



# Growth arrest-specific 5 (GAS5) in colorectal cancer: From molecular mechanisms and tumor suppression to clinical promise and therapeutic challenges

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## ABSTRACT

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Colorectal cancer (CRC) is a major global health burden and remains a leading cause of cancer-related morbidity and mortality. Despite advances in surgery, chemotherapy, targeted therapy, and immunotherapy, treatment resistance, tumor heterogeneity, and the limited response of microsatellite-stable/proficient mismatch repair (MSS/pMMR) tumors continue to present significant clinical challenges. Long non-coding RNAs (lncRNAs) have emerged as important regulators of cancer-related processes, and growth arrest-specific 5 (GAS5) has attracted increasing attention because of its potential tumor-suppressive functions. This review summarizes the current evidence regarding the role of GAS5 in colorectal cancer, with particular emphasis on its molecular characteristics, regulatory mechanisms, and effects on tumor progression and therapeutic response. Available studies suggest that GAS5 expression is frequently reduced in CRC and that its dysregulation may be associated with increased tumor proliferation, invasion, disease progression, and unfavorable clinical outcomes. GAS5 may regulate CRC biology through interactions with signaling pathways, microRNAs, transcriptional regulators, and other molecular components involved in cancer development. Its potential involvement in treatment response and resistance further highlights its possible therapeutic relevance. However, most available evidence remains preclinical, and differences among study populations and experimental models limit the translation of current findings into clinical practice. Further well-designed clinical and mechanistic studies are needed to validate the prognostic and predictive value of GAS5 and to determine whether it can serve as a reliable biomarker or therapeutic target. Overall, GAS5 represents a promising area of investigation in CRC and may contribute to the development of more effective approaches to disease stratification and treatment.

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## 1. Introduction

Colorectal cancer (CRC) remains a major health concern worldwide. Each year, more than 1.9 million new cases are diagnosed and over 900,000 people die from the disease, making CRC one of the most frequently diagnosed cancers and an important cause of cancer-related mortality [1]. Treatment options have expanded considerably, including surgery, chemotherapy, targeted therapies, and immunotherapy. However, these advances have not eliminated several important limitations. Differences between tumors and the emergence of treatment resistance can reduce therapeutic effectiveness. In addition, the benefit of immunotherapy remains limited for many patients with microsatellite-stable or proficient mismatch repair (MSS/pMMR) tumors, which account for the majority of CRC cases [2]. Long non-coding RNAs (lncRNAs) have become increasingly relevant to cancer research as their roles in tumor biology have become clearer. Rather than functioning simply as transcriptional by-products, many lncRNAs participate in the regulation of gene expression and signaling and can affect processes such as metabolism, cell survival, tumor–microenvironment interactions, and responses to therapy [3]. One of these molecules is Growth Arrest-Specific 5 (GAS5). GAS5 was initially identified in cells undergoing growth arrest, although later work showed that its functions extend well beyond this setting. Depending on the cellular context, GAS5 has been implicated in the regulation of proliferation, apoptosis, invasion, and other aspects of tumor progression [4]. Evidence from CRC studies generally points to reduced GAS5 expression in tumor tissue. Lower levels of GAS5 have also been associated with more aggressive disease and less favorable clinical outcomes, suggesting that changes in this lncRNA may have biological as well as clinical significance [5]. These observations have led to growing interest in GAS5 as a possible prognostic marker and, potentially, as a target for therapeutic intervention.

In this review, we examine the available evidence concerning the role of GAS5 in CRC. We first consider its molecular characteristics and the mechanisms through which it may affect cancer cells, followed by its reported effects on tumor progression and response to treatment. Finally, we consider the clinical evidence surrounding GAS5 and the limitations that still need to be addressed before its use as a biomarker or therapeutic target can be considered in practice.

## 2. GAS5 biology and pathway analysis

The GAS5 gene is located on chromosome 1q25.1 and gives rise to a multi-exonic lncRNA that also serves as a host transcript for several intronic small nucleolar RNAs (snoRNAs). Both its genomic organization and several of its biological functions are conserved across species [6]. GAS5 is generally considered a tumor-

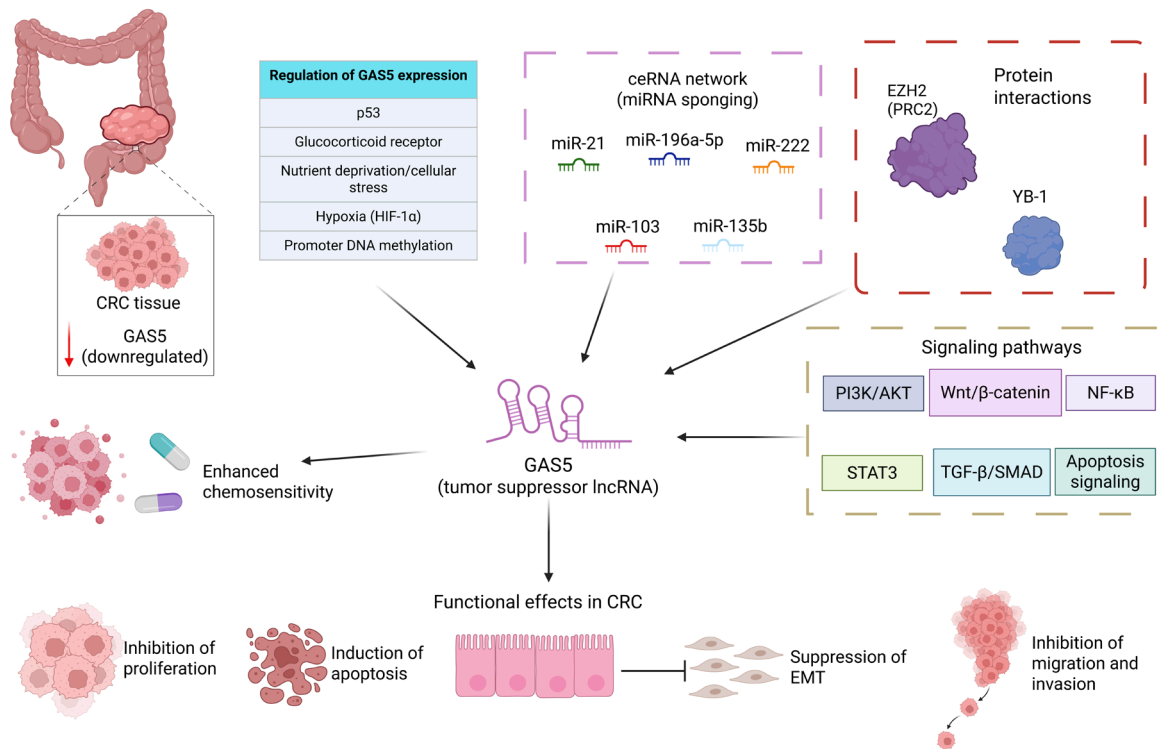
suppressive lncRNA, and its expression is reduced in a number of cancers, including CRC. Under normal physiological conditions, GAS5 expression is closely related to growth arrest and cellular responses to stress, particularly conditions such as nutrient deprivation. Its expression and activity have also been linked to signaling pathways involving p53 and the glucocorticoid receptor [7]. One of the ways GAS5 exerts its effects is through interactions with microRNAs. For example, GAS5 can bind miR-196a-5p, which reduces the inhibitory effect of this microRNA on homeobox A5 (HOXA5) and may thereby contribute to the suppression of tumor-associated processes [8]. More broadly, GAS5 has been described as a competing endogenous RNA (ceRNA), allowing it to interact with several oncogenic microRNAs, including miR-21, miR-196a, miR-222, miR-103, and miR-135b. By limiting the availability of these microRNAs, GAS5 can reduce their repression of downstream tumor-suppressive genes and, in turn, restrain malignant cell behavior [6,9,10].

GAS5 is not restricted to interactions with RNA. It can also associate with proteins and regulators involved in chromatin function. Among these are enhancer of zeste homolog 2 (EZH2), a component of the Polycomb Repressive Complex 2 (PRC2), and Y-box binding protein 1 (YB-1). Through these interactions, GAS5 may affect chromatin organization and epigenetic regulation, with consequences for transcriptional programs involved in tumor development and progression [11].

These different molecular activities place GAS5 at the intersection of several signaling pathways relevant to cancer, including phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) [12], Wnt/ $\beta$ -catenin, nuclear factor kappa B (NF- $\kappa$ B) [12], signal transducer and activator of transcription 3 (STAT3), transforming growth factor beta (TGF- $\beta$ )/SMAD, and apoptosis signaling [9]. The effects of GAS5 can also be seen at the level of cell-cycle regulation. In particular, GAS5 promotes G1-phase arrest by suppressing cyclin-dependent kinase-6 (CDK6) and cyclin D1, which limits the ability of cells to proliferate [8]. At the same time, GAS5 expression itself is subject to regulation. Epigenetic mechanisms, including promoter DNA methylation, can influence its expression, while transcriptional and post-transcriptional networks involving p53 and hypoxia-related signaling, including hypoxia-inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ), may further contribute to its regulation [11] (Figure 1).

## 3. Functional effects of GAS5 in CRC

In CRC, GAS5 appears to act mainly as a tumor suppressor. Studies have shown that higher GAS5 expression can slow the growth of CRC cells by reducing proliferation, colony formation, and progression from G0/G1 into the S phase of the cell cycle [13].



**Figure 1.** The regulatory network and tumor-suppressive functions of the long non-coding RNA Growth Arrest-Specific 5 (GAS5) in colorectal cancer (CRC). (Note: The schematic is divided into three main panels: upstream regulators, downstream molecular interactions, and resulting functional effects. (A) Upstream Regulation of GAS5 Expression: The left panel depicts the factors that modulate GAS5 transcription and stability. GAS5 expression is positively regulated by the tumor suppressor p53 and the Glucocorticoid receptor. Conversely, its expression is suppressed by promoter DNA methylation. Cellular stress conditions, such as nutrient deprivation, hypoxia (mediated by HIF-1α), and other forms of cellular stress, also influence GAS5 levels, indicating its role as a stress-responsive transcript. (B) Downstream Molecular Network of GAS5: The central panel details the molecular mechanisms through which GAS5 exerts its effects. GAS5 functions as a competitive endogenous RNA (ceRNA) by acting as a molecular sponge for several oncogenic microRNAs, including miR-21, miR-196a-5p, miR-222, miR-103, and miR-135b. By sequestering these miRNAs, GAS5 relieves their repression of target mRNAs. Furthermore, GAS5 directly interacts with proteins, including the histone methyltransferase EZH2 (a component of the PRC2 complex) and the transcription factor YB-1, thereby modulating their activity. Through these interactions, GAS5 negatively regulates several key oncogenic signaling cascades, such as the PI3K/AKT, Wnt/β-catenin, NF-κB, STAT3, and TGF-β/SMAD pathways, while concurrently promoting apoptosis signaling. (C) Functional Consequences in CRC: The right panel summarizes the downstream biological effects of GAS5 in CRC cells. The restoration or high expression of GAS5 leads to the inhibition of proliferation, induction of apoptosis, and suppression of epithelial-mesenchymal transition (EMT). Consequently, this results in the inhibition of migration and invasion, effectively curbing the metastatic potential of CRC cells. These tumor-suppressive functions collectively contribute to enhanced chemosensitivity. Ultimately, this molecular network highlights that GAS5 is frequently downregulated in CRC tissues, and its loss is associated with disease progression and unfavorable clinical outcomes, positioning it as a potential prognostic biomarker and therapeutic target.)

Another important effect of GAS5 is its association with apoptosis. Increased GAS5 expression has been linked to higher B-cell lymphoma 2 (BCL-2)-associated X protein (BAX) levels and caspase activation, together with lower expression of the anti-apoptotic protein BCL-2. Taken together, these changes favor the induction of apoptosis and reduce the survival of CRC cells [14]. GAS5 has also been linked to changes in the invasive behavior of CRC cells. In particular, it can interfere with epithelial-mesenchymal transition (EMT), a process that allows epithelial tumor cells to acquire characteristics associated with migration and invasion. When GAS5 expression increases, E-cadherin is upregulated, whereas several mesenchymal markers, including N-cadherin, vimentin, Snail, and Twist, are reduced. This pattern is consistent with a less invasive cellular phenotype [15]. Experimental studies have further shown that GAS5 can reduce CRC cell migration and invasion, with suppression of matrix

metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) suggested as one of the mechanisms involved [16]. There is also evidence that GAS5 is relevant to chemotherapy response. CRC cells with increased GAS5 expression show greater sensitivity to 5-fluorouracil (5-FU) and oxaliplatin. In chemotherapy-resistant cells, restoring GAS5 has been associated with stronger drug-induced apoptosis, an effect involving the miR-128-3p/BAX axis. Thus, reduced GAS5 expression may be one factor contributing to poor response to chemotherapy. Still, some of the proposed mechanisms should be interpreted cautiously. At present, there is insufficient evidence to say that GAS5 directly controls ATP-binding cassette (ABC)-transporter-mediated drug efflux, autophagy, or DNA-damage responses in CRC. These possibilities remain to be clarified rather than established functions of GAS5 [17]. The tumor-suppressive effects of GAS5 are not limited to cell culture models. In CRC xenograft

and metastasis models, increasing GAS5 expression has resulted in smaller tumors and less metastatic dissemination. Reduced metastatic colonization has been reported in both the liver and lungs, providing additional experimental support for a role of GAS5 in limiting CRC progression [18]. GAS5 may also affect the environment in which CRC cells grow. Some evidence points to an effect on inflammatory and angiogenic signaling, including regulation of IL-10 and vascular endothelial growth factor A (VEGF-A) through the NF- $\kappa$ B/ extracellular signal-regulated kinase 1/2 (ERK 1/2) pathway. GAS5 overexpression has also been associated with reduced tumor angiogenesis. Whether these effects extend to other components of the tumor microenvironment is less clear [19]. In particular, direct evidence for GAS5-mediated regulation of fibroblast activation or immune-cell infiltration in CRC is still limited. More work will therefore be needed to determine how much of the reported tumor-suppressive activity of GAS5 is due to direct effects on cancer cells and how much involves changes in the surrounding tumor microenvironment (Table 1).

#### 4. Clinical implementation

GAS5 expression is generally lower in CRC tissues, and several studies have found an even greater reduction in patients with more advanced disease. Lower GAS5 levels have been associated with higher tumor–node–metastasis (TNM) stage (Table 1), lymph-node metastasis, poor tumor differentiation, and shorter survival [13,18].

Reduced expression has also been linked to poorer overall survival, recurrence, and distant metastasis in clinical studies [20]. These findings suggest that the amount of GAS5 present in a tumor may be related to how the disease progresses. Even so, the evidence available at present does not justify using GAS5 as a routine clinical marker. The reported associations still need to be confirmed in larger prospective cohorts, preferably including patients with different clinical and molecular characteristics.

GAS5 has also been detected in plasma and circulating exosomes, which has opened up another

possible area of clinical use. Changes in circulating GAS5 have been associated with disease stage, lymph-node metastasis, recurrence, and survival [16]. Because these measurements can be made from blood, circulating GAS5 is of interest as a potential liquid-biopsy biomarker. This could be particularly useful in situations where repeated sampling of tumor tissue is difficult. However, it is not yet clear whether circulating GAS5 can provide sufficiently reliable information for clinical decision-making. Another strategy has been to use GAS5 together with other lncRNAs rather than relying on GAS5 alone. Multi-lncRNA prognostic signatures that include GAS5 may improve CRC risk stratification and survival prediction, although their performance will also need to be confirmed in larger patient cohorts [21]. The reduced expression of GAS5 in CRC has naturally raised the question of whether restoring it could have therapeutic value. Several approaches have been investigated for this purpose, including plasmid-based systems, viral vectors, and nanoparticle-based delivery. The underlying idea is to increase GAS5 levels in tumor cells and, in doing so, restore some of its tumor-suppressive activity. GAS5 restoration could also be combined with chemotherapy or targeted therapy. Such combinations may be particularly relevant if increasing GAS5 makes cancer cells more sensitive to treatment or helps to overcome drug resistance [22]. There are still substantial practical difficulties, though. Delivering an RNA molecule to tumor cells is not simply a matter of getting it into the body; the molecule has to remain stable, reach the tumor, and be taken up by the appropriate cells. Ideally, delivery should also be selective enough to minimize exposure of normal tissues. These issues remain unresolved for GAS5-based approaches. RNA instability, off-target effects, and the possibility of immunogenic responses are additional concerns that will have to be addressed before restoration of GAS5 can realistically be considered as a treatment for CRC [23]. For now, the clinical evidence for GAS5 in CRC is still limited and is largely based on preclinical work. Only a small number of prospective clinical studies have examined its potential as a diagnostic or prognostic marker or as a therapeutic target [13,16].

**Table 1.** Summary of GAS5 Functions and Clinical Associations in Colorectal Cancer

| Category                                | Observed effect of GAS5                                                                         | Key associated molecules / Markers                                                                  |
|-----------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Cell Proliferation                      | Inhibits growth; reduces colony formation and cell cycle progression (G0/G1 to S phase).        | (Cell cycle regulators)                                                                             |
| Apoptosis                               | Promotes programmed cell death; increases survival reduction.                                   | ↑ BAX, ↑ Caspase activation, ↓ BCL-2                                                                |
| Epithelial–Mesenchymal Transition (EMT) | Suppresses EMT; maintains epithelial phenotype and reduces invasive characteristics.            | ↑ E-cadherin, ↓ N-cadherin, ↓ Vimentin, ↓ Snail, ↓ Twist                                            |
| Migration & Invasion                    | Reduces cell motility and invasive capacity.                                                    | ↓ MMP-2, ↓ MMP-9                                                                                    |
| Chemotherapy Response                   | Enhances sensitivity to chemotherapeutic agents (e.g., 5-FU, oxaliplatin); reverses resistance. | miR-128-3p / BAX axis                                                                               |
| Tumor Microenvironment                  | Reduces inflammatory and angiogenic signaling.                                                  | ↓ IL-10, ↓ VEGF-A (via NF- $\kappa$ B/ERK1/2 pathway)                                               |
| In Vivo Tumor Growth                    | Reduces tumor size and metastatic dissemination in xenograft models.                            | (Liver and lung metastasis models)                                                                  |
| Clinical/Prognostic Association         | Lower expression correlates with advanced disease and poorer outcomes.                          | ↑ tumor–node–metastasis (TNM) stage, ↑ Lymph-node metastasis, ↓ Differentiation, ↓ Overall survival |

More consistent methods for measuring GAS5 are therefore needed, together with large, multicenter prospective studies. Such work would help determine whether specific GAS5 expression cutoffs can be reproduced across patient groups and, more importantly, whether GAS5 measurement can actually improve patient stratification or help guide treatment decisions [24].

## 5. Future directions

An important next step is to test GAS5 in models that better represent the variation found among CRC patients. Conventional cell lines are useful for studying individual mechanisms, but they cannot reproduce the full complexity of human tumors. Patient-derived organoids and xenograft models may offer a better way to examine whether the effects of GAS5 are maintained across different tumor types and molecular backgrounds. These models could also help determine whether certain CRC subgroups are particularly dependent on, or responsive to, changes in GAS5 expression. There is a separate practical problem: getting GAS5 to the right place. A therapeutic RNA has little value if it is degraded before reaching the tumor or taken up inefficiently by the intended cells. Nanoparticles and engineered extracellular vesicles or exosomes are therefore being considered as possible delivery systems [25]. They may improve RNA stability and facilitate tumor delivery, but neither approach has yet overcome all of the challenges involved. Tumor specificity, delivery efficiency, RNA stability, and potential off-target biological effects remain important concerns, and GAS5-based therapeutic strategies are still largely confined to preclinical research. Experimental studies in CRC models have demonstrated tumor-suppressive effects of GAS5 through several molecular pathways, including Yes-associated protein (YAP) signaling and the miR-182-5p/ forkhead box O3a (FOXO3a) axis [18,26].

It may ultimately be more realistic to use GAS5 as part of a treatment strategy rather than as a stand-alone therapy. This possibility is supported by experimental evidence that GAS5 can influence treatment response; for example, GAS5 overexpression has been shown to increase the sensitivity of 5-fluorouracil-resistant CRC cells through regulation of the miR-128-3p/BAX pathway [17] (Table 1).

CRC differs considerably from one patient to another, so restoring GAS5 is unlikely to produce the same response in every tumor. Molecular profiling could therefore help identify patients in whom a GAS5-directed approach is more likely to be effective. Combining GAS5 restoration with targeted therapies or immunotherapy is another potential strategy, particularly if GAS5 influences pathways involved in treatment response or resistance. However, these combinations require systematic experimental and clinical evaluation rather than being assumed to be

beneficial [27]. The next stage of GAS5 research should therefore focus not only on demonstrating its tumor-suppressive effects, but also on identifying the patients, treatment settings, and delivery approaches in which those effects are most likely to have clinical relevance.

## 6. Conclusion

Overall, the evidence available so far points to GAS5 having a tumor-suppressive function in CRC. In tumor samples, GAS5 is commonly expressed at lower levels, and reduced expression has been associated with features of more advanced disease, including metastasis and poorer clinical outcomes. Experimental work has also shown that increasing GAS5 can restrain CRC cell proliferation and invasion and can reduce metastatic behavior in animal models. These observations have made GAS5 an interesting candidate for prognostic assessment and, potentially, therapeutic intervention. Still, most of the work supporting these ideas has been performed in experimental systems, and there is not yet enough clinical evidence to establish GAS5 as a routine biomarker or treatment target. The regulation of GAS5 is unlikely to be explained by one mechanism. Its abundance and activity can change as a result of transcriptional, post-transcriptional, and epigenetic regulation.

GAS5 also interacts with microRNAs and proteins involved in chromatin regulation, creating several points at which its function can be altered. Through these interactions, GAS5 has been connected with a range of pathways involved in CRC biology. This broad regulatory network is one reason GAS5 is difficult to place into a simple tumor-suppressor model. Understanding which of these interactions are most important in human tumors will be necessary if GAS5 is to move beyond an experimentally observation and become clinically useful.

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## Declaration of artificial intelligence (AI) in the writing process

The authors declare whether AI or AI-assisted technologies were used during the preparation of this manuscript. If used, AI tools were employed solely to improve language quality, grammar, readability, and organizational structure. The authors carefully reviewed and edited all AI-generated content and take full responsibility for the accuracy, integrity, and originality of the final manuscript. No AI tool was used to generate, analyze, or interpret scientific data or images, or to draw scientific conclusions. The use of AI-assisted technologies complies with current publication ethics recommendations and journal policies.

## Authors' contributions

NF: Writing - original draft of the main sections and preparation of Figure, Conceptualization of the review structure and content. MTN: Writing - review and editing of the final manuscript, preparation of Table and critical revision of all sections for intellectual content, and supervision of the overall framework. All authors have read and approved the final version of the manuscript.

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No potential conflict of interest was reported by the authors.

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