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Chloride intracellular channels in oncology as potential novel biomarkers and personalized therapy targets: a systematic review

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ABSTRACT

Background: The chloride intracellular channels (CLICs) family includes six ion channels (CLIC1-CLIC6) expressed on the cellular level and secreted into interstitial fluid and blood. They are involved in the physiological functioning of multiple systems as well as the pathogenetic processes of cancer. CLICs play essential roles in the tumor microenvironment. The current systematic review aimed at identifying and summarizing the research of CLICs in oncology on clinical material to assess CLICs' potential as novel biomarkers and personalized therapy targets.

Materials and methods: The authors systematically searched the PubMed database for original articles concerning CLIC research on clinical material of all types of cancer — fluids and tissues.

Results: Fifty-three articles investigating in summary 3944 clinical samples were qualified for the current review. Studied material included 3438 tumor samples (87%), 437 blood samples (11%), and 69 interstitial fluid samples (2%). Studies investigated 21 cancer types, mostly hepatocellular carcinoma, colorectal, ovarian, and gastric cancer. Importantly, CLIC1, CLIC2, CLIC3, CLIC4, and CLIC5 were differently expressed in cancerous tissues and patients' blood compared to healthy controls. Moreover, CLICs were found to be involved in several cancer-associated signaling pathways, such as PI3K/AKT, MAPK/ERK, and MAPK/p38.

Conclusion: CLIC family members may be candidates for potential novel cancer biomarkers due to the contrast in their expression between cancerous and healthy tissues and secretion to the interstitial fluid and blood. CLICs are investigated as potential therapeutic targets because of their involvement in cancer pathogenesis and tumor microenvironment.

Key words: biomarker; therapy target; targeted treatment; microenvironment; CLIC1; CLIC4; liquid biopsy

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Introduction

Novel oncological treatment strategies pursue individualization. Personalized therapies are becoming accessible due to extensive investigation of cancer biomarkers and targeted treatment [1]. Worldwide research leads to the development of combinatorial therapies targeting multiple cancer-associated processes [2]. A comprehensive investigation of tumor microenvironment (TME) increases the number of possible diagnostic and therapeutic targets [3]. Recent oncological

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research focuses on various types of potential predictive factors, such as microRNA [4], cancer-associated fibroblasts [5], or neutrophil-to-lymphocyte ratio [6]. The current article presents a promising group of molecules with the potential to influence future personalized oncological treatment.

The chloride intracellular channels (CLIC) family contains six genes encoding ion channels — CLIC1, CLIC2, CLIC3, CLIC4, CLIC5, and CLIC6. On the cellular level, CLICs are located in membranes and cytoplasm in soluble forms [7]. They are expressed in several organs and systems and play particular roles in cellular processes, including ion channel activity, phagosomal acidification, endosomal trafficking, and angiogenesis [8]. CLICs take part in multiple physiological processes of cardiovascular, respiratory, and nervous systems, but also in pathological conditions of these, as well as in hearing impairment and cancer development [9].

CLICs expression is deregulated in various types of cancers, as they are involved in carcinogenetic processes on the molecular level [9]. Several papers reported a significant role of CLICs in the TME, including correlation with immune cells infiltration, taking part in progression and metastasis, and CLIC1 secretion into interstitial fluid [10–13]. Cancer cells secrete CLIC proteins into blood, enabling a potentially feasible approach to monitor their level by the conception of *liquid biopsy* [11, 14–18]. In the literature, most CLIC-related articles concern CLIC1 and CLIC4 — other family members received less scientific attention.

The current systematic review aimed at identifying and summarizing research papers concerning the potential use of CLICs in oncological diagnostics and personalized treatment.

Materials and methods

The authors searched the PubMed database using the 'chloride intracellular channel AND cancer' formula. Inclusion criteria were original papers investigating CLICs in all types of cancer performed on the clinical material. Exclusion criteria were reviews and original articles concerning only bioinformatic analyses, animal studies, or *in vitro* experiments without clinical material investigation and articles unrelated to cancer. Systematically qualified studies were collated in the comparative tables and discussed in the narrative summary. Following data were extracted: article's authors, publication year, cancer type, research type, potential application of investigated CLIC, and the type of studied material. We present the process of identification of articles on the flow diagram (Fig. 1).

Results

Data acquisition

PubMed search identified 587 records. Following the screening of titles and abstracts, 385 papers were rejected. Afterwards, following analysis of full-text articles, 53 articles were qualified for the current review (Tab. 1). The articles related to particular chloride intracellular channels were: CLIC1 — 37 pieces, CLIC2 — 2 pieces, CLIC3 — 2 pieces, CLIC4 — 8 pieces, and CLIC5 — 4 pieces. We identified no articles reporting CLIC6 original research.

Qualified articles investigated in summary 3944 clinical samples: tumor tissue — 3438 samples (87%) [15, 19–61], blood collected from cancer patients — 437 samples (11%) [11, 14–18, 62], and interstitial fluid from breast cancer microenvironment — 69 samples (2%) [63]. The mean of analyzed samples in a study was 74, the median was 60, the minimum was three samples [39], and the maximum was 421 [57]. Research material included only clinical samples in 27 articles (51%), clinical samples and *in vitro* experiments in 16 pieces (30%), clinical samples, *in vitro* and animal experiments in 6 articles (11%), and clinical samples and bioinformatic analyses in 4 articles (8%).

The potential role of chloride intracellular channels in personalized therapy of various types of cancer

Included studies investigated CLICs on clinical samples of 21 cancer types — acute myeloid leukemia (AML), breast cancer, cervical cancer, childhood acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), clear cell renal cell carcinoma (ccRCC), colorectal cancer, esophageal squamous cell carcinoma (ESCC), gallbladder cancer (GBC), gastric cancer, glioblastoma multiforme (GBM), gliomas, hepatocellular carcinoma (HCC), lung adenocarcinoma, lower lip squamous cell carcinoma (LLSCC), nasopharyngeal carcinoma (NPC), oral squamous cell carcinoma (OSCC), ovarian cancer, pancreatic

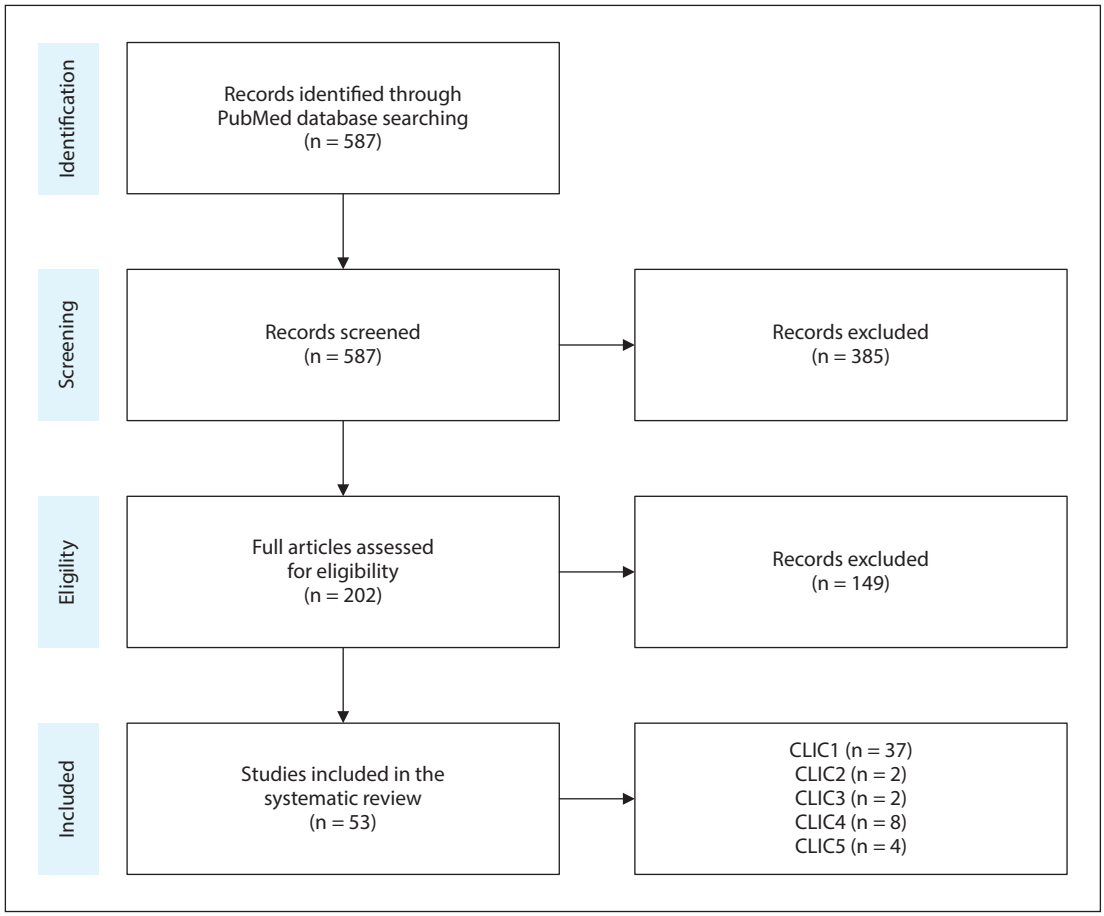

Figure 1. Flow diagram. CLIC — chloride intracellular channels

cancer, salivary gland mucoepidermoid carcinoma (MEC), and urinary bladder cancer (Tab. 2). The most research concerned HCC, colorectal cancer, ovarian cancer, and gastric cancer. All qualified studies reported significant changes in CLIC family member expression in the tissues or fluid of cancer (Tab. 3).

Discussion

The systematic review of CLIC family role in pathogenesis of various types of cancer found their significant impact on TME. CLICs expression may differ between cancerous and healthy tissue and they could be secreted into interstitial fluid and blood. Moreover, CLICs are involved in numerous cancer-associated signaling pathways such as PI3K/AKT, MAPK/ERK, and MAPK/p38. Therefore, CLIC family members may constitute as novel candidates for cancer tissue and blood biomarkers as well as therapeutic targets.

CLIC1 is the most investigated chloride intracellular ion channel. Different patterns of CLIC1 expression were found in various types of cancer in 37 studies. CLIC1 was proposed as a potential tissue, blood, and interstitial fluid biomarker, and therapeutic target. In breast cancer, Xia et al. found increased *CLIC1* gene tissue expression on the mRNA and protein level [23]. *CLIC1* overexpression correlated with poorer overall survival, tumor size, TNM stage, grading, and lymph node metastases. Authors hypothesized that CLIC1 plays a role in the invasion and metastases of breast cancer. Furthermore, Gromov et al. reported increased CLIC1 protein expression in the TME and tumor interstitial fluid compared to normal tissues [63]. Finally, Raica et al. proposed prognosis stratification based on the breast cancer type and CLIC1 protein expression in tumor and blood vessels, collectively with E-cadherin and P-cadherin [26].

In cervical cancer, Wang et al. found increased CLIC1 protein tissue expression. They proposed

Table 1. Articles concerning research on chloride intracellular channels in cancer performed on clinical material qualified to the systematic review

Author	Year	Cancer, number of clinical samples	Type of research	Potential application
CLIC1 (37 studies)				
Geng et al. [19]	2023	Esophageal squamous cell carcinoma (n = 86)	*In vitro* and clinical	Tissue biomarker
Wang et al. [62]	2023	Bladder cancer: blood serum (n = 30)*, tumor tissue (n = 66)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Wojtera et al. [14]	2023	Oral squamous cell carcinoma (n = 13), laryngeal squamous cell carcinoma (n = 7)*	Clinical	Blood plasma biomarker
Barbieri et al. [20]	2022	Glioblastoma multiforme (n = 14)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Fericiani et al. [21]	2022	Clear cell renal cell carcinoma (n = 60)	Clinical	Tissue biomarker and therapeutic target
Wei et al. [22]	2022	Hepatocellular carcinoma (n = 67)	Animal, *in vitro*, and clinical	Tissue biomarker and therapeutic target
Xia et al. [23]	2022	Breast cancer (n = 25)	Clinical	Tissue biomarker
Yasuda et al. [24]	2022	Lung adenocarcinoma (n = 74)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Geng et al. [11]	2021	Chronic lymphocytic leukemia (n = 16)*	*In vitro* and clinical	Blood biomarker and therapeutic target of CLL exosomes in the tumor microenvironment
Qiu et al. [25]	2021	Gastric cancer (n = 60)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Raica et al. [26]	2021	Breast cancer (n = 97)	Clinical	Tissue biomarker
Wang et al. [27]	2021	Cervical cancer (n = 30)	Animal, *in vitro*, and clinical	Tissue biomarker and therapeutic target
Adelmann et al. [28]	2020	Urinary bladder cancer (n = 50)	Clinical	Tissue biomarker
Jiang et al. [29]	2020	Hepatocellular carcinoma (n = 80)	Animal, *in vitro*, and clinical	Tissue biomarker and therapeutic target
Nesiu et al. [30]	2019	Clear cell renal cell carcinoma (n = 50)	Clinical	Tissue biomarker
Li et al. [31]	2018	Gastric cancer (n = 54)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Yu et al. [32]	2018	Ovarian cancer (n = 266)	Clinical	Tissue biomarker
Zhou et al. [33]	2017	Gallbladder cancer (n = 80)	Clinical	Tissue biomarker, target of hsamiR372
Jia et al. [34]	2016	Pancreatic ductal adenocarcinoma (n = 70)	Clinical	Tissue biomarker
Ding et al. [35]	2015	Gallbladder cancer (n = 75)	Clinical	Tissue biomarker
Lu et al. [36]	2015	Pancreatic cancer (n = 75)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Wei et al. [37]	2015	Hepatocellular carcinoma (n = 69)	*In vitro* and clinical	Tissue biomarker and therapeutic target
Ye et al. [38]	2015	Ovarian cancer (n = 120)	Clinical	Tissue biomarker
Cristofaro et al. [39]	2014	Gingival cancer (n = 3)	Clinical	Tissue biomarker
Megger et al. [40]	2013	Hepatocellular carcinoma (n = 26)	Clinical	Tissue biomarker
Tang et al. [16]	2013	Ovarian cancer (n = 18)*	Animal, *in vitro*, and clinical	Blood plasma biomarker
Zhang et al. [41]	2013	Hepatocellular carcinoma (n = 69), cholangiocarcinoma (n = 16)	*In vitro* and clinical	Tissue biomarker of hepatic tumor
Wang et al. [42]	2012	Gliomas (n = 128)	Clinical	Tissue biomarker
Wang et al. [43]	2011	Lung adenocarcinoma (n = 103)	Clinical	Tissue biomarker
Zheng et al. [44]	2011	Gastric adenocarcinoma (n = 40)	*In vitro* and clinical	Therapeutic target associated with PA28b
Gromov et al. [63]	2010	Breast cancer (n = 69)**	Clinical	Interstitial fluid biomarker

Table 1. Articles concerning research on chloride intracellular channels in cancer performed on clinical material qualified to the systematic review

Author	Year	Cancer, number of clinical samples	Type of research	Potential application
Chang et al. [15]	2009	Blood plasma samples*: Nasopharyngeal carcinoma (n = 70), colorectal carcinoma (n = 45), lung cancer (n = 43); Tumor samples: Nasopharyngeal carcinoma (n = 40)	*In vitro* and clinical	Tissue and blood plasma biomarker of nasopharyngeal carcinoma
Petrova et al. [45]	2008	Colorectal cancer (n = 6)	Clinical	Tissue biomarker
Chen et al. [46]	2007	Gastric cancer (n = 56)	Clinical	Tissue biomarker and therapeutic target
Blanc et al. [47]	2005	Hepatocellular carcinoma (n = 14)	Clinical	Tissue biomarker
Baek et al. [48]	2004	Erosive gastritis, peptic ulcer or gastric cancer (n = 60)	Clinical	Tissue biomarker of gastric cancer
Tomonaga et al. [49]	2004	Colorectal cancer (n = 10)	Clinical	Tissue biomarker
CLIC2 (2 studies)				
Ozaki et al. [51]	2021	Meningioma (n = 39), Glioblastoma multiforme (n = 24)	Animal, *in vitro*, and clinical	Therapeutic target in advanced GBM treatment
Ueno et al. [50]	2019	Hepatocellular carcinoma (n = 32), metastatic colorectal carcinoma located in the liver (n = 14), colorectal carcinoma (n = 6)	*In vitro* and clinical	Therapeutic target in the prevention of distant metastases
CLIC3 (2 studies)				
Chen et al. [52]	2020	Bladder cancer (n = 11)	Bioinformatic and clinical	Tissue biomarker
Wang et al. [53]	2015	Salivary gland mucoepidermoid carcinoma (n = 58)	Clinical	Tissue biomarker
CLIC4 (8 studies)				
Yokoyama et al. [54]	2021	Colorectal cancer (n = 79)	Clinical	Tissue biomarker
Huang et al. [17]	2020	Acute myeloid leukemia (n = 185)*	Bioinformatic and clinical	Blood biomarker and therapeutic target
Lima et al. [55]	2020	Lower lip squamous cell carcinoma (n = 50)	Clinical	Tissue biomarker and therapeutic target
Peng et al. [18]	2019	Epithelial ovarian carcinoma (n = 10)*	Clinical	Blood biomarker
Zou et al. [56]	2016	Pancreatic ductal adenocarcinoma (n = 106)	Clinical	Tissue biomarker
Deng et al. [57]	2014	Colorectal cancer (n = 421)	Clinical	Tissue biomarker and therapeutic target
Okudela et al. [58]	2014	Lung adenocarcinoma (n = 180), lung squamous cell carcinoma (n = 39), lung large cell carcinoma (n = 16)	*In vitro* and clinical	Tissue biomarker of lung adenocarcinoma
Yao et al. [59]	2009	Ovarian cancer (n = 30)	*In vitro* and clinical	Tissue biomarker and therapeutic target
CLIC5 (4 studies)				
Bian et al. [60]	2023	Lung adenocarcinoma (n = 167)	Bioinformatic and clinical	Tissue biomarker, immunomodulator
Huang et al. [10]	2023	Ovarian cancer (n = 29)	Bioinformatic and clinical	Tissue biomarker of changes in TME
Neveu et al. [64]	2016	Childhood acute lymphoblastic leukemia (n = 18)	*In vitro* and clinical	Therapeutic target
Flores-Téllez et al. [61]	2015	Hepatocellular carcinoma (n = 9)	Animal, *in vitro*, and clinical	Tissue biomarker

*Research investigated blood samples from cancer patients. ** Research investigated interstitial fluid from the tumor environment. CLIC — chloride intracellular channels; CLL — chronic lymphocytic leukemia; GBM — glioblastoma multiforme; TME — tumor microenvironment

Table 2. The potential role of chloride intracellular channels in personalized therapy of various types of cancer based on research on clinical sample

Type of cancer	Number of studies	CLIC1	CLIC2	CLIC3	CLIC4	CLIC5
Acute myeloid leukemia	1				Blood biomarker and therapeutic target [17]	
Bladder cancer	3	Tissue biomarker [28, 62] Therapeutic target [62]		Tissue biomarker [52]		
Breast cancer	3	Interstitial fluid biomarker [63] Tissue biomarker [23, 26]				
Cervical cancer	1	Tissue biomarker [27] Therapeutic target [27]				
Childhood acute lymphoblastic leukemia	1					Therapeutic target [64]
Chronic lymphocytic leukemia	1	Blood biomarker and therapeutic target of CLL exosomes in the tumor micro-environment [11]				
Clear cell renal cell carcinoma	2	Tissue biomarker [21, 30] Therapeutic target [21]				
Colorectal cancer	6	Tissue biomarker [45, 49]	Therapeutic target [50]		Tissue biomarker [54, 57] Therapeutic target in colorectal cancer treatment [57]	
Esophageal squamous cell carcinoma	1	Tissue biomarker [19]				
Gallbladder cancer	2	Tissue biomarker [33, 35] hsa-miR-372 target [33]				
Gastric cancer	5	Tissue biomarker [25, 31, 46, 48] Therapeutic target [25, 31, 44]				
Glioblastoma multiforme	2	Tissue biomarker and therapeutic target [20]	Therapeutic target (51)			
Gliomas	1	Tissue biomarker [42]				
Hepatocellular carcinoma	8	Tissue biomarker [22, 29, 37, 40, 41, 47] Therapeutic target [22, 29, 37]	Therapeutic target [50]			Tissue biomarker [61]

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Table 2. The potential role of chloride intracellular channels in personalized therapy of various types of cancer based on research on clinical sample

Type of cancer	Number of studies	CLIC1	CLIC2	CLIC3	CLIC4	CLIC5
Lung adenocarcinoma	4	Tissue biomarker [24, 43] Therapeutic target [24]			Tissue biomarker [58]	Tissue biomarker, immuno-modulator [60]
Lower lip squamous cell carcinoma	1				Tissue biomarker, therapeutic target [55]	
Nasopharyngeal carcinoma	1	Tumor and blood plasma biomarker [15]				
Oral squamous cell carcinoma	2	Blood plasma biomarker [14] Tissue biomarker [39]				
Ovarian cancer	6	Blood plasma biomarker [16] Tissue biomarker [32, 38]			Tissue biomarker, therapeutic target [59] Blood biomarker [18]	Tissue biomarker of changes in TME [10]
Pancreatic cancer	3	Tissue biomarker [34, 36] Therapeutic target [36]			Tissue biomarker [56]	
Salivary gland mucoepidermoid carcinoma	1			Tissue biomarker [53]		

CLIC — chloride intracellular channels; CLL — chronic lymphocytic leukemia; GBM — glioblastoma multiforme; TME — tumor microenvironment

a cancer progression pathway associated with nuclear factor kappa B (NF-κB), which could be used in treatment by regulating CLIC1 expression or its acetylation [27].

In chronic lymphocytic leukemia (CLL), Geng et al. found increased CLIC1 mRNA expression in peripheral blood mononuclear cells (PBMC) and in exosomes isolated from CLL patients compared to healthy volunteers [11]. Following these results, authors transferred exosomal CLIC1 from CLL cell culture (MEC-1) into human umbilical vein endothelial cells (HUVECs), resulting in activating ITGβ1-MAPK/ERK signaling and promoting HUVECs' proliferation, angiogenesis, and metastasis. These findings led to the hypothesis of CLIC1 as a potential therapeutic target of CLL exosomes in TME.

In clear cell renal cell carcinoma (ccRCC), Nesiu et al. stratified different ccRCC types depending on CLIC1 expression, pattern of CLIC1 distribution, and grading [30]. Furthermore, CLIC1 expression significantly correlated with metastasis in G3 tumors. In another study, Ferician et al. found CLIC1 expression in both ccRCC tumors and tumor vessels endothelium [21]. The authors classified the study group depending on CLIC1 expression in the tumor and in the tumor vessels. The CLIC1 microvessel density (CLIC1-MVD) in the group with CLIC1 expression in tumor tissues and tumor vessels endothelium correlated with tumor and metastasis staging.

In colorectal cancer, two studies found significant overexpression of CLIC1 protein in cancer tissues, suggesting CLIC1 as a colorectal cancer biomarker [45, 49].

In esophageal squamous cell carcinoma (ESSC), Geng et al. found significant overexpression of CLIC1 on the level of mRNA and protein in the cancer tissues in comparison with normal adjacent tissues and correlation of CLIC1 expression with the TNM classification [19]. Knockdown of CLIC1 in ESCC tissues inhibited cells' proliferation. Authors associated ESCC promotion by CLIC1 with mTOR signaling.

Table 3. Changes in expression of chloride intracellular channels in various types of cancer

Type of cancer	CLIC1	CLIC3	CLIC4	CLIC5
Cancer tissue expression comparing to healthy tissues				
Bladder cancer [28, 52, 62]	↑	↑		
Breast cancer [23]	↑			
Cervical cancer [27]	↑			
Chronic lymphocytic leukemia [11]	↑			
Colorectal cancer [45, 49, 54]	↑		↓	
Esophageal squamous cell carcinoma [19]	↑			
Gallbladder cancer [35]	↑			
Gastric cancer [25, 31, 46]	↑			
Glioblastoma multiforme [20]	↑			
Gliomas [42]	↑			
Hepatocellular carcinoma [22, 29, 37, 40, 41, 47, 61]	↑			↑
Lung adenocarcinoma [24, 43, 58, 60]	↑		↓	↓
Lower lip squamous cell carcinoma [55]			↑	
Nasopharyngeal carcinoma [15]	↑			
Oral squamous cell carcinoma [39]	↑			
Ovarian cancer [10, 18, 32, 38, 59]	↑		↑	↑
Pancreatic cancer [34, 36, 56]	↑		↑	
Salivary gland mucoepidermoid carcinoma [53]		↑		
Cancer patients' blood expression comparing to healthy controls				
Acute myeloid leukemia [17]			↑	
Nasopharyngeal carcinoma [15]	↑			
Oral squamous cell carcinoma [14]	↑			
Ovarian cancer [16, 18]	↑		↑	
Cancer tissues interstitial fluid expression comparing to healthy tissues				
Breast cancer [63]	↑			

CLIC — chloride intracellular channels

In gallbladder cancer (GBC), Ding et al. found significantly higher expression of *CLIC1* mRNA and protein in the cancer tissues — higher *CLIC1* expression was associated with worse prognosis and overall survival [35]. Zhou et al. reported downexpression of hsa-miR-372 in GBC tissues, which was associated with poor prognosis — finding the *CLIC1* gene to be the target for hsa-miR-372 [33].

Plenty of research was performed regarding CLIC1 in gastric cancer. Baek et al. found that CLIC1 protein is downexpressed in the gastric mucosa tissues infected by helicobacter pylori, concluding that lower CLIC1 activity might be associated with oxidative stress, cell proliferation, and carcinogenesis [48]. However, three other studies reported contrary results – CLIC1 expression is higher in gastric cancer tissues than healthy adjacent tissues [25, 31, 46]. CLIC1 high expression correlated with lymph node metastasis, TNM staging, and lymphatic and perineural invasion [25, 46]. Patients with higher CLIC1 expression had lower overall survival [46]. CLIC1 expression was correlated inversely with PA28β protein in gastric cancer tissues [44]. *In vitro* research showed CLIC1 involvement in gastric cancer progression by regulating PI3K/AKT, MAPK/ERK, and MAPK/p38 [31].

In glioblastoma multiforme (GBM), Barbieri et al. [20] found that CLIC1 mRNA and protein are highly expressed in tumor tissues. Based on *in vitro* experiments, authors concluded that CLIC1 is the biomarker of response to therapy with biguanide derivatives. Wang et al. found higher

CLIC1 mRNA expression in glioma tissues than in normal brain tissues [42]. CLIC1 protein expression correlated with World Health Organization (WHO) glioma grading. It was significantly higher in patients with low Karnofsky performance scores. High CLIC1 protein expression was associated with shorter overall survival.

Concerning hepatocellular carcinoma (HCC), six studies confirmed higher CLIC1 expression in HCC tissues compared to healthy adjacent tissues [22, 29, 37, 40, 41, 47]. High CLIC1 expression correlated with tumor size, vascular invasion, metastasis worse overall and disease-free survival, TNM staging, and Barcelona Clinic Liver Cancer (BCLC) staging [22, 29, 37, 41]. *In vitro* CLIC1 knockdown inhibited HCC cells proliferation, migration, and invasion and induced cells apoptosis [22, 29, 37].

In lung adenocarcinoma, Wang et al. found that CLIC1 protein expression in the cancer tumors correlated with the tumor staging and overall survival [43]. It was consistent with the study by Yasuda et al. who found that high CLIC1 protein expression was associated with worse overall survival [24]. *In vitro* analyses showed that CLIC1 is involved in the p38/MAPK signaling pathway — knockdown of CLIC1 inhibited proliferation and migration of lung adenocarcinoma cells.

In nasopharyngeal cancer (NPC), Chang et al. found higher CLIC1 protein expression in both tumor tissues and blood plasma than in healthy tissues and controls. CLIC1 protein expression in blood plasma was significantly higher even in early TNM stages compared to the healthy controls, suggesting it could be a feasible nasopharyngeal carcinoma biomarker [15].

In oral cancer, Cristofaro et al. found significantly higher CLIC1 protein expression in gingival squamous cell carcinoma tissues than normal tissues [39]. CLIC1 protein expression was investigated in the blood — Wojtera et al. found CLIC1 association with lymph node metastases in OSCC patients [14].

In ovarian cancer, two studies found higher expression of the *CLIC1* gene on the level of mRNA and protein in cancer tissues compared to healthy tissues and benign ovarian tumors [32, 38]. According to Ye et al., CLIC1 protein expression was higher in advanced stages of ovarian cancer, and it correlated positively with ascites volume and negatively with histopathological grading. High CLIC1 protein expression correlated with intraperitoneal metastasis — the sensitivity and specificity of CLIC1 protein expression in detecting intraperitoneal metastasis were 97.4% and 88.1%, respectively [38]. Furthermore, Yu et al. reported that high CLIC1 protein expression was associated with a worse response to cisplatin chemotherapy and poorer overall survival and progression-free survival [32]. Finally, Tang et al. found significantly higher CLIC1 protein expression in ovarian cancer patients' blood plasma compared to benign ovarian tumor patients and healthy controls [16].

In pancreatic cancer, two studies found significantly higher CLIC1 protein expression in the tumor compared to healthy adjacent tissues [34, 36]. Both studies confirmed that CLIC1 overexpression was associated with histological grading, tumor size, TNM staging, and worse overall survival. Lu et al. knocked down CLIC1, reducing pancreatic cancer cells invasion [36].

In urinary bladder cancer, two studies found significantly higher CLIC1 protein expression in the tissues of bladder cancer than in healthy adjacent tissues [28, 62]. According to Wang et al., CLIC1 expression correlated with tumor staging, and high *CLIC1* expression was associated with poor overall survival and low TME infiltration of CD8 lymphocytes [62].

Different patterns of *CLIC2* expression were found in hepatocellular carcinoma, colorectal carcinoma, meningioma, and GBM [50, 51]. Ueno et al. found decreased CLIC2 protein expression in the tumor endothelial cells, which was associated with a lack of tight junctions in hepatocellular carcinoma, colorectal carcinoma, and metastatic tumors. The authors suggested that therapeutical upregulation of CLIC2 expression might suppress cancer angiogenesis and distant metastases [50]. Ozaki et al. reported higher *CLIC2* mRNA and protein expression in grade I meningioma than in more advanced stages, associated with better progression-free survival [51].

CLIC3 overexpression was found in bladder cancer and salivary mucoepidermoid carcinoma (MEC) [52, 53]. Chen et al. reported overexpression of *CLIC3* mRNA in bladder cancer tissues and correlated the expression with poor prognosis of patients. Whereas Wang et al. found overexpression of the *CLIC3* gene and hypomethylation of its promotor region in the tissues of MEC [53].

CLIC4 is the second most studied molecule from CLIC family. Different patterns of *CLIC4* expression were found in acute myeloid leukemia (AML), colorectal cancer, lower lip squamous cell carcinoma (LLSCC), lung adenocarcinoma, ovarian cancer, and pancreatic ductal adenocarcinoma [17, 18, 54–59]. Huang et al. found significant overexpression of the *CLIC4* gene in bone marrow and $CD34^+$ peripheral blood cells of patients with AML [17]. Patients with high *CLIC4* expression had worse treatment outcomes, overall survival, and more frequent recurrences than patients with low *CLIC4* expression. The authors found several signaling and cellular pathways associated with *CLIC4* in AML with bioinformatic research.

In colorectal cancer, Yokoyama et al. found decreased CLIC4 protein expression in malignant stroma tissues compared to the adjacent normal tissues [54]. CLIC4 expression correlated negatively with tumor and TNM staging. Furthermore, Deng et al. proposed a three-protein model including CLIC4, ERp29, and Smac/DIABLO in colorectal cancer prognosis stratification, significantly predicting disease-specific survival independently of clinical features [57].

Lima et al. found higher cytoplasmatic CLIC4 (CLIC4c) protein expression in patients with advanced LLSCC compared to early stages [55]. CLIC4c expression correlated negatively with nuclear CLIC4 (CLIC4n), suggesting that the progression of LLSCC is associated with the change of CLIC4 expression pattern from the nuclear to the cytoplasmatic. In the research investigating the proteome modulated by oncogenic KRAS, Okudela et al. found decreasing levels of CLIC4 protein correlated with the progression of lung adenocarcinoma, suggesting CLIC4 may be a tumor suppressor [58]. Zou et al. found higher expression of CLIC4 protein in pancreatic ductal adenocarcinoma tissues compared to adjacent tissues, benign pancreatic lesions, and normal tissues [56]. The authors correlated CLIC4 expression with poor overall survival, tumor grading, and lymph node metastasis.

In ovarian cancer, Yao et al. found that expression of CLIC4 protein was associated with overexpression of α-SMA myofibroblast marker in the stroma of ovarian cancer tissues [59]. On the contrary, CLIC4 protein expression was absent in the stroma and surface epithelium of a normal ovary. Moreover, authors reported up-regulated CLIC4 expression associated with converting fibroblasts to myofibroblasts in ovarian cancer pathogenesis regulated by transforming growth factor beta 1 (TGF-β1), suggesting CLIC4 to be the potential therapy target. On the other hand, Peng et al. reported CLIC4 protein overexpression in blood-secreted exosomes and ovarian cancer tissues, proposing CLIC4 protein as a potential epithelial ovarian carcinoma blood biomarker [18].

Different patterns of *CLIC5* expression were found in childhood acute lymphoblastic leukemia (ALL), lung adenocarcinoma, HCC, and ovarian cancer [10, 60, 61, 64]. Bian et al. reported decreased *CLIC5* gene expression in lung adenocarcinoma tissues, which was associated with poor overall survival [60]. Authors found low *CLIC5* expression to be related with reduction of dendritic cells and T-cell inflirtation — suggesting that *CLIC5* plays a role in TME immunomodulation. On the other hand, Flores-Téllez et al. reported overexpression of CLIC5 protein in the tissues of HCC [61]. Authors suggested that CLIC5 might be a scaffold for EZR and PODXL proteins, and this complex collectively plays a role in invasion and migration of HCC cells. High CLIC5 protein expression was correlated with increased infiltration of CD163+ M2 macrophages and decreased infiltration of CD8+ T cells in the ovarian cancer TME [10]. Finally, Neveu et al. reported that *CLIC5* could be the ETV6 target gene in childhood ALL and hypothesized that CLIC5A overexpression generates a permissive environment for consecutive mutations leading to leukemic transformation [64].

The systematic review identified no original studies investigating CLIC6 in oncology. Thus, it may be an exciting area for preliminary research.

Conclusion

Current systematic research revealed growing interest in chloride intracellular channels research in oncology. Different CLICs tumor and blood expression between cancer and healthy patients provoke the potential to become easily accessible cancer biomarkers. The significant role of CLICs in signaling pathways associated with carcinogenesis makes them promising therapy targets. Further CLICs research may bring a considerable develop-

ment of personalized clinical oncology treatment strategies.

Ethical permission

Ethical approval was not necessary for the preparation of this article.

Conflict of interest

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