Type of the Paper (Systematic Review)

A Review of the Role of SIRT6 in the Prognosis of Colorectal Cancer

Reham S. E. Esmail[1], Dalia N. Abdelhafez[1], Heba H. Mahmmoud[1]*

[1]Anatomic Pathology Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

*Correspondence: Heba H. Mahmmoud, hhm11@fayoum.edu.eg, Tel: (002) 01140691960.

Received: 23 July, 2024 Reviewed: 12 November, 2024
Accepted: 20 February, 2025 Published online: 20 March, 2025

Abstract:

Introduction: Colon carcinoma (CRC) ranks as the 3rd most prevalent malignancy globally. Each year about 1.4 million people develop colon cancer, and about 700,000 die from the disease. Sirtuin 6 (SIRT6) was discovered in recent years as a factor in the suppression of malignancy. This research aimed to summarize the current evidence regarding the impact of SIRT6 status on colon malignancy. In addition, we reviewed and summarized its correlation with various tumor characteristics as well as its relation to patient survival.

Methods: Research articles which studied cases with colorectal carcinoma were eligible for inclusion in this review. We included the studies which studied the relationship between survival outcomes and SIRT 6 expression in colorectal carcinoma patients. English Clinical trials and observational studies were included.

Results: Three research articles were summarized in this review representing about 253 cases. According to the T stage, T I-II was detected among 107 patients whereas T III-IV was detected among 96 patients. Positive nodal status was confirmed in 134 patients. Regarding the Immunohistochemical detection of SIRT 6 expression, it showed positive expression in 69 patients and negative expression in 184 patients. The three studies agreed that CRC specimens show lower levels of SIRT6 expression in comparison to normal colon specimens. Zhang et al. 2019 as well as Tian and Yuan 2018 found that lower levels of SIRT6 were incriminated for smaller survival durations.

Conclusion: SIRT6 could be regarded as a tumor suppressor factor that protects against the transformation of normal colon tissue to cancerous tissue. Also, it is important in the prognosis of the disease since its level was shown to be significantly correlated to patients' survival. Most of the studies agreed that the T stage significantly correlates to the level of SIRT6 expression within tumor tissue, whereas age and gender showed insignificant correlations.

Keywords: SIRT6; Sirtuin 6; Colorectal Carcinoma.

1. Introduction

Colon carcinoma (CRC) ranks as the 3rd most prevalent malignancy globally. Each year about 1.4 million people develop colon cancer, and about 700,000 die from the disease [1].

Sirtuin 6 (SIRT6), a member of the histone deacetylase sirtuin family, is widely expressed in mammalian cells and is crucial for various biological processes such as metabolism, DNA stability, aging, repair, cell proliferation, and differentiation. Recent studies have demonstrated that SIRT6 acts as a suppressive factor of malignancy in multiple contexts. [2].

Decreased levels of SIRT6 have been noted in several malignancies, including colorectal malignancies, ovary malignancies, and hepatic malignancies [3].

In contrast to these studies, many authors present SIRT6 as an oncogenic promotor in solid and hematologic tumors. Examples include human skin squamous cell carcinoma (SCC), hepatocellular carcinoma, prostate cancer, and breast cancer [4].

Reduced SIRT6 levels have been observed in the initial phases of colorectal malignancy and remain low throughout cancer advancement. Thus, this suggests that SIRT6 may be considered a significant factor in both the commencement and advancement of colon cancer [2]. However, the functions of SIRT6 concerning colon malignancies are still controversial [5].

This research aimed to summarize the current evidence regarding the impact of SIRT6 status on colon malignancy. In addition, we reviewed and summarized its correlation with various tumor characteristics as well as its relation to patient survival.

2. Methods

2.1. Subjects and Study Design

Cases diagnosed with colorectal carcinoma were eligible for inclusion in this study.

Inclusion criteria

We included the studies which studied the relationship between survival outcomes and SIRT 6 expression in colorectal carcinoma patients. English

Clinical trials and observational studies were included.

Exclusion criteria

We excluded studies that studied SIRT6 in cancers other than colorectal cancer as esophageal cancer, hepatic cancer, and pancreatic and hepatic cancers. Additionally, we excluded editorials, letters, reviews, conference abstracts or articles in languages other than English.

2.2. Study design

This is a Systematic review. We collected studies published from inception until June 2024.

We searched Scopus, PubMed, Web of Science, and Cochrane using a combination of the following keywords and their relevant synonyms (Colorectal adenocarcinoma and SIRT6)

The results of the literature search were collected in an Excel sheet and screened. Titles and abstracts were used for the initial filtration of the articles. Finally, full texts of eligible articles were screened.

We gathered the data of the eligible articles as: "the author and year, study design, sample size, and evaluation method". We also collected the baseline characteristics of patients as: "age, gender, T stage, nodal status, and SIRT6 expression".

Finally, we assessed the quality of the eligible articles.

2.3. Statistical analysis:

We conducted our systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Cochrane Handbook guidelines in doing all the steps Descriptive statistics were applied for the summarization of data. Significance was determined by "*P*- value < 0.05". data were summarized as mean and SD or number and frequencies in Excel spreadsheets.

3. Results

The database search resulted in the collection of 246 papers. After the removal of the duplicated papers, 173 articles were evaluated based on their titles and abstracts. Only 17 articles qualified for full-text screening. Finally, three research articles were summarized in this review as shown in **Figure 1.**

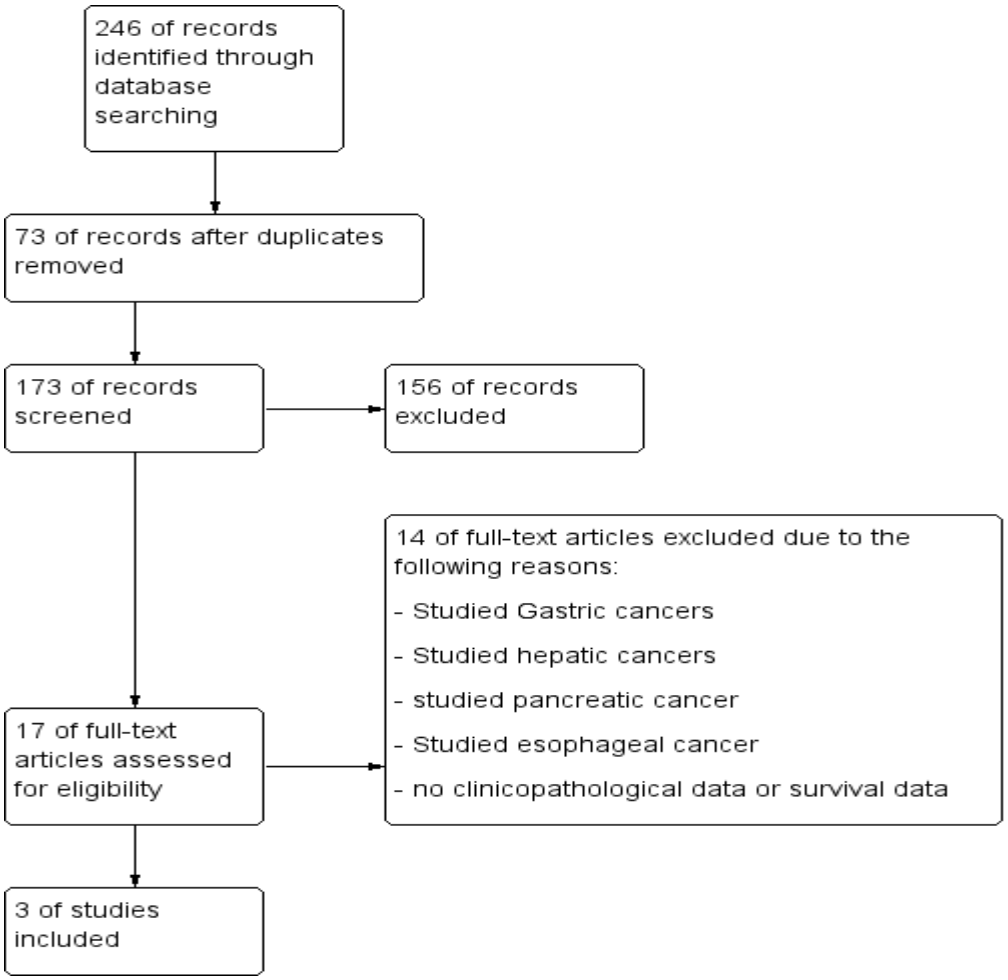

Figure 1: Studies collection process.

This review included a total sample size of 253 specimens from patients diagnosed with colorectal carcinoma. The articles were published between 2018 and 2019. All the included studies were cohort studies conducted in China.

Immunohistochemistry was used in the assessment of the expression of SIRT6.

General information about the articles discussed within this review is shown in **Table 1.**

Table 1: Summary of the included articles including name, publication year, type of article, sample size, entry requirements for patients, and SIRT 6 evaluation method.

Name	Publication year	Country	Type of article	Cases studied	Entry requirements	Evaluation method
Zhang et al. [5].	2019	China	Cohort	50	Colorectal carcinoma excised tissues and their adjacent healthy tissues were collected and examined	Immuno-histochemistry
Qi et al. [6].	2018	China	Cohort	113	Patients diagnosed with CRC by histological assessment and treated by radical colectomy.	Immuno-histochemistry
Tian and Yuan [7].	2018	China	Cohort	90	Also, the excised tumor and healthy tissue are available.	Immuno-histochemistry

The gender distribution of patients in this review should be near percentages where 106 males were included as compared to 97 females. Also, the number of patients below the age of 65 was slightly larger than those above the age of 65. According to the T stage, T I-II was detected among 107 patients whereas T III-IV was detected among 96 patients. Positive nodal status was confirmed in 134 patients. Regarding the Immunohistochemical detection of SIRT 6 expression, it showed positive expression in 69 patients and negative expression in 184 patients (**Table 2**).

Table 2: Summary of baseline data of the included patients.

Variables		Qi et al., 2018 [5]	Zhang et al., 2019 [6]	Tian and Yuan, 2018 [7]
Gender	Males	65 (57.5%)	NA	41(45.56%)
	Females	48 (42.48%)	NA	49 (54.44%)
Age		<64: 57, >64: 56	NA	<60: 51, >60: 39
T-stage	T1	7 (6.19%)	NA	I-II: 62 (68.89%) III-IV: 28 (31.11%)
	T2	38 (33.63%)	NA	
	T3	17 (15%)	NA	
	T4	51 (45.13%)	NA	
Positive nodal status		72 (63.72%)	NA	37 (41.11%)
SIRT6 positive		25 (22.12%)	16 (32%)	28 (31.11%)
SIRT6 negative		88 (77.88%)	34 (68%)	62 (68.89%)

All of the included cohorts have shown high quality, ranging from fair to good quality according to the Newcastle Ottawa scale (NOS) of cohorts. Tian and Yuan 2018 and Qi et al. (2018) have shown good quality since they fulfilled all of the domains of the scale [6,7]. Zhang et al. (2019) showed fair quality since it didn't fulfil the comparability domain of the scale [5]. **Table 3** shows the results of the quality assessment of the studies.

Table 3: Quality assessment summary.

	Variables	Qi et al., 2018 [5]	Zhang et al., 2019 [6]	Tian and Yuan, 2018 [7]
Selection	Representativeness of the exposed cohort	*	*	*
	Selection of the non-	*	*	*

	exposed cohort			
	Ascertainment of exposure	*	*	*
	The outcome was not present at the start of the study	*	*	*
Comparability	Control for 2 important factors (Age and T stage)	*	*	*
Outcome	Assessment of outcome	*	*	*
	Follow-up long enough	*	*	*
	Adequacy of follow-up of cohort	*	*	*
Total Score		8 (good)	7 (fair)	8 (good)

Qi et al. (2018) reported that SIRT6 expression showed significantly low levels in healthy specimens in comparison to the malignant specimens. About 22.12% of CRC had positively expressed SIRT6, in comparison to 80.53% of healthy specimens (p <0.01). They found that only the T stage and stage of lymph node metastases were the only factors that significantly correlated to SIRT6 expression (P values equal 0.023 and 0.048 respectively). On the other hand, neither age, sex, tumor size nor distant metastasis showed a significant correlation to SIRT6 expression.

Zhang et al. (2019) as well as Tian and Yuan 2018 also agreed that CRC specimens show lower levels of SIRT6 expression in comparison to normal colon specimens. They assessed the effect of SIRT6 expression on survival rates and they found that lower expression of SIRT6 was associated with shorter overall and disease-free survival durations. Tian and Yuan (2018) reported that T stage, Lymphovascular invasion and differentiation status significantly correlated to the status of SIRT6 expression.

4. Discussion

This review summarizes the evidence regarding the status of SIRT6 in colon malignancy, its correlation with various tumor characteristics and its relation to patient's survival.

The expression of SIRT6 was found to be lower in the tumor specimens. Qi et al. (2018) documented positive SIRT6 staining in only (22.12%) of CRC [6]. Geng et al. (2018) documented high SIRT6 levels in malignant specimens in comparison to the healthy specimens [8]. Li et al. (2018) found that 66%of normal colon tissue showed positive SIRT6 expression [9]. Another study documented increased expression of SIRT6 in normal colon tissue (80.53%) [6].

Regarding correlation to age, Geng et al. (2018) and Qi et al. (2018) found no relation between age of patients and SIRT6 expression [6,8]. Regarding gender, the available evidence showed high rates of SIRT6 expression in females. All the mentioned studies' results were also statistically insignificant [6,8,9].

As regards the tumor grade, Li et al. (2018) reported that no positive statistically significant association was detected between SIRT6 expression and tumor grade, in their study, they reported 0% of GI, 60% of GII and 43% of grade III cases showed positive SIRT6 expression (0%of G1 cases might be attributed to the narrow samples, three cases only) [9]. On the other hand, Geng et al. (2018) documented decreasing SIRT6 expression with loss of differentiation with a statistically significant association between tumor grade and SIRT6 expression [8].

Concerning the T-stage, Li et al. (2018) also found a statistically significant relation between SIRT6 expression and T-stage with (100%,100%,52% and 35%) for (T1, T2, T3, and T4) stage groups respectively. That could be explained by SIRT6's role in the inhibition of colon cancer cell proliferation and promotion of apoptosis via inactivation of the JAK2/STAT3 pathway [9]. Qi et al. (2018) demonstrated the same results with decreased SIRT6 expression in higher stages (28.6%, 36.8%, 17.6%, and 11.8%) for (T1, T2, T3, and T4) stage groups, respectively [6]. However, Geng et al. (2018) documented increasing SIRT6 expression with increasing T stage. They divided cases in their studies into two groups according to T stage: T1 and (T2-T4) with 36.3% and

68.5% positive SIRT6 expression, respectively [8].

Regarding the relation between SIRT6 expression and distant metastasis (M stage), a previous study showed SIRT6 expression in (54%) of M0 while not expressed in (M1) cases [9]. Also, Qi et al. (2018). Another showed higher expression of SIRT6 expression in non-metastatic (24.2%) than in metastatic cases (11.1%) [6]. This is probably due to its role as tumor suppressor through inhibition of the "Warburg effect" which is the reprogramming of the cellular energy metabolism to support continuous cell growth and proliferation in malignancy [10].

Regarding the N stage of the tumor, Li et al. (2018 also found no statistically significant relationship was detected between SIRT6 expression and N stage but with different rates, expression of SIRT6 was positive in 48.5% of cases with lymph node metastasis and 58.6% of cases without lymph node metastasis [9]. According to Geng et al. (2018) the rate of SIRT6 expression was positively associated with LN status where it was maximally expressed in N-positive cases (61.1%). In their study, they refer to its role as an oncogene in cancer cells through induction of the epithelial-mesenchymal transition (EMT) pathway via interaction with a snail a key transcription factor of EMT [8]. In contrast, Qi et al. (2018) reported that the lymph node status was inversely related to the level of SIRT6 expression where it was maximally expressed in N-negative cases (61.1%) and related this finding to SIRT6 metabolic mechanisms involved in the tumor suppression [6].

This systematic review summarizes important insights about the prognostic value of SIRT6 in CRC. An important limitation of the study is the relatively small sample size, thus further studies are needed with a larger sample to more reliably assess the effect of SIRT6 on the survival of the patients.

5. Conclusion

To sum up, SIRT6 could be regarded as a tumor suppressor factor that protects against the transformation of normal colon tissue to cancerous tissue. Also, it is important in the prognosis of the disease since its level was shown to be significantly correlated to overall and disease-free survival. Most of the studies agreed that the T stage significantly correlates to the level of SIRT6 expression within tumor tissue,

whereas age and gender showed insignificant correlations.

Ethical committee approval: not applicable

Competing interests: All authors declare no conflict of interest.

Funding: This research is not funded.

AI declaration statement: Not applicable.

References

1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenterol Rev. 2019;14(2):89–103. doi:10.5114/pg.2018.81072.
2. Sebastián C, Zwaans BM, Silberman DM, Gymrek M, Goren A, Zhong L, et al. The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. Cell. 2012;151(6):1185–99. doi:10.1016/j.cell.2012.10.047.
3. Lai CC, Lin PM, Lin SF, Hsu CH, Lin HC, Hu ML, et al. Altered expression of SIRT gene family in head and neck squamous cell carcinoma. Tumor Biol. 2013;34(3):1847–54. doi:10.1007/s13277-013-0698-7.
4. Liu Y, Xie QR, Wang B, Shao J, Zhang T, Liu T, et al. Inhibition of SIRT6 in prostate cancer reduces cell viability and increases sensitivity to chemotherapeutics. Protein Cell. 2013;4(9):702–10. doi:10.1007/s13238-013-3054-5.
5. Zhang Y, Nie L, Xu K, Fu Y, Zhong J, Gu K, et al. SIRT6, a novel direct transcriptional target of FoxO3a, mediates colon cancer therapy. Theranostics. 2019;9(8):2380–94. doi:10.7150/thno.29732.
6. Qi J, Cui C, Deng Q, Wang L, Chen R, Zhai D, et al. Downregulated SIRT6 and upregulated NMNAT2 are associated with the presence, depth and stage of colorectal cancer. Oncol Lett. 2018;16(5):5829–37. doi:10.3892/ol.2018.9406.
7. Tian J, Yuan L. Sirtuin 6 inhibits colon cancer progression by modulating PTEN/AKT signaling. Biomed Pharmacother. 2018;106:109–16. doi:10.1016/j.biopha.2018.06.099.
8. Geng C, Zhang C, Zhang J, Gao P, He M, Li Y. Overexpression of SIRT6 is a novel biomarker of malignant human colon carcinoma. J Cell Biochem. 2018;119(5):3957–67. doi:10.1002/jcb.26539.
9. Li N, Mao D, Cao Y, Li H, Ren F, Li K. Downregulation of SIRT6 by miR-34c-5p is associated with poor prognosis and promotes colon cancer proliferation through inhibiting apoptosis via the JAK2/STAT3 signaling pathway. Int J Oncol. 2018;52(5):1515–27. doi:10.3892/ijo.2018.4302.
10. Vander Heiden MG, Cantley LC, Thompson CB. The metabolic requirements of cell proliferation. Science. 2009;324(5930):1029–33. doi:10.1126/science.1160809.