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REVIEW ARTICLE

Comprehensive analysis of the role of NLRC5 in gastrointestinal cancer: a systematic review

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ABSTRACT

BACKGROUND

Gastrointestinal (GI) cancer is affecting millions of people globally, leading to high incidence and mortality rates and a heavy economic burden. Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are a family of cytosolic pattern recognition receptors that regulate host defense responses against microorganisms. Among these, NLR family CARD domain-containing 5 (NLRC5) is assumed to function as a regulator of proinflammatory responses to intracellular pathogens. NLRC5 has been known to regulate immune responses, although its association with cancer remains controversial. This systematic review aimed to explore the roles and functions of NLRC5 in GI cancers.

METHODS

Three electronic databases, PubMed, Scopus, and ProQuest, were used for literature searching on March 18, 2024. From 921 articles found, 157 duplicates were removed, 671 were excluded based on title and abstract screening, and 84 were excluded based on full-text assessment, resulting in 19 articles included in this review.

RESULTS

Elevated NLRC5 levels have been observed in tumor tissues compared to normal tissues across esophageal, gastric, colorectal, and liver cancers. NLRC5 is also associated with increased tumor cell proliferation, migration, and invasion. Cancer cell sensitivity to 5-fluorouracil chemotherapy was found to be negatively correlated with NLRC5 expression. NLRC5 expression levels and genetic variations were also associated with cancer susceptibility to chemotherapeutic drugs and cancer survival.

CONCLUSION

NLRC5 potentially exhibits diverse functions in GI cancers, acting as a biomarker for diagnosis, disease progression, prognostic assessment, and determining therapeutic implications. Further investigations are warranted to explore these mechanisms and their potentials for the development of effective treatment of GI cancers.

Keywords: Biomarker, gastrointestinal cancer, GI cancer, NLRC5, diagnostic, prognostic

INTRODUCTION

Gastrointestinal (GI) cancers account for 26% of cancer incidence and 35% of all cancer-related deaths worldwide.[1,2] In 2018, there were 4.8 million new cases of GI cancer and an estimated 3.4 million related deaths.[2] Colorectal cancer (CRC) ranked fourth in cancer incidence in Indonesia, followed by liver cancer in the fifth, pancreatic cancer in the fifteenth, and gastric cancer in the eighteenth place.[3] The survival rates are varied but mostly poor. Indonesia's tertiary hospital, dr. Cipto Mangunkusumo General Hospital Jakarta, has several reports regarding GI cancer survival rates. The collective five-year survival rate for CRC stood at 43%, with the majority of individuals (52.8%) being diagnosed at stage IV.[4] In the case of liver cancer, the median overall survival rate was recorded at 17 months post-diagnosis, while the three-year mortality rate was reported to be 94.4% according to findings from a multicenter study.[5]

A tube-shaped network connects digestive organs, from the esophagus to the anus. Its functions are to provide nourishment, remove debris, and maintain the functionality of the immune system. Malnutrition, bleeding, obstructions, and various other life-threatening health complications may result from the development of malignancies within this organ system.[6,7] Cancerous cells must evade immune surveillance in order to proliferate. The substantial contribution of nucleotide-binding domain and leucine-rich repeats containing (NLR) family, caspase activation and recruitment domain (CARD) domain containing 5 (NLRC5) receptors to the immune evasion mechanism by malignancies has been documented in a multitude of studies.[8–10] Immune evasion by malignancies frequently targets NLRC5, the transcriptional activator of major histocompatibility complex (MHC) class I gene expression.[11–15] Additionally, survival rates and the mechanisms by which NLRC5 functions in cancer have been found to be correlated with its expression.[14–17]

Numerous studies have indicated a correlation between NLRC5 expression and various types of cancer.[12] Previous studies have indicated that low NLRC5 expression was present in melanoma, ovarian cancer, breast cancer, and prostate cancer tissues, and was associated with poor survival in melanoma, head-neck, bladder, uterine, cervical, and rectal cancers, suggesting a role for NLRC5 in anti-cancer responses.[14,15] Nevertheless, recent findings on NLRC5 have presented data suggesting that NLRC5 has a role in facilitating the growth, movement, and infiltration of cancer cells associated with increasing levels of inflammation.[18,19] Higher expression of NLRC5 was detected within tumor cells compared to normal cells in some studies using renal cell carcinoma,[19] glioma,[20,21] non-small cell lung carcinoma,[17] and endometrial cancer.[22–24] Moreover, NLRC5 expression was found to be inversely correlated with patient survival and clinical outcomes in some cancers, including brain cancer,[14,15] renal cell carcinoma,[19] and non-small cell lung cancer.[17] Because of the considerable number of studies carried out in recent years on these topics and the importance of obtaining a comprehensive view for guiding future studies and the search for novel therapeutic approaches, we aimed to provide a comprehensive review of the role of NLRC5 in GI cancers, disease diagnostics, its significance in the survival of patients, and its potential to affect the therapy of GI cancers.

METHODS

Search strategy

Literature searches were performed on three databases (PubMed, Scopus, and ProQuest) on March 18, 2024. The search term "NLRC5" along with its synonyms was utilized for the PubMed database, while "NLRC5", "cancer", and "gastrointestinal" along with their respective synonyms were utilized for the other two databases. Additionally, manual searching was carried out to gather additional studies. The protocol of this systematic review was registered with the Open Science Framework at https://doi.org/10.17605/OSF.IO/A8BGW.

Study selection and data extraction

Studies in this systematic review were required to fulfill the following inclusion criteria: (i) include GI tract cancer as their study population and (ii) NLRC5 as one of the study variables. Articles were excluded if they were: (i) published more than 10 years ago, (ii) reviews, commentaries, or book chapters, (iii) not analyzing GI cancer as a separate group, (iv) not accessible, and (v) not written in English or Bahasa Indonesia. First author, year of publication, country of origin, tumor type, study population, sample size, and outcomes were extracted from the included studies.

RESULTS

Study selection

The literature selection process for this systematic review followed the PRISMA[25] 2020 flow diagram, illustrated in **Figure 1.** A total of 921 articles were identified through database searching and no additional studies were found through manual searching. After eliminating duplicate articles, 764 articles remained for the initial screening. During this phase, 671 articles were excluded as they did not meet the predetermined inclusion criteria. Subsequently, a thorough examination of the full-text versions was conducted on the remaining 93 articles, leading to the exclusion of 74 articles for various reasons, such as being review articles (20 articles), not including GI cancer as the study population (14 articles), not including NLRC5 as one of the variables (39 articles), and not being written in English or Bahasa Indonesia (1 article). Consequently, 19 articles were deemed eligible and included in this systematic review.

The studies included in this systematic review were published between 2014 and 2022, examining various types of GI cancer. Specifically, this review identified three studies that focused on esophageal cancer, four on gastric cancer, eight on colorectal cancer, three on liver cancer, and one on both colorectal and liver cancer. The study designs differed across each study, encompassing experimental, case-control, prospective cohort, and retrospective cohort studies. Furthermore, these studies included a diverse study population, including genetic association studies, human studies, animal models, and *in-vitro* studies. Notably, these studies investigate different roles of NLRC5 in relation to GI cancers, probing its involvement as a risk factor, a biomarker for diagnostic and disease progression, a prognostic indicator, as well as a potential therapeutic target. A summary of the characteristics of included studies can be seen in **Table 1**.

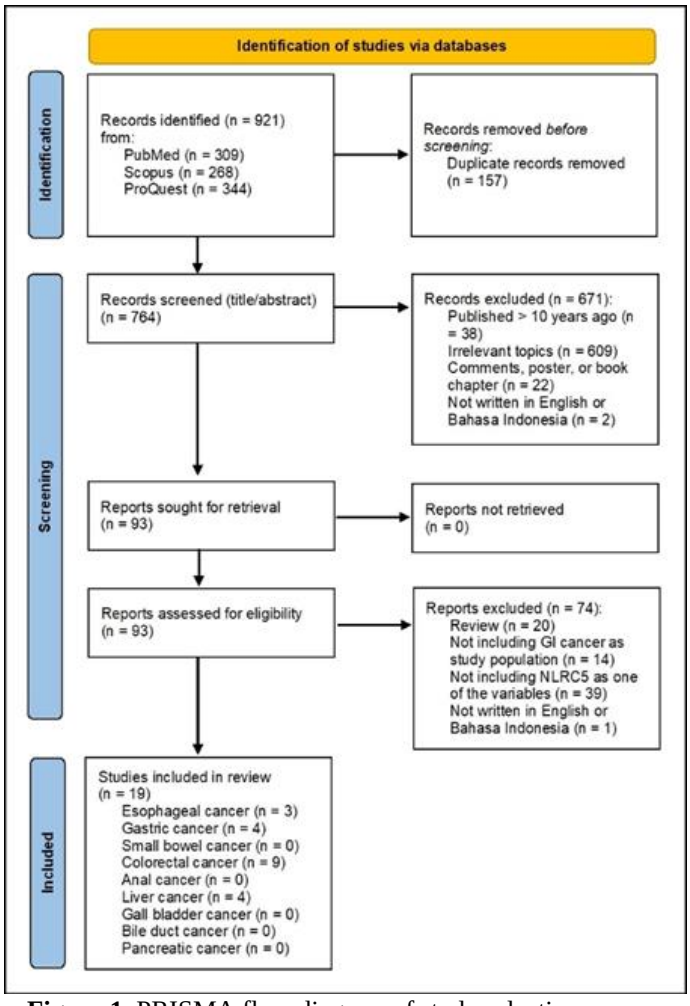

Figure 1. PRISMA flow diagram of study selection process

Table 1. Study characteristics and outcomes.

Author	Year	Country	Design	Tumor type	Population	Sample Size	NLRC5's role	Outcome	Conclusion
Lu et al.[26]	2022	China	Retrospective cohort	ESCC	Human	743	Diagnostic Prognostic	NLRC5 mRNA expression Survival	NLRC5 was highly expressed in ESCC tissue and associated with lower survival rate
Hu et al. [27]	2020	China	Experimental	ESCC	Cell lines	N/A	Disease progression Therapeutic target	Cell proliferation Colony formation Cell cycle arrest	Overexpression of NLRC5 promoted cell proliferation, colony formation, and cell cycle arrest
Dighe et al. [28]	2021	US	Case-control	EAC	Human	27.438	Risk factor	Genetic association	There were significant gene-associations of NLRC5 with the risk of BE and EAC within Bonn and Cambridge cohorts, respectively.
Liang et al. [29]	2022	China	Experimental	GC	Cell lines	N/A	Diagnostic Disease progression	NLRC5 expression Colony formation Migration ability Invasion ability	NLRC5 mRNA and protein expression was significantly higher in GC cells. NLRC5 silencing notably reduced colony formation, migration, and invasion ability of GC cells as well as increased cell apoptosis in response to 5-FU chemotherapy.
Chonwerawong et al. [30]	2020	US	Experimental	Gastric MALT lymphoma	Human biopsies Mice Cell lines	30	Diagnostic Prognostic	NLRC5 expression BAFF expression Gastric MALT lymphoma development	NLRC5 expression was elevated in response to chronic *H pylori* infection in mouse and human gastric biopsies Higher BAFF expression was reported in NLRC5 -/- cells stimulated with LPS, *H pylori*, and *H felis* NLRC5 knockout mice infected with *H felis* exhibited exacerbated inflammation, increased glandular hyperplasia, and a greater abundance of lymphoid structures.
Li[31]	2018	China	Retrospective cohort	GC	GC patients	97	Diagnostic Prognostic	Clinicopathlogical features Adverse outcomes	NLRC5 was related to tumor site, lymph nodes, TNM stage, and adverse outcomes.
Castaño-Rodríguez[34]	2014	Australia	Experimental	GC	Cell lines	N/A	Diagnostic	NLRC5 expression	The expression of NLRC5 was reduced by at least half in cells that were exposed to *H. pylori*.
Ozcan[36]	2018	Germany	Case-control	CRC	CRC patients	529	Diagnostic	NLRC5 mutations	Higher NLRC5 mutations were found in MSI compared to non-MSI colorectal cancer
Liu[37]	2015	China	Case-control	CRC	Human	237	Diagnostic	NLRC5 expression	The expression of NLRC5 did not show any significant differences between

									colorectal cancer (CRC) samples and the control group.
Grasso[38]	2018	US	Case-control	CRC	Human	1.211	Diagnostic	NLRC5 mutations	NLRC5 mutations were higher in MSI-high samples and associated with decreased HLA class I expression
Li et al. [36]	2022	China	Case-control	CRC	CRC patients	41	Diagnostic	NLRC5 genomic alterations	CRC with *situs inversus totalis* had more NLRC5 genomic alteration
Catalano et al. [40]	2018	Czech Republic	Case-control	CRC	Human	2.538	Risk factor	Genetic association	Two NLRC5 SNPs, rs1684575 and rs3751710, were associated with the risk of CRC.
Huhn et al. [41]	2018	Czech Republic	Prospective cohort	CRC	Human	2.024	Prognostic	Survival	Two NLRC5 SNPs, rs289723 and rs74439742, have been identified as having a significant association with the overall survival and event-free survival rates of CRC patients
Catalano et al. [42]	2018	Czech Republic	Retrospective cohort	CRC	CRC patients	589	Prognostic	Survival	Two NLRC5 SNPs were associated with overall and event-free survival of CRC patients (rs27194 and rs289747) and CRC patients undergoing 5-FU treatment (rs289747 and rs12445252)
Siu et al. [40]	2019	China	Experimental	CRC	Cell lines	N/A	Prognostic	Response to 5-FU chemotherapy	5-FU resistant cells had higher NLRC5 RNA abundance
Peng et al. [41]	2016	China	Experimental	HCC	Human biopsies Cell lines	11 patients	Diagnostic Disease progression	NLRC5 expression Cell proliferation	NLRC5 expression was higher in HCC cell lines and promoted higher proliferation rate
He et al. [42]	2016	China	Experimental	HCC	Human biopsies Cell lines	9 patients	Diagnostic Disease progression	NLRC5 expression VEGF-A expression Cell proliferation	NLRC5 and VEGF-A expression were upregulated in HCC tissue and cell lines, and enhanced cell proliferation
Zhang et al. [46]	2020	China	Retrospective cohort	HCC	Human	424	Diagnostic Prognostic	NLRC5 expression Clinicopathological features Survival	NLRC5 expression was higher in tumor samples and associated with higher rate of cirrhosis and TNM stage, as well as lower 3-year overall survival rate.
Yoshihama et al. [15]	2016	US	Retrospective cohort	COAD HCC	Human	628 for COAD 210 for HCC	Diagnostic Prognostic	NLRC5 expression Survival	NLRC5 expression was higher in HCC and COAD but not associated with 5 year survival rate for both diseases.

Notes: EAC: esophageal adenocarcinoma; BE: Barrett's esophagus; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; MALT: mucosa-associated lymphoid tissue; CRC: colorectal cancer; HCC: hepatocellular carcinoma; COAD: colon adenocarcinoma; 5-FU: 5-fluorouracil; BAFF: B-cell-activating factor; VEGF-A: vascular endothelial growth factor A; MSI: microsatellite instability.

DISCUSSION

Role of NLRC5 in esophageal cancer

An analysis of transcriptomic data was performed by Lu et al.[26] on a dataset comprising samples of esophageal squamous cell carcinoma (ESCC) and normal tissue. The findings revealed a significant upregulation of NLRC5 mRNA expression in ESCC tissue compared to normal tissue. Consistent with prior studies, an *in-vitro* study by Hu et al.[27] utilizing ESCC cell lines revealed that overexpression of NLRC5 led to enhanced ESCC cell growth, formation of colonies, and arrest of the cell cycle.

Genetic association between NLRC5 and esophageal cancer

Dighe et al.[28] recently conducted a genome-wide association study to explore the gene-level association between NLRC5 and the progression of Barett's esophagus (BE), a condition recognized as the precursor to esophageal carcinoma (EAC), as well as EAC itself. The study revealed a significant association in smaller cohort datasets, indicating the potential involvement of NLRC5 variations in these conditions. However, when the results were analyzed in a larger meta-analysis dataset, the level of significance did not reach the threshold.

NLRC5 and survival outcomes in esophageal cancer

Lu et al.[26] also analyzed the survival rates between ESCC patients with higher and lower expression of NLRC5 in ESCC tissue and found a significant correlation between higher NLRC5 expression in ESCC tissue and lower rates of patient survival.

NLRC5 and its role in esophageal cancer therapy

Besides elucidating the role of NLRC5 in ESCC progression, Hu et al.[27] further detected a specific binding site for miR-4319 within NLRC5. Their research revealed that miR-4319 has the capability to inhibit NLRC5 expression in ESCC cell lines, suggesting its potential as a therapeutic target.

Role of NLRC5 in gastric cancer

The potential role of NLRC5 in gastric cancer (GC) was also confirmed in several GC cell lines, as studied by Liang et al.[29] using wound healing, transwell, and western blotting assays. They discovered that the knockdown of NLRC5 reduced the proliferation, migration, and invasion abilities of GC cells. A study of gastric B-cell mucosa associated lymphoid tissue (MALT) lymphoma, a type of GC, was conducted by Chonwerawong et al.[30] to investigate its association with NLRC5 expression. NLRC5 expression exhibited a significant increase in both murine and human gastric biopsies when exposed to chronic *H. pylori* infection, as indicated by the research findings. Furthermore, the study demonstrated a positive correlation between NLRC5 expression and severe gastritis, although no significant association with tumor formation was established.

A study of NLRC5 in GC was conducted by Li et al.[31] by analyzing data from 97 GC patients who underwent gastrectomy without receiving radiotherapy or chemotherapy before the procedure. The results showed that 72.2% were positive for NLRC5 expression. The negative and positive groups did not exhibit any notable disparities in terms of age, sex, tumor size, or tumor differentiation. However, a significant correlation was found between NLRC5 expression and tumor site, lymph node number, and TNM stage. Interestingly, NLRC5 -/- cell lines showed substantially higher levels of B-cell–activating factor (BAFF) expression, a well-known driver of gastric B-cell MALT lymphoma,[32,33] when exposed to lipopolysaccharides (LPS), *Helicobacter pylori*, or *H. felis* as stimuli, in comparison to wild-type (WT) cells. Additionally, NLRC5-knockout mice displayed more severe inflammation, glandular hyperplasia, and a higher number of lymphoid structures or follicles following *H. felis* infection.[30]

Genetic association between NLRC5 and gastric cancer

Castaño-Rodríguez et al.[34] reported the role of genetic polymorphisms and genes expressed specifically in the NLR signaling pathway in cases of *H. pylori* infection-related GC. Among the 51 genetic polymorphisms genotyped from 310 ethnic Chinese (87 non-cardia GC cases and 223 controls with functional dyspepsia), CARD8-rs11672725, NLRP3-rs10754558, NLRP3-rs4612666, NLRP12-rs199475867, and NLRX1-rs10790286 were the single-nucleotide polymorphisms (SNPs) that had significant associations with GC. NLRC5, a member of the NLR gene family, exhibited significant regulation in cells challenged with *H. pylori* based on gene expression analyses.

NLRC5 and survival outcomes in gastric cancer

Li et al.[31] found that the elevated expression of NLRC5 in GC tissue was correlated with a poorer prognosis. The positive NLRC5 expression cases were observed to have a 69% higher risk of unfavorable outcomes. Since NLRC5 expression in Li's study[31] was related to TNM stage and lymph node metastasis, multivariate regression analysis revealed that there was a significantly higher risk in advanced-stage cases, and in mortality risk in lymph node metastasis.

NLRC5 and its role in gastric cancer therapy

An experimental study by Liang et al.[29] found that NLRC5 had significant associations with the responsiveness of GC cells to 5-fluorouracil (5-FU). By using western blotting and flow cytometry, cellular apoptosis markers were upregulated in the 5-FU + si-NLRC5 group compared to the 5-FU + negative controls. From the experiment, it can be concluded that the knockdown of NLRC5 would increase the responsiveness of GC cells to 5-FU chemotherapy. It is known that Yin Yang1 (YY1) has a significant effect on an increase in GC cell proliferation.[35] Liang's study [29] confirmed and tested the role of NLRC5 in relation to YY1 effects on GC cell sensitivity to 5-FU through Cell Counting Kit 8 (CCK-8) and colony formation assays. The result showed a decrease in cell proliferation in the YY1 overexpressed group + 5-FU + si-NLRC5 group in comparison to the control group. Furthermore, it was also reported that apoptosis of GC cells increased in combination with si-NLRC5. This showed that silencing or knocking down of NLRC5 would further decrease the YY1 effect that promotes GC cell proliferation.[29]

Role of NLRC5 in colorectal cancer

One study in Germany by Ozcan et al.[36] analyzed the complex pattern of immune evasion, focusing on HLA class I antigen presentation in microsatellite instability (MSI) colorectal cancer (CRC). Among the 91 samples, 26.4% had mutations in the NLRC5 gene, which was significantly higher compared to non-MSI CRC. The NLRC5 mutation was associated with a low level of HLA class I antigen expression. Examination of gene expression data from the cancer genome atlas (TCGA) database by Liu et al.,[34] using 22 healthy control samples and 215 colorectal cancer (CRC) samples resulted in a slight decrease in NLRC5 expression within the CRC group in comparison to the control group, although statistical significance was not attained. Furthermore, the analysis of NLRC5 expression profiles using biopsy specimens from 40 CRC patients revealed no notable difference between CRC tissue and adjacent healthy tissue, as well as among various stages of cancer progression. In a more recent study conducted by Yoshihama et al.,[15] using gene expression data from the TCGA database with a larger sample size (345 healthy samples and 285 colon cancer samples), found a significant increase in NLRC5 expression in tumor samples compared to normal ones. Similar findings were also reported in a more recent study by Grasso et al.,[38] which utilized a larger samples.

Particularly in CRC with *situs inversus totalis* (SCRC), Li et al.[36] found that NLRC5 mutation occurs more frequently compared to CRC without *situs inversus totalis* (NSCRC). Besides NLRC5, they also found that mutations in CHEK2, MDC1, GNAQ, SMAD4, BRCA1, HLA-B, and LATS2 were more frequent among eight samples of SCRC versus 33 NSCRC patients.

Genetic association between NLRC5 and the risk and survival of colorectal cancer

A study in the Czech Republic by Catalano et al.[40] searched for the significant SNP of NLRC5 and Programmed death-ligand 1 (PD-L1) that have potential single and synergistic effects on CRC through *in-silico* analysis of 1424 patients with CRC and 1114 controls. Two NLRC5 SNPs, rs1684575 and rs3751710, were reported to have a moderate association with rectal cancer risk. Furthermore, there were several interactions between NLRC5 variants with the PD-L1 and IFNGR2 genes, which are involved in the immune regulation of CRC. An elevated risk of CRC was shown by the interactions between at least a minor allele of NLRC5 rs12445252 and PD-L1 rs2890657.

Huhn et al.[41] investigated SNPs within the NLR genes, including NLRC5, and their association with overall survival (OS) and event-free survival (EFS) outcomes in 1237 CRC patients and found two NLRC5 variants associated with CRC survival, rs289723 and rs74439742. Analysis of the SNP rs289723, which involves an amino acid change from glutamine (Q) to lysine (K) at position 1105, revealed no significant correlation with OS in all patients. Similarly, for metastasis-free patients upon diagnosis (pM0), this SNP showed no

significant associations with OS. However, decreased EFS outcomes demonstrated a significant association with the SNP rs289723, particularly for patients with the A/C genotype. Moreover, analysis of SNP rs74439742, resulting in a change from proline (P) to leucine (L) at position 191, revealed significant associations with OS and EFS outcomes in patients with or without metastases upon diagnosis (pM1&0), for both genotypes C/T and T/T. A similar study conducted by Catalano et al.[42] using 589 CRC cases found a significant link between two NLRC5 polymorphisms, rs27194 and rs289747, and CRC survival. In a recessive model, pM1&0 and pM0 individuals, both of whom were homozygous carriers of the minor allele of rs27194, exhibited a reduction in OS and EFS. OS also experienced a reduction in all patients, as well as in patients with pM0 status who possessed a minimum of one rs289747 minor allele. In CRC patients treated with 5-FU chemotherapy, rs12445252 was associated with decreased OS for all patients and for pM0 patients, respectively, as well as decreased EFS for pM0 patients.

NLRC5 and its role in colorectal cancer therapy

In the experimental study carried out by Siu et al.,[43] a comparison was made regarding the abundance of mRNA in parental CRC cell lines, which are sensitive to 5-FU chemotherapy, and in 5-FU resistant cells. The study revealed that NLRC5 mRNA abundance was observed to be higher in the 5-FU resistant cells in comparison to the parental cells.

Role of NLRC5 in liver cancer

An experimental *in-vitro* study by Peng et al.[41] using human hepatocellular carcinoma (HCC) and normal liver cells revealed that the expression of NLRC5 protein was significantly increased in HCC cells compared to normal ones. Additionally, the study demonstrated that knockdown of NLRC5 using siRNA in HCC cells led to a decreased proliferation rate in comparison to negative controls. Supportive outcomes were also obtained by enforcing expression of NLRC5 in HCC cells. Another experimental study conducted by He et al.[42] using a similar design also yielded consistent findings. Zhang et al.,[46] who reported elevated expression of NLRC5 mRNA and protein in HCC tissues relative to normal cases, corroborate these results, which were also supported by the gene expression analysis conducted by Yoshihama et al.[15] utilizing The Cancer Genome Atlas (TCGA) gene-expression dataset. The latter study revealed a notable increase in NLRC5 expression levels in liver cancer cells when compared to normal cells. Furthermore, Zhang et al.[46] also investigated the relationship between NLRC5 and clinicopathological profiles and found that increased NLRC5 levels were substantially correlated with an increased incidence of cirrhosis and a more advanced TNM stage.

Genetic association between NLRC5 and liver cancer

Gene set enrichment analysis conducted by Zhang et al.[46] found that the NLRC5-high phenotype exhibited increased expression of gene sets associated with the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway, apoptosis, cancer pathways, cell adhesion molecules, focal adhesion, and VEGF signaling pathways.

NLRC5 and survival outcomes in liver cancer

In addition to analyzing the clinicopathological profile, Zhang et al.[46] also assessed the NLRC5 expression profile along with its association with survival outcomes using the mRNA expression dataset from the TCGA database. The findings of their study indicated that patients displaying higher NLRC5 protein expression levels had lower three-year overall survival rates. However, in the study carried out by Yoshihama et al.,[15] there was no disparity in the five-year survival rate between the high and low NLRC5 expression groups.

NLRC5 has long been recognized as a master regulator of MHC Class I (MHC-I) gene expression by translocating into the nucleus and subsequently activating the transcription of MHC-I genes.[47–49] MHC-I plays a crucial role in anti-tumor immunity by presenting endogenous antigens, a process for signaling intracellular changes, including malignant transformation, to the immune system, thereby triggering $CD8^+$ T-cell responses.[10] Therefore, impairment in the antigen presentation pathway mediated by MHC-I is a significant immune evasion strategy observed in different types of cancer.[50] This is supported by the study carried out by Chonwerawong et al.,[30] which demonstrated an increased number of B-cell follicles related to gastric MALT lymphoma development in response to *Helicobacter* infection within mice lacking NLRC5, suggesting the NLRC5 function in anti-tumor immunity as reported in recent

studies utilizing mouse models and samples from cancer patients which underscored the critical role of NLRC5 in anti-cancer immune responses by activating cytotoxic CD8+ T-cells.[51,52]

In contrast to its recognized role in anti-tumor immunity,[14–16] the majority of studies examining NLRC5 expression levels in GI cancers, specifically esophageal,[26] gastric,[29] colorectal,[15] and liver cancers,[15,41–43] have consistently identified an elevated NLRC5 expression in tumor tissues compared to healthy tissues. Some studies also discovered NLRC5's roles in promoting tumor progression, such as enhancing tumor cell proliferation, colony formation, as well as migration and invasion abilities in esophageal [27] and liver cancers.[41–43] Higher levels of NLRC5 expression were also found to be correlated with lower survival rates in esophageal[26] and liver cancers.[46]

Based on the available evidence, NLRC5 has been found to have diverse roles in GI cancers, including its involvement in genetic susceptibility to GI cancer, its role in disease progression, its utility as a diagnostic and prognostic indicator, and its potential as a therapeutic intervention target. The role of NLRC5 in GI cancer contradicts the previous notion of NLRC5 as part of anti-tumor immunity, indicating that the function of NLRC5 varies depending on the tissue involved. Therefore, further research is needed to precisely unravel the pathogenetic pathways associated with the role of NLRC5 in the growth and development of GI cancer. This knowledge can help in developing more targeted and effective therapies for GI cancer patients, ultimately improving their outcomes. Therefore, continued investigation into the role of NLRC5 in GI cancer is essential for advancing our understanding and treatment of this complex disease.

CONCLUSION

NLRC5 exhibits diverse functions in GI cancers, acting as a biomarker for diagnosis, disease progression, and prognosis, as well as determining therapeutic implications. Numerous studies have consistently reported upregulation of NLRC5 in tumor tissues of GI cancer patients, which is associated with increased rates of tumor cell proliferation. However, the precise mechanisms through which NLRC5 contributes to disease progression and resistance to therapy remain incompletely understood. Therefore, further investigations are warranted to explore these mechanisms and their potential implications for the development of effective GI cancer therapies.

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None.

Conflict of Interest

No relevant disclosures.

Author Contributions

The author contributions to the paper were as follows: study conception and design: NR, MG; data collection: MG, DLD, NR; data analysis and interpretation: NR, MG, DLD; manuscript drafting: NR; critical revision: MG, DLD. All authors have reviewed the results and approved the final version of the manuscript.

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Data Availability Statement

Data are available upon request from the authors.

Declaration of use of AI in Scientific Writing

Nothing to declare.

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