hasan et al., 2022; Poillet-Perez & White, 2019).

Autophagy is a multistep carefully regulated process consisting of initiation, nucleation, elongation, maturation and lysosomal destruction. Autophagy is mainly activated by inhibition of the mammalian target of rapamycin (mTOR) pathway during metabolic stress, leading to activation of the unc-51-like kinase 1 (ULK1) complex. The formation of phagophore is triggered by the further recruitment of the Beclin-1/class III phosphatidylinositol 3-kinase (PI3K) complex, while the elongation of the membrane is mediated by the ATG5–ATG12–ATG16L1 conjugation system and the conversion of microtubule-associated protein 1 light chain 3 (LC3-I) to its lipidated form (LC3-II). Afterwards, mature autophagosomes fuse with lysosomes, leading to breakdown of the intracellular cargo and recycling of metabolic substrates critical for cellular survival (Ma et al., 2023; Hasan et al., 2022; Cabrera-Serrano et al., 2025). The sequential steps and key regulatory molecules involved in autophagy are summarized in Figure 2.

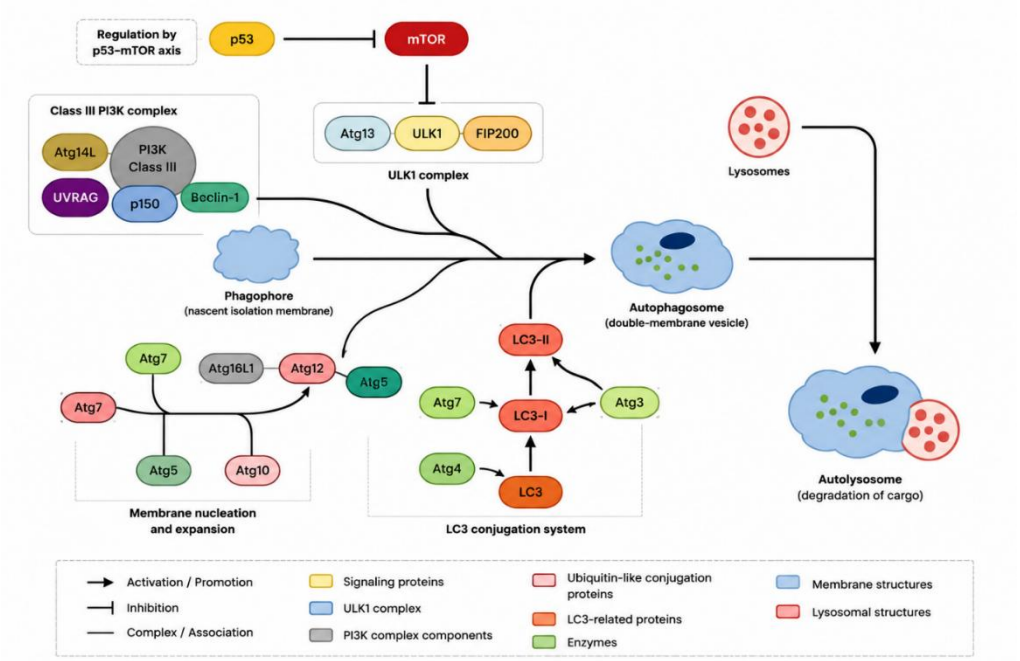


Figure 2. Autophagy mechanism. Autophagy is initiated by activation of the ULK1 complex, followed by autophagosome formation, lysosomal fusion, and degradation of damaged cellular components

Autophagy's biological significance in CRC is very situation dependant. In the early stages of carcinogenesis autophagy primarily has a tumor-suppressive role by removing

defective mitochondria and oxidatively damaged macromolecules thus decreasing the accumulation of reactive oxygen species and the genomic instability. But as tumour progression proceeds, CRC cells increasingly use autophagy to overcome the metabolic stress and adapt to hypoxic and nutrient-deficient microenvironment. This adaptive process facilitates prolonged proliferation, boosts invasive capacity, facilitates metastatic spread and leads to resistance to chemotherapy and radiotherapy (Cabrera-Serrano et al., 2025; Hsu et al., 2022; Xu et al., 2024).

Several autophagy-related proteins were widely studied as possible indicators in CRC. Microtubule-associated protein 1 LC3B is the most acknowledged hallmark of autophagosome formation and p62/SQSTM1 is a selective autophagy adapter that carries ubiquitinated proteins to lysosomal degradation. p62 accumulation usually represents poor autophagic flux, however chronic overexpression may potentially suggest sustained activation of adaptive autophagy in aggressive tumours. Other regulatory proteins such as Beclin-1, ATG5, ATG7 and ATG12 further support autophagosome production and cancer cell homeostasis (Cabrera-Serrano et al., 2025; Hasan et al., 2022; Ma et al., 2023; Nickoloff et al., 2020).

Accumulating clinical evidence demonstrated the tight correlation between autophagy-related biomarker dysregulation and CRC progression and patient prognosis. LC3B and p62 have been consistently associated with advanced tumour stage, greater risk of recurrence, shorter overall survival and lower responsiveness to traditional anticancer therapy. These results have led to increasing interest in the pharmaceutical manipulation of autophagy as a therapeutic approach. Agents that block lysosomal degradation and autophagic flux such as chloroquine and hydroxychloroquine are being studied as adjunctive therapies to improve tumour sensitivity to chemotherapy and radiotherapy (Cabrera-Serrano et al., 2025; Dera & Al Fayi, 2025; Zhang et al., 2023).

Overall, current data suggest that autophagy is both a key process for cellular adaptability and a major predictor of tumour behaviour in CRC. Autophagy has a dual biological function, as a tumour suppressor in early carcinogenesis and as a survival mechanism in established malignancy, making it an intriguing source of prognostic indicators, as well as a viable therapeutic target. These context-dependent roles must be understood before discussing the complicated molecular crosstalk between autophagy and oxidative stress, which is the topic of the next section.

Crosstalk Between Oxidative Stress and Autophagy Pathways: Implications for Prognostic Biomarkers in CRC

Evidence is growing indicating oxidative stress and autophagy are not independent biological processes but components of a linked adaptive network influencing CRC progression. Chronic oxidative stress induces autophagy, and autophagy, in turn, promotes the re-establishment of intracellular redox balance by clearing damaged mitochondria, oxidised proteins and other defective cellular components. This reciprocal control enables tumour cells to survive under adverse conditions, including hypoxia, food deprivation and therapeutic stress, enabling tumour growth and treatment resistance (Cabrera-Serrano et al., 2025; Hasan et al., 2022; Prime et al., 2024).

One of the main molecular linkages between these pathways is the nuclear factor erythroid 2-related factor 2 (NRF2)–Kelch-like ECH-associated protein 1 (KEAP1) signalling axis. Oxidative stress induces conformational changes in KEAP1 leading to the release of NRF2, its translocation into the nucleus and activation of antioxidant response genes. At the

same time, the autophagy adaptor protein p62/SQSTM1 interacts with and sequesters KEAP1 to sustain NRF2 activation in a positive regulatory feedback loop that protects normal cells from excessive oxidative damage but, in malignant cells, persistent activation increases their antioxidant capacity, drives metabolic adaptation, and causes resistance to cytotoxic therapy (Dera & Al Fayi, 2025; Pan & Valapala, 2022; Shan et al., 2024).

Another point of convergence between oxidative stress and autophagy is metabolic stress. Increased intracellular reactive oxygen species (ROS) activate AMP-activated protein kinase (AMPK), which inhibits mammalian target of rapamycin (mTOR) signalling and subsequently induces autophagy. This adaptive process enables the tumor cells to recycle intracellular constituents and to maintain energy production under hypoxic environment, nutritional starvation and anticancer treatment. This leads to CRC cells with increased metabolic flexibility, allowing them to continue their development in an increasingly hostile tumor microenvironment (Hsu et al., 2022; Koustas et al., 2025; Prime et al., 2024).

The cross-talk between oxidative stress and autophagy also affects genomic integrity through the activation of the DNA damage response. Excessive ROS generate oxidative DNA damage and activate both DNA repair mechanisms and autophagic activity. These systems are critical for maintaining genomic integrity in normal tissues, but established cancer cells can exploit the same adaptive responses to repair treatment-induced damage, dodge apoptosis and survive chemotherapy or radiotherapy. Such adaptive capacity underlies cancer persistence and illness recurrence after conventional treatment (Abugable et al., 2024; Caldecott, 2024; Nickoloff et al., 2020).

In addition to intracellular signals, the tumour microenvironment is also influenced by the mutual control of oxidative stress and autophagy. Sustained activation of both pathways results in chronic inflammatory signalling, angiogenesis, extracellular matrix remodelling, metabolic reprogramming and maintenance of cancer stem cell-like phenotypes, all of which promote tumour invasion, metastatic spread and therapeutic resistance. These observations indicate that the biological consequences of oxidative stress-autophagy crosstalk extend far beyond intracellular homeostasis, to encompass a number of processes associated with aggressive tumour behaviour and poor clinical outcome (Cabrera-Serrano et al., 2025; Damiano et al., 2025; Vickridge et al., 2022).

During CRC evolution oxidative stress and autophagy become incorporated in a coordinated adaptation plan rather than being independent molecular activities. In the early stage of carcinogenesis, autophagy mainly restricts oxidative harm by eliminating damaged mitochondria and lowering intracellular ROS buildup, thus maintaining cellular homeostasis. However, with cancer progression, sustained activation of the same pathways increasingly sustains metabolic adaptability, tumour survival, immunological evasion, treatment resistance and metastatic propagation. This molecular shift helps explain why indicators related with oxidative stress and autophagy often exhibit complementary rather than independent predictive significance.

Recognition of this coordinated biological network has redirected current research from examination of separate molecular markers to integrated biomarker methodologies that better reflect the biological complexity of CRC. Biomarkers of oxidative stress such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) and NRF2 reflect oxidative DNA damage and antioxidant defence, respectively, while autophagy-related biomarkers such as microtubule-associated protein 1 light chain 3 beta (LC3B) and p62/SQSTM1 reflect autophagic activity and the adaptive capacity of tumour cells. These biomarkers reflect complementary biological

processes, rather than redundant molecular changes, and their joint evaluation may improve prognostic stratification beyond conventional clinicopathological parameters, and allow more personalised therapeutic decision-making (Cabrera-Serrano et al., 2025; Dera & Al Fayi, 2025; Prime et al., 2024).

Although promising progress has been made, a number of difficulties still hamper the clinical adoption of integrated biomarker panels. Published research differ considerably with respect to patient characteristics, laboratory techniques, immunohistochemistry scoring systems and biomarker cut-off values, thereby hampering comparisons and external validation. Furthermore, the majority of accessible data derive from retrospective observational studies. Therefore, large prospective multicentre investigations with harmonised methodology are needed to confirm the predictive performance of combined oxidative stress and autophagy-related indicators before their introduction into regular precision oncology for CRC.

Current evidence indicates that that oxidative stress and autophagy should be viewed as interconnected adaptive mechanisms rather than isolated biological pathways in CRC. Although previous studies have substantially improved our understanding of each process individually, their interaction appears to provide a more comprehensive explanation for tumour behaviour, particularly in relation to disease progression, therapeutic response, and clinical heterogeneity. This view is in line with the dynamic CRC biology in which multiple molecular events happen simultaneously and together dictate tumour aggressiveness and patients' outcome (Cabrera-Serrano et al., 2025; Hasan et al., 2022; Prime et al., 2024).

One of the main findings that emerge from the literature reviewed is that the use of a single molecular marker is unlikely to benefit the prognostic assessment. Instead, increasing evidence supports the use of integrated biomarker panels that reflect different but complementary aspects of tumour biology. Oxidative stress markers reflect the cellular redox imbalance and oxidative damage, while autophagy-associated proteins reflect the adaptive ability of tumour cells in metabolic stress. Thus, simultaneous assessment of these biological processes can provide a more complete picture of tumour behaviour than the analysis of either pathway alone. This integrated approach is particularly relevant as the progression of CRC is driven by multiple interacting mechanisms rather than a single dominant molecular event (Catalano et al., 2025; Dera & Al Fayi, 2025; Kang et al., 2023).

An additional contribution of this review lies in bringing together evidence that has largely been discussed separately in previous publications. Most earlier reviews focused predominantly on oxidative stress or autophagy as individual mechanisms involved in colorectal carcinogenesis. By integrating findings from both pathways within a single conceptual framework, the present review emphasises their complementary roles in tumour adaptation and highlights the potential clinical relevance of combining biomarkers from both biological systems. Rather than proposing new molecular markers, this review supports a more integrated interpretation of existing evidence that may better reflect the biological complexity of CRC and facilitate future translational research (Hasan et al., 2022; Shan et al., 2024).

From a clinical point of view, this integrated view is consistent with the current trend towards precision oncology. Conventional prognostic parameters remain indispensable for disease staging and treatment planning; however, they do not always explain the variability in treatment response or recurrence observed among patients with similar pathological characteristics. Incorporating biomarkers that reflect complementary biological processes may improve prognostic stratification and help identify patients who are more likely to benefit from intensified surveillance or personalised therapeutic strategies. These applications are still being investigated, but there is increasing evidence that integrated biomarker assessment has significant translational potential for future management of CRC (Cabrera-Serrano et al., 2025; Liang et al., 2025; Zhang et al., 2023).

However, despite these promising advances, several issues remain that limit the translation of current evidence into routine clinical practice. There remains considerable methodological heterogeneity between published studies with respect to patient populations, immunohistochemical protocols, antibodies used, scoring systems and biomarker cut-off values. Such variability limits comparability between studies and remains a significant barrier to external validation. In addition, the majority of the available evidence is derived from retrospective observational studies, highlighting the need for prospective multicentre studies with harmonized methodologies before integrated biomarker panels can be incorporated into routine pathological assessment (Catalano et al., 2025; Xu et al., 2024; Yagishita et al., 2020).

Future research should move beyond the validation of individual biomarkers towards the development of clinically applicable multimarker models integrating molecular and pathological information. The combination of immunohistochemical biomarkers with emerging technologies, including digital pathology, artificial intelligence, transcriptomics and proteomics, may improve the prognostic modelling and strengthen the personalised treatment strategies. The successful translation of these integrated approaches into routine clinical practice will ultimately depend on the rigorous prospective validation and international standardisation of laboratory and analytical methods (Cabrera-Serrano et al., 2025; Carretero-Fernández et al., 2025; Liang et al., 2025; Nordengen et al., 2024).

CONCLUSION

In the present narrative review, we highlight the tight relationship between oxidative stress and autophagy as biological mechanisms that in concert affect CRC growth, resistance to therapy and prognosis of patients. The available evidence indicates that an integrated assessment of 8-OHdG, NRF2, LC3B and p62/SQSTM1 offers a more comprehensive evaluation of tumour biology than each biomarker separately. However, large-scale prospective studies with standardised assessment methodologies are needed before widespread clinical adoption to validate these results and confirm the promise of integrated biomarker panels for prognostic stratification and precision oncology.

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