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Mini review

Long non-coding RNA polymorphisms and expression profiles in colorectal cancer: A step toward precision medicine in Egyptian patients

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Abstract

Colorectal cancer (CRC) ranks among the most prevalent malignancies worldwide and remains a major contributor to cancer-related death. Genetic predisposition, particularly that involving long non-coding RNAs (lncRNAs), has come to be recognized as a significant contributor to individual susceptibility and tumor progression, despite the substantial roles played by environmental and dietary factors in the genesis of CRC. Recent findings demonstrate that lncRNAs influence microRNA networks, drive processes such as the epithelial-mesenchymal transition, and modify key signaling pathways through their polymorphisms and altered expression. Although prior work has explored lncRNA polymorphisms in general populations, data specific to Egyptian CRC patients remain limited and under-analyzed. In this mini-review, we summarize evidence from several studies conducted on Egyptian CRC patients, focusing on the association of lncRNA polymorphisms (CCAT2 rs6983267, HULC rs7763881, MALAT1 rs3200401, PVT1 rs13255292, MEG3 rs7158663 and rs941576, and HOTTIP rs1859168) and the expression profiles of their corresponding lncRNAs with CRC risk, progression, and obesity-related tumorigenesis. We further discuss their transformative potential as therapeutic targets and biomarkers and their added value in the precision medicine of CRC.

Keywords:

CRC; lncRNA; miRNA; Obesity-related CRC; SNP.

1. Introduction

Colorectal cancer (CRC) accounts for over 1.9 million new cases and 930,000 deaths globally each year, ranking as the third most diagnosed cancer and the second leading cause of cancer-related deaths.[1] Colon and rectal cancers are the ninth and eighteenth most prevalent malignant tumors in Egypt, respectively.[2] Approximately 35% of Egyptian patients with CRC develop the disease before the age of forty, with an expected increase in this number. These young patients are frequently diagnosed at an advanced stage, which has a poor prognosis and dramatically low 5-year survival.[3,4] The five-year survival rate for CRC patients diagnosed at later stages (metastatic CRC, stage IV) is 14%, while it can increase to 90% if detected early (localized or regional CRC).[5] Therefore, to advance the precision medicine of CRC, it is essential to fully understand the molecular foundations of its initiation and progression.

CRC incidence is influenced by lifestyle factors such as diet, physical inactivity, obesity, and smoking in over 50% of all CRC cases and deaths.[6] Nevertheless, genetic predisposition substantially contributes to CRC risk, particularly in individuals with familial clustering or hereditary syndromes.[7]

Long non-coding RNAs (lncRNAs), defined as transcripts longer than 200 nucleotides that do not encode proteins, have emerged as crucial regulators of gene stability and expression at transcriptional, post-transcriptional, and epigenetic levels in CRC.[8] lncRNAs are involved in key cellular processes related to CRC promotion or suppression, including chromatin remodeling, splicing, RNA decay, and microRNA (miRNA) sequestration, that affect tumor microenvironment, cell-to-cell communication, and tumorigenic signaling pathways.[8,9,10] In addition, lncRNAs have an impeccable role in colorectal precancerous lesions and CRC molecular subgroups.[8] Advancements in molecular profiling and transcriptomic techniques have identified multiple lncRNAs that are associated with tumor diagnosis, treatment response, and prognosis prediction.[11] This approach is powered by their intricate relationship with tumor biology, tissue- or cell-specific expression, and stability in circulation.[11] The elucidation of the role of lncRNAs in the intricate regulatory networks governing CRC progression holds transformative potential for

its early detection and treatment. Advancing our understanding of these mechanisms may enable novel diagnostic and therapeutic strategies to improve clinical outcomes in CRC.

Single nucleotide polymorphisms (SNPs), which are universally found in lncRNA genes, are currently the most common genetic variation. These SNPs may impact lncRNA expression, stability, interactions, or its secondary structure to gain or lose the miRNA binding site, thereby modifying cancer risk.[12] SNPs can therefore be employed as markers for prognosis, clinical outcome, medication tolerance, cancer incidence, and susceptibility to environmental variables.[13]

Several SNPs at lncRNA loci have been linked to CRC susceptibility, progression, prognosis, and chemoresistance. Furthermore, dysregulated lncRNA expression, whether driven by germline variants or acquired alterations, contributes to CRC pathogenesis by modulating cell proliferation, apoptosis, epithelial-mesenchymal transition (EMT), metabolic reprograming, invasion, metastasis, and response to therapy.[14,15,16,17] Elucidating the impact of these SNPs could have translational potential in the clinical setting of CRC.

In this review, we focus on research findings from studies conducted on Egyptian CRC patients, which shed light on the relationship between lncRNA polymorphisms, expression profiles, and CRC risk, particularly in the context of obesity-related carcinogenesis and EMT-associated tumor progression.

2. Methodology

To carry out this mini-review, two online medical databases, PubMed, and NCBI, were searched for the following terms: "lncRNA polymorphism", "lncRNA expression", "colorectal cancer", and "Egyptian patients". The search was completed by June 2025. Papers with strong experimental and clinical evidence such as original articles, randomized clinical studies, clinical guidelines, systematic reviews, and meta-analysis were included.

3. LncRNA SNPs and CRC risk in Egyptian patients

Through a number of studies, SNPs at lncRNA genes have emerged as potential contributors to CRC risk and progression in the Egyptian population. These SNPs were proposed to alter lncRNA expression and function, potentially influencing CRC development and metastasis through multiple molecular mechanisms. The following are a

summary of the findings from Egyptian studies linking lncRNA SNP associations with CRC risk.

3.1 CCAT2 rs6983267 SNP at 8q24 and CCAT2 expression in CRC

The 8q24 chromosomal region is known as a gene desert, because they lack protein-coding genes. Nonetheless, it harbors several cancer susceptibility loci identified through genome-wide association studies in multiple cancer types, including CRC.[18] The rs6983267 SNP, located within the colon cancer associated transcript 2 (CCAT2) lncRNA gene at the 8q24 genomic region, is one of the most consistently replicated CRC risk variants.[19,20,21] Indeed, the rs6983267 GG genotype significantly increased CRC risk among Egyptian patients, with an odds ratio comparable to previous reports in other populations.[21] Notably, this SNP exhibited age and gender-specific associations with CRC risk. Specifically, the GG-associated risk was significant among older (> 50 years) as well as male Egyptian patients.[21] Additionally, the finding that rs6983267 GG predicted early CRC detection in the non-CRC group [healthy controls and patients with adenomatous polyps (AP)], suggests it as a genetic marker of CRC. In the later study, CCAT2 expression was significantly elevated in the serum of CRC patients compared to healthy controls.[21] This observation aligns with reports suggesting that CCAT2 may serve as a non-invasive biomarker for CRC detection.[22] These results are consistent with the oncogenic function of CCAT2 and support its therapeutic targeting potential. Mechanistically, CCAT2 promotes carcinogenesis through modulation of the Wnt/β-catenin signaling pathway, upregulation of MYC, and chromosomal instability.[19,23,24] Interestingly, the rs6983267 GG genotype was associated with higher serum CCAT2 than other genotypes in Egyptian subjects[21], aligning with another report.[19] This association supports a model whereby genetic variation at this locus enhances CCAT2 expression, contributing to tumorigenesis.

3.2 HULC rs7763881 SNP and expression in CRC

Highly upregulated in liver cancer (HULC) is another oncogenic lncRNA that modulates cell cycle progression, angiogenesis, metabolic reprogramming, immune evasion, epithelial mesenchymal transition (EMT), and metastasis. [25] Analysis of HULC rs7763881 in Egyptian CRC patients revealed that individuals carrying the AC genotype exhibited reduced CRC risk compared to AA carriers, suggesting a possible protective effect of the C allele.[21]

Interestingly, rs7763881 AC was protective against CRC risk among male as well as younger Egyptian patients (≤50 years), suggesting an age- and gender-specific effect.[21] Interestingly, the rs7763881 AC genotype was inversely associated with mucinous adenocarcinoma, an aggressive CRC tumor type.[21] Mechanistically, CRC patients harboring the rs7763881 AA had higher serum HULC levels than those carrying the AC genotype.[21] Although the precise functional impact of rs7763881 on HULC biology remains unclear, this finding indicates that this SNP may modulate expression or structural features relevant to its activity.

Notably, elevated serum HULC levels were reportedly observed in Egyptian CRC cases, and its potential as a non-invasive biomarker of CRC was unraveled.[21,26] This elevation is consistent with its proposed oncogenic function in CRC through multiple mechanisms, including suppressing NKD2 expression [27] and promoting cell proliferation, EMT, and metastasis.[28] Intriguingly, serum HULC was shown as an independent predictor of early CRC detection among non-CRC subjects (healthy controls and AP patients).[21] Together, serum HULC is a potential candidate for early CRC diagnosis and therapeutic targeting.

3.3 MALAT1 and PVT1 variants and their role in EMT and microRNA regulation in CRC

3.3.1 MALAT1 rs3200401 SNP and expression

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a well-characterized lncRNA involved in alternative splicing, gene expression regulation, and metastasis promotion.[29,30] The MALAT1 rs3200401 minor T allele was associated with a higher risk of CRC in an Egyptian study[31], suggesting an oncogenic role potentially mediated by altered secondary structure or miRNA binding capacity. In the latter study, although the association of rs3200401 with serum MALAT1 levels was not significant, this SNP was associated with the EMT marker, E-cadherin. EMT is a process where epithelial cells lose their cell-cell adhesion and gain migratory and invasive properties and is characterized by loss of epithelial markers such as E-cadherin and increase in mesenchymal markers such as N-cadherin and vimentin. Indeed, harboring the risk CT + TT genotypes was associated with lower serum E-cadherin levels than the CC genotype carriers. Notably, serum E-cadherin levels were lower in metastatic CRC than in non-metastatic CRC [31], consistent with the

functional role of E-cadherin as an epithelial marker, and its loss is an indicator of EMT.[32] The association between MALAT1 rs3200401 and the lymph node status [31], reflects its role in CRC progression and highlights its prognostic significance.

Serum samples from Egyptian CRC patients showed marked MALAT1 upregulation, and heightened MALAT1 level was shown as a potential biomarker and a predictor of the propensity of developing CRC .[31] This upregulation was particular in CRC cases with advanced stage and lymph node involvement, where MALAT1 showed correlations with tumor stage, lymph node status, and distant metastasis [31], suggesting its prognostic value. In the same CRC cases, circulating MALAT1 upregulation was associated with decreased levels of miR-101 [31], a tumor-suppressive miRNA involved in regulating EZH2, CREB1, and other oncogenes.[33,34] This inverse relationship supports the competing endogenous RNA hypothesis, whereby MALAT1 acts as a sponge for miR-101[35], reducing its availability to repress target oncogenes. Serum MALAT1 also shown an inverse relationship with E-cadherin [31], supporting its role in promoting an invasive phenotype and highlighting its prognostic potential. These findings align with the mechanistic role of MALAT1 in promoting EMT and cancer metastasis through miRNA interplay [36,37] and point at MALAT1 as a target for CRC therapeutics.

3.3.2 PVT1 rs13255292 SNP and expression

Plasmacytoma variant translocation 1 (PVT1) is an oncogenic lncRNA located at 8q24, co-amplified with MYC in various cancers.[38] The PVT1 rs13255292 SNP was associated with decreased CRC susceptibility in an Egyptian cohort compared with healthy controls, where the minor T allele was a candidate protective factor.[31] In parallel, serum samples exhibited marked PVT1 upregulation, which was not affected by the rs13255292 SNP genotypes.[31] In another Egyptian study, CRC or AP patients harboring the CT + TT genotypes had higher serum PVT1 levels than the CC genotype carriers, suggesting that the presence of T allele was associated with PVT1 overexpression.[39] The increase in serum PVT1 correlated with decreased miR-186 levels [31], a tumor suppressor miRNA implicated in cell cycle control, apoptosis regulation, EMT, and metastasis in CRC.[40] Circulating PVT1 was correlated with tumor stage, lymph node status, and distant metastasis in CRC patients, suggesting its prognostic significance.[31] PVT1 upregulation correlated with EMT marker alterations,

including increased N-cadherin and vimentin[41] and reduced E-cadherin level [31], highlighting their role in promoting CRC invasion. While the predictive power of serum PVT1 didn't suffice in CRC patients, it was uncovered in Egyptian women with breast cancer in terms of breast tumor malignancy and metastatic tendency.[42]

3.4 MEG3 rs941576 SNP and expression in obesity-related CRC and miRNA regulation

Obesity significantly increases CRC risk through mechanisms involving chronic inflammation, insulin resistance, and altered adipokine profiles.[43] The maternally expressed gene 3 (MEG3) is a tumor suppressor lncRNA that activates p53 and inhibits angiogenesis in multiple cancers, including CRC.[44]

In Egyptian patients, prior research has focused on MEG3 genetic variants, in particular rs7158663 and rs941576, and their association with CRC.[45,46] The rs7158663 polymorphism, specifically the AA genotype, has been associated with CRC risk and lower serum MEG3 expression in Egyptian patients.[45] This association has been explained by the contribution of the rs7158663 A allele to the binding of miR-4307 and miR-1265 to MEG and the changes in the local RNA folding structure.[47]

A recent Egyptian study by Senousy et al. examined the association of MEG3 rs941576 SNP with overall CRC and obesity-related CRC risk.[46] The authors found that the minor G allele and the GG genotype were associated with increased CRC risk with age- and gender-specific associations, implying the SNP's usefulness in the prediction of CRC predisposition and risk stratification. Nonetheless, this SNP was not associated with CRC risk when patients and controls were dichotomized into obese and non-obese.[46] Studying the possible mechanism of this SNP revealed no association with serum MEG3 levels or its downstream target miR-27a/insulin-like growth factor-1 (IGF-1)/IGF binding protein 3 (IGFBP3) or miR-181a/sirtuin 1 (SIRT1) axes.[46] However, the MEG3 rs941576 AA genotype was associated with reduced serum MEG3 and BAX levels and elevated hypoxia-inducible factor-1α and vascular endothelial growth factor levels in Egyptian rheumatoid arthritis patients.[48]

Analysis of the rs941576 SNP association with tumor-related data in overall CRC patients revealed the association of the G allele-containing genotypes with lymph node metastasis and late tumor stages. When classifying CRC patients into obese and non-obese, this SNP cross-interacted with distant

metastasis and tumor stage in obese CRC patients [46], highlighting the significance of this SNP as a genetic marker in obesity-related CRC prognosis.

Serum samples from CRC patients exhibited significantly reduced MEG3 expression in Egyptian cohorts [45,46], aligning with previous studies.[49,50] Serum MEG3 downregulation was concordant with the upregulation of miR-27a and miR-181a and was accompanied by differential expression of the downstream target genes, IGF-1/IGFBP and SIRT1.[46] However, only the MEG3/miR-27a/IGF1/IGFBP3 axis was differentially expressed in the serum of obese versus non-obese CRC patients.[46] Indeed, this axis plays an impeccable role in metabolic reprogramming, a key driver of obesity-related CRC development.[47,50,51] These findings suggest that MEG3 loss may mediate the pro-tumorigenic effects of obesity, supporting its role as a critical link between metabolic dysregulation and CRC.

Although serum MEG3 was hardly diagnostic for CRC patients versus healthy controls, it was a promising discriminator between obese and non-obese CRC patients.[46] While serum MEG3 expression showed an inverse correlation with tumor stage in overall CRC patients, it was positively correlated with anatomical site (colon versus rectum) in obese CRC patients.[46] Together, these findings highlight the relevance of serum MEG3 in the detection and prognosis of obesity-related CRC. To note, no evidence exists to link obesity-related CRC with the other lncRNAs.

3.5 HOTTIP rs1859168 SNP and expression in CRC

Aberrant expression of lncRNA HOXA transcript at the distal tip (HOTTIP) has been associated with the emergence and spread of CRC, consistent with its oncogenic role.[52,53] Studies on Egyptian cohorts revealed HOTTIP rs1859168 SNP as a risk factor for CRC.[54,55] While the AC conferred CRC susceptibility among AP patients and controls in one study [54], the C allele and the CC genotype posed CRC risk in another study [55], both point at the C allele as a risk factor. Interestingly, differential expression of serum HOTTIP was observed across different rs1859168 genotypes [54], implying a possible role of this SNP to regulate HOTTIP levels. In parallel, augmented expression of HOTTIP in serum was shown in CRC patients compared to AP or controls and was suggested as a diagnostic biomarker.[54] These heightened levels, along with rs1859168, were associated with distant metastasis, lymph node metastasis, and grade III CRC [54], denoting their potential prognostic

value. These results agree with those showing elevated HOTTIP expression in peripheral blood mononuclear cells (PBMCs) and tissues in Egyptian CRC cases, with higher tissue expression than that of PBMCs.[55] HOTTIP tissue and PBMC expression levels were portrayed as diagnostic biomarkers of CRC, and its tissue expression differentiated between grade II and III CRC, [55] suggesting its potential clinical significance.

4. Clinical implications and biomarker potential

Collectively, these studies support the utility of lncRNA SNP genotyping for CRC risk stratification, particularly in populations with unique genetic backgrounds such as Egyptians. SNP analysis (rs6983267, rs7763881, rs3200401, rs13255292, rs7158663, rs941576, and rs1859168) could inform individual risk profiles and guide screening strategies, leading to the development of more targeted and personalized screening approaches. This could enhance the accuracy of screening frequency and modality. When combined with other risk factors (e.g., family history, lifestyle), SNP profiles improve risk assessment models, allowing for more effective allocation of screening resources. Understanding how these SNPs affect lncRNA function could guide the development of targeted therapies or preventive measures for CRC patients with genetic predispositions. Table 1 lists the lncRNA SNP associations with CRC risk in Egyptian patients and their association with tumor-related data.

Additionally, the studies also support the usefulness of lncRNA expression profiling, particularly in the circulation, in CRC detection, diagnosis, and prognosis. Serum lncRNAs have translational potential in clinical practice as minimally invasive screening tests of CRC for its early identification and prognosis (Table 2).

Beyond diagnostics, lncRNAs represent promising therapeutic targets and hold promise for clinical translation. Antisense oligonucleotides, small molecules, or CRISPR-based strategies could be developed to modulate lncRNA expression or disrupt pathogenic lncRNA-miRNA interactions, offering new avenues for prevention and treatment. For instance, targeting MALAT1 or PVT1 may inhibit EMT and metastasis, while restoring MEG3 function could counteract obesity-driven tumorigenesis.

In addition, lncRNAs can contribute to the heterogeneity of CRC tumors. Studying the lncRNA expression patterns could

inform clinicians about the diverse characteristics of CRC tumors and potentially tailor screening and treatment strategies to specific tumor subtypes. Understanding the role of lncRNAs in epigenetic changes associated with CRC could provide insights into early disease development and lead to the identification of novel screening targets. Given Egypt's rising CRC rates, these findings could inform region-specific screening and treatment strategies.

However, current studies addressing the lncRNA polymorphisms and expression in the Egyptian population have several limitations, including small sample sizes, cross-sectional design, and lack of functional validation. This warrants further mechanistic studies on larger cohorts to fully elucidate how these SNPs could affect the lncRNA and its downstream targets.

5. Future directions

To translate these findings into clinical practice, future studies should validate these associations in larger, multiethnic cohorts; elucidate the molecular mechanisms by which SNPs alter lncRNA function, using structural modeling and in vitro assays; explore the integration of lncRNA biomarkers into existing CRC screening programs (e.g., FIT or colonoscopy); and investigate the therapeutic potential of targeting lncRNAs in preclinical CRC models. Further research into these lncRNA-related genetic variations could lead to improved diagnostics, risk assessment, and personalized treatment strategies for CRC.

6. Conclusion

LncRNA polymorphisms and expression profiles significantly influence CRC susceptibility, tumor progression, and response to metabolic risk factors such as obesity. Studies in Egyptian patients highlight the potential of lncRNA-focused biomarkers and therapeutic strategies tailored to individual genetic and environmental contexts for the precision medicine of CRC. This mini-review establishes both a molecular framework for understanding lncRNA polymorphisms and expression profiles in CRC and a mechanistic foundation for clinical translation. The resultant evidence not only redefines therapeutic paradigms for CRC but also positions lncRNA/miRNA interplay as a precision medicine target with direct implications for CRC outcome optimization. Future work should aim to integrate lncRNA data into precision oncology frameworks for CRC prevention, diagnosis, and treatment.

7. Declarations

Consent for Publication: Not applicable.

Table 1. Summary of lncRNA SNP associations with CRC risk in Egyptian patients

lncRNA	SNP	Chromosomal location	Risk allele/ genotype(s)	Proposed mechanism	Association with clinicopathologic features	References
CCAT2	rs6983267 (G/T)	8q24	GG	Enhances CCAT2 expression, may promote Wnt/β-catenin signaling via MYC activation	-----	19*,21
HULC	rs7763881 (A/C)	6p24.3	AA	Elevates HULC expression	Associates with mucinous adenocarcinoma	21
MALAT1	rs3200401 (C/T)	11q13	T allele TT genotype	Correlates with E-cadherin and EMT process	Associates with lymph node status	31
PVT1	rs13255292 (C/T)	8q24	C allele	Affects PVT-1 expression	------	31,39
MEG3	rs7158663 (G/A)	14q32.3	A allele AA genotype	Affects MEG3 expression possibly via altering RNA folding and miRNA binding sites.	-----	45,47*
	rs941576 (A/G)	14q32.2	G allele GG genotype	May alter MEG3 expression	Associates with lymph node metastasis and late tumor stages in overall CRC and with distant metastasis in obesity-related CRC	46,48
HOTTIP	rs1859168 (A/C)	7p15.2	AC genotype	Affects HOTTIP expression	Associates with distant metastasis, lymph node metastasis, and grade III CRC	54
			C allele, CC genotype	------	-------	55

*Refers to non-Egyptian studies to support the proposed mechanism.

Table 2. Expression patterns of lncRNAs in Egyptian CRC Patients

lncRNA	Sample type	Study design	Expression in CRC	Biomarker potential for CRC	Correlation with clinicopathologic features of CRC	References
CCAT2	Serum	120 CRC, 30 AP, and 96 healthy controls	Elevated	Early diagnosis	------	[21]
HULC	Serum	120 CRC, 30 AP, and 96 healthy controls	Elevated	Early diagnosis, predictor of CRC risk among non-CRC subjects	----	[21]
MALAT1	Serum	140 CRC, 40 AP, and 100 healthy controls	Elevated	Early diagnosis, predictor of CRC risk among non-CRC subjects	Correlate with the EMT marker E-cadherin, tumor stage, lymph node status, and distant metastasis	[31]
PVT1	Serum	140 CRC, 40 AP, and 100 healthy controls	Elevated	Early diagnosis	Correlate with the EMT marker E-cadherin, tumor stage, lymph node status, and distant metastasis	[31]
MEG3	Serum	130 CRC (70 obese and 60 non-obese) and 120 healthy controls	Reduced in overall CRC and in obese-CRC patients	Discriminates obese versus non-obese CRC	Correlate with tumor stage in overall CRC and with anatomical site in obese CRC patients	[46]
HOTTIP	Serum	140 CRC, 45 AP, and 150 healthy controls	Elevated	Early diagnosis and prognosis	Correlates with distant metastasis, lymph node metastasis, and grade III CRC	[54]
	PBMCs and tissue	30 CRC and 30 healthy controls.	Elevated	Diagnosis and prognosis	Correlates with CRC grade	[55]

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