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Autophagy-related lncRNAs and exosomal lncRNAs in colorectal cancer: focusing on lncRNA-targeted strategies

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Abstract

Autophagy is a cellular process that involves the degradation and recycling of cellular components, including damaged proteins and organelles. It is an important mechanism for maintaining cellular homeostasis and has been implicated in various diseases, including cancer. Long non-coding RNAs (lncRNAs) are a class of RNA molecules that do not code for proteins but instead play regulatory roles in gene expression. Emerging evidence suggests that lncRNAs can influence autophagy and contribute to the development and progression of colorectal cancer (CRC). Several lncRNAs have been identified as key players in modulating autophagy in CRC. The dysregulation of autophagy and non-coding RNAs (ncRNAs) in CRC suggests a complex interplay between these two factors in the pathogenesis of the disease. Modulating autophagy may sensitize cancer cells to existing therapies or improve the efficacy of new treatment approaches. Additionally, targeting specific lncRNAs involved in autophagy regulation could potentially be used as a therapeutic intervention to inhibit tumor growth, metastasis, and overcome drug resistance in CRC. In this review, a thorough overview is presented, encompassing the functions and underlying mechanisms of autophagy-related lncRNAs in a range of critical areas within tumor biology. These include cell proliferation, apoptosis, migration, invasion, drug resistance, angiogenesis, and radiation resistance.

Keywords Colorectal cancer, Autophagy, Long non-coding RNAs, Exosomal long non-coding RNAs

Introduction

One biological mechanism that helps break down and recycle cellular components is called autophagy. Cells are able to eliminate misfolded proteins, malfunctioning organelles, and other cellular waste through this strictly controlled mechanism. The Greek terms "auto" (self) and "phagy" (eating) are the roots of the word "autophagy," which refers to the self-eating character of this activity. Maintaining cellular homeostasis, stress response, and cellular viability all depend on autophagy. By carefully removing faulty or outdated cellular components, it serves as a quality control system, limiting the buildup of dangerous materials and enhancing cell health [1, 2]. Numerous physiological systems, such as development, aging, immunology, and metabolism, are impacted by autophagy. The creation of the distinctive double-membrane structure known as the autophagosome is a step in the autophagy process. After engulfing the targeted cellular constituents, such as organelles or protein aggregates, the autophagosome merges with lysosomes to produce an autolysosome. Lysosomal enzymes break down the material sequestered within the autolysosome, recycling

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the breakdown products back into the cytoplasm for further usage.

Pathogen invasion, oxidative stress, and food scarcity are just a few of the cellular stressors that might trigger autophagy. By giving cells the essential building blocks and energy sources during times of food deprivation, it functions as a survival strategy. Furthermore, selective autophagy is the ability of autophagy to specifically target and degrade particular cellular components [2, 3]. Examples of selective autophagy include mitophagy [4], aggrephagy [5], and xenophagy [6]. Numerous illnesses, such as cancer, neurological conditions, and metabolic diseases, have been linked to dysregulation of autophagy in their etiology [3]. Autophagy may play two distinct functions in cancer: it can eliminate damaged cellular components to restrict tumor development or it can operate as a pro-survival mechanism by supplying nutrients to encourage tumor growth. Depending on the circumstances and stage of the illness, autophagy plays a different function in cancer. It has also been shown by researchers that a complex network of genes and signaling pathways controls autophagy [7]. Different proteins, such as the autophagy-related genes (ATGs), are involved in coordinating the various phases of autophagy [3]. Furthermore, a number of signaling pathways, including the mTOR pathway, are essential for controlling autophagy in response to intracellular cues [7]. It is very desirable to comprehend the molecular processes and control of autophagy for both fundamental science and therapeutic uses. Modulating autophagy has the potential to treat a number of illnesses. Improving autophagy has the potential to safeguard against neurodegenerative illnesses and increase cell viability, whereas reducing autophagy might make cancer cells more vulnerable to targeted treatments like chemotherapy.

Proteins are not encoded by ncRNAs, which are RNA molecules that are produced from the genome [8]. They are crucial regulators of a number of cellular functions, including autophagy. A subclass of ncRNAs with longer than 200 nucleotides is called lncRNAs. Through a variety of processes, including chromatin remodeling, transcriptional control, and post-transcriptional regulation, they serve as adaptable regulators of gene expression (8). Certain lncRNAs have been shown to regulate autophagy-associated gene expression and impact autophagic flux in the setting of autophagy. To influence the activities and roles of autophagy-related proteins or microRNAs (miRNAs), for instance, some lncRNAs can operate as scaffolds or decoys. Through interactions with chromatin modifiers or transcription factors, these lncRNAs can control the expression of genes relevant to autophagy. They can also change how autophagy-related mRNAs translate or remain stable [9]. Small ncRNAs, miRNAs have a length of around 21–25 nucleotides. By attaching to target mRNAs' 3′ untranslated region, they control the expression of genes by either causing translational repression or mRNA destruction. MiRNAs have been linked to the regulation of autophagy through their targeting of genes or signaling pathways involved in autophagy. Certain miRNAs have the ability to directly target and control the expression of genes associated to autophagy that are involved in the production of autophagosomes, lysosomal activity, or autophagy regulation. MiRNAs can affect cellular homeostasis and the autophagic process in general by modifying the expression of these genes. Dysregulation of lncRNAs and autophagy has been linked to the onset, spread, and response to therapy of cancer. In cancer, lncRNAs have been linked to the control of autophagy [9].

LncRNAs

Diversity in the genomic origins of lncRNAs is evident; they might arise from enhancer regions, their own promoters, or shared promoters with differently transcribed coding or non-coding genes [10]. This broad range of genomic regions from which lncRNAs arise contributes to their functional diversity and regulatory roles. Previous studies have uncovered a wide range of lncRNAs within the human genome, which are regarded as potential transcripts devoid of protein-coding ability. However, a notable observation from these studies is that a significant proportion of these lncRNAs possess certain features, such as a poly-A + tail and a 5′ cap, which are typically associated with protein-coding mRNAs [11]. LncRNAs lack open reading frames (ORFs) that can be translated into proteins, in contrast to mRNAs, which act as templates for the creation of proteins. Rather, lncRNAs undergo transcription and processing to produce RNA molecules with functional activities that are unrelated to the creation of proteins [12]. Additional research has indicated the existence of lncRNAs that have a greater potential to encode peptides. This inference is drawn from their genomic proximity to protein-coding genes that have shorter and fewer exons [13]. lncRNAs have distinct evolutionary patterns that have been preserved, and they frequently show a greater degree of tissue specialization [14]. Many known lncRNAs control many regulatory paradigms, according to years of extensive research. These lncRNAs have a large effect on a wide range of cellular functions and are functionally associated with both normal development and the pathophysiology of different disorders [15].

Numerous parameters, including the length of the transcripts, their correlation with annotated protein-coding genes, their resemblance to mRNAs, and other distinctive characteristics, have been taken into consideration

in order to identify different types of lncRNAs [16]. LncRNAs exert a substantial influence on diverse facets of both human development and the onset and progression of diseases [17]. Gaining a comprehensive understanding of the process of lncRNA biogenesis is crucial, as it serves two key purposes. Firstly, it helps in distinguishing lncRNAs from other types of RNA, enabling researchers to identify and classify them accurately. Furthermore, it is essential in elucidating the functional importance of long noncoding RNAs. The biogenesis of lncRNAs is intricately linked to the specific cell type and developmental stage in which they are produced. Different cell types and stages of development exhibit distinct patterns of lncRNA expression and processing. The many stimuli that are unique to the corresponding cell types and developmental stages control this specialization in biogenesis [18]. Several DNA elements present in eukaryotic genomes, such as intergenic regions, promoters, and enhancers, are the source of transcription for several classes of lncRNAs (Fig. 1) [19].The process of lncRNA biogenesis encompasses several mechanisms. These consist of the addition of caps made up of short nucleolar RNA (snoRNA) and protein (snoRNP) complexes at their ends, the cleavage of lncRNA precursors by ribonuclease P (RNaseP) to produce mature ends, and the creation of circular structures [20]. It has been discovered recently that there are unique sub-nuclear structures known as "paraspeckles." These structures are seen to emerge during the biogenesis of certain lncRNAs in close proximity to one another [21]. They are characterized by their unique morphology and composition, consisting of a core structure surrounded by a less dense shell. Although the precise mechanisms governing the synthesis and regulation of different lncRNAs remain elusive, ongoing studies are anticipated to greatly advance our comprehension of lncRNA biogenesis and functions in the foreseeable future. It will be possible for researchers to investigate the complex mechanisms and regulatory networks behind lncRNA production and function thanks to a variety of approaches and methodologies [22, 23].

Numerous lncRNAs have been linked to a broad spectrum of illnesses, including diabetes, rheumatoid arthritis, neurological diseases, atherosclerotic coronary artery disease, and several forms of cancer [24]. In fact, it has been shown that lncRNAs can participate in both activation and inhibition of gene expression, according to recent research findings. It has been discovered that lncRNAs take part in a variety of processes that control the amounts of gene expression (25–27). For instance, some lncRNAs function as scaffolds, bringing together multiple proteins to form ribonucleoprotein complexes. These complexes facilitate the assembly of regulatory complexes involved in transcriptional regulation or chromatin remodeling [28]. Additionally, certain lncRNAs act as decoys by binding to specific transcription factors, preventing their interaction with target DNA sequences. This sequestration of transcription factors disrupts their intended binding sites, thereby modulating gene

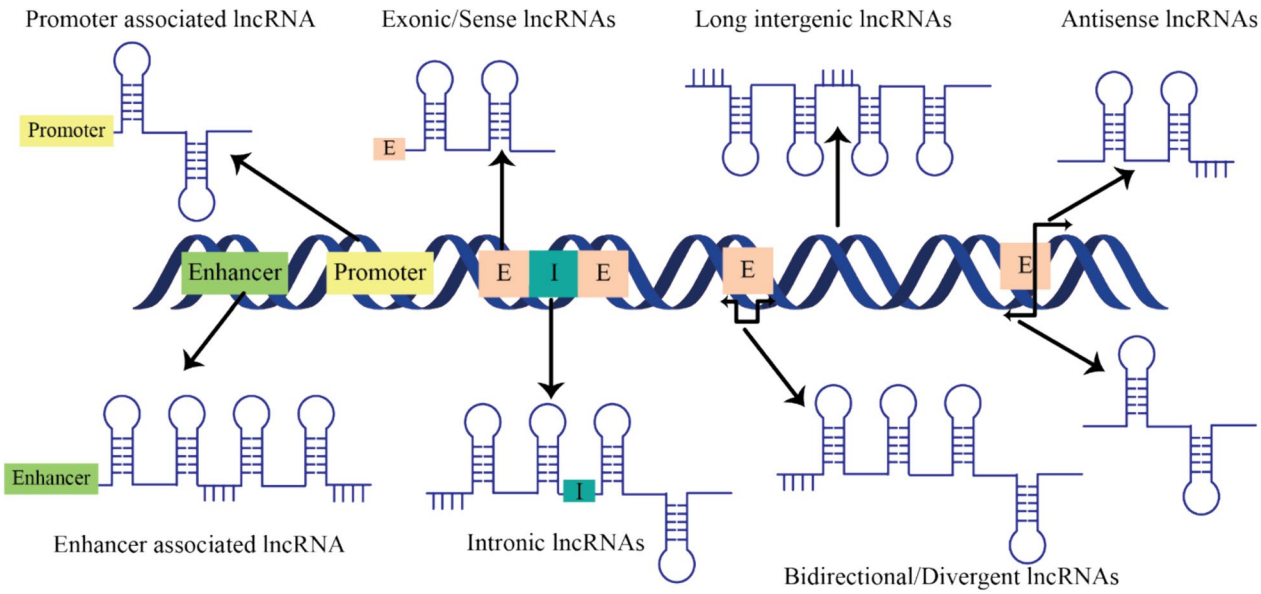

Fig. 1 Long non-coding RNAs are widely distributed throughout the genome in a variety of locations. The figure illustrates the different types of lncRNAs categorized by their transcriptional sources: a) complete or partial natural antisense transcripts (NAT), b) coding genes, c) intergenic regions, d) within introns, e) promoters, and f) enhancers (I = Intron; E = Exon)

expression [29, 30]. Furthermore, select lncRNAs serve as guides or templates, facilitating the recruitment of chromatin-modifying complexes to specific genomic loci. By guiding these complexes to their target sites, these lncRNAs contribute to alterations in chromatin structure and subsequent changes in gene expression [31]. Moreover, specific lncRNAs can function as signaling molecules or intermediates in cellular signaling pathways. They engage in interactions with proteins or other RNAs, transmitting signals and influencing downstream gene expression programs [32].

Autophagy

Programed cell death (PCD) of type II includes autophagy [1]. Two important cellular processes that keep the equilibrium of cellular proteins are autophagy and the ubiquitin–proteasome system (UPS) (Fig. 2). But their functions are different; the UPS plays a major part in the quick degradation of short-lived proteins, whereas autophagy breaks down long-lived proteins and organelles [33]. Under typical circumstances, autophagy aids in preserving the metabolic balance of cells and enhancing their ability to survive. After cellular constituents are broken down in lysosomes, the breakdown products are discharged back into the cytoplasm, where they are reconverted to produce energy [34]. Nevertheless, autophagy is essential for maintaining cellular homeostasis under stressful conditions such as low oxygen levels, starvation, DNA damage, and pathogen invasion. It helps flush out intracellular infections, destroys damaged organelles like the mitochondria and endoplasmic reticulum, and helps remove misfolded or clumped proteins. Eliminating these components results in a major upregulation of this process to provide adequate quality control [35]. On the other hand, excessive or inadequate autophagy can cause cell death. As a result, deficiencies in autophagy have been linked to the emergence of a number of illnesses, such as cancer and neurological conditions [36]. The function of autophagy in cancer biology is multifaceted and situational. It can function as both a tumor promoter and a tumor suppressor, having opposing effects on the onset and spread of tumors. Through its function as a tumor suppressor, autophagy helps to preserve cellular homeostasis by removing damaged proteins and organelles and halting the build-up of potentially hazardous cellular constituents. By eliminating damaged DNA and controlling cell development and division, it can also aid in limiting genomic instability and preventing the beginning of tumors. In this way, autophagy serves as a preventative measure against the growth of cancer. But autophagy can play a different function when cancer advances. When the tumor microenvironment is subjected to stressors such as hypoxia, food restriction, or other common circumstances, autophagy has the ability to increase the survival rate of tumor cells. Autophagy is a process that allows cancer cells adapt to hostile environments and survive by recycling internal components and producing energy. This process enables the cancer cells to multiply, develop, and resist treatment interventions. Autophagy functions as a pro-tumorigenic mechanism in this situation. Therapeutic intervention is challenged by the dual nature of autophagy in cancer biology. Clinical trials and continuing research are being conducted on autophagy targeting as a potential cancer therapy.

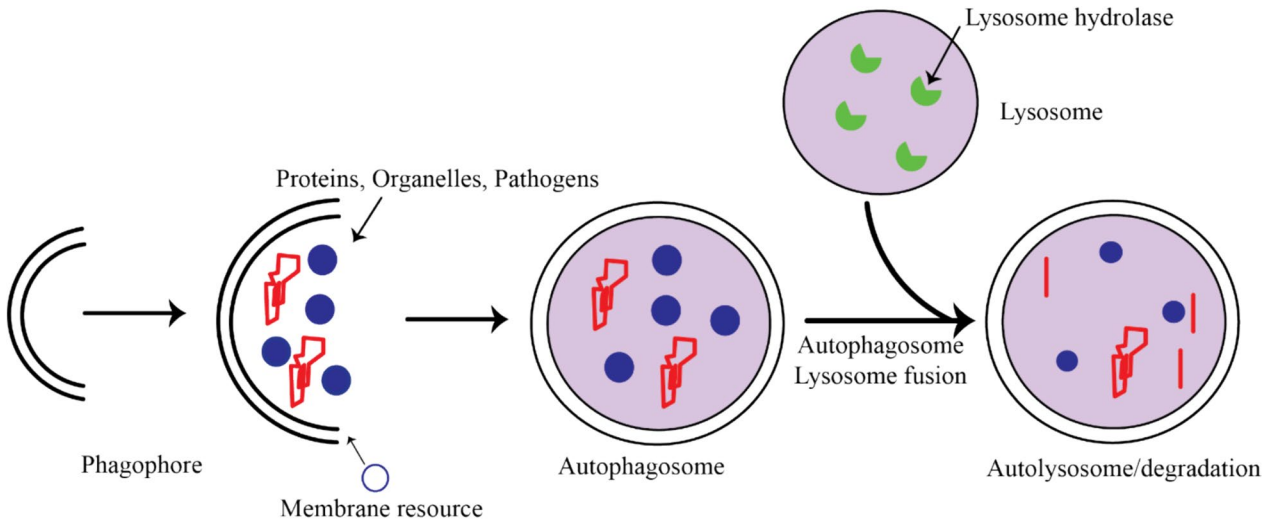

Fig. 2 Basic molecular diagram of the autophagy process

The objective is to create methods for modulating autophagy selectively in order to inhibit tumor development and improve the efficacy of cancer treatments [37].

Types of autophagy

Depending on how it enters the lysosome, autophagy may be divided into three categories: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy (Fig. 3). The most well-known and thoroughly researched kind of autophagy is macroautophagy. A double-membrane structure known as an autophagosome develops around the cargo that is going to be degraded during macroautophagy. After then, an autophagosome and a lysosome combine to create an autolysosome, where lysosomal enzymes degrade the cargo. The turnover of damaged organelles, intracellular pathogens, and long-lived proteins is largely dependent on macroautophagy [38]. The direct engulfment of cytoplasmic components via invagination or protrusion of the lysosomal membrane characterizes microautophagy, in contrast to macroautophagy. This happens when the cargo inside the lysosome is engulfed by the lysosomal membrane as it invaginates or bulges inward. More research is needed to fully understand the roles and regulatory processes of microautophagy, which is thought to be less well-characterized than macroautophagy [39]. CMA is a mechanism of selective autophagy that specifically targets and degrades certain proteins. In CMA, the chaperone protein Hsc70 recognizes cytosolic proteins that have a particular recognition pattern known as the KFERQ motif. The lysosomal membrane receptor LAMP2A is subsequently bound by the Hsc70-chaperoned proteins, causing their translocation across the membrane to be degraded. Unlike macroautophagy, which breaks down cargo in large quantities, CMA breaks down individual proteins [1]. Although research on autophagy's function in cancer has mostly focused on macroautophagy, the significance of microautophagy and CMA in the genesis and spread of tumors is being increasingly acknowledged.

ATGs are a class of evolutionarily conserved genes that precisely regulate the dynamic production and subsequent disintegration of autophagosomes, which are structures made up of two membranes that seize cellular

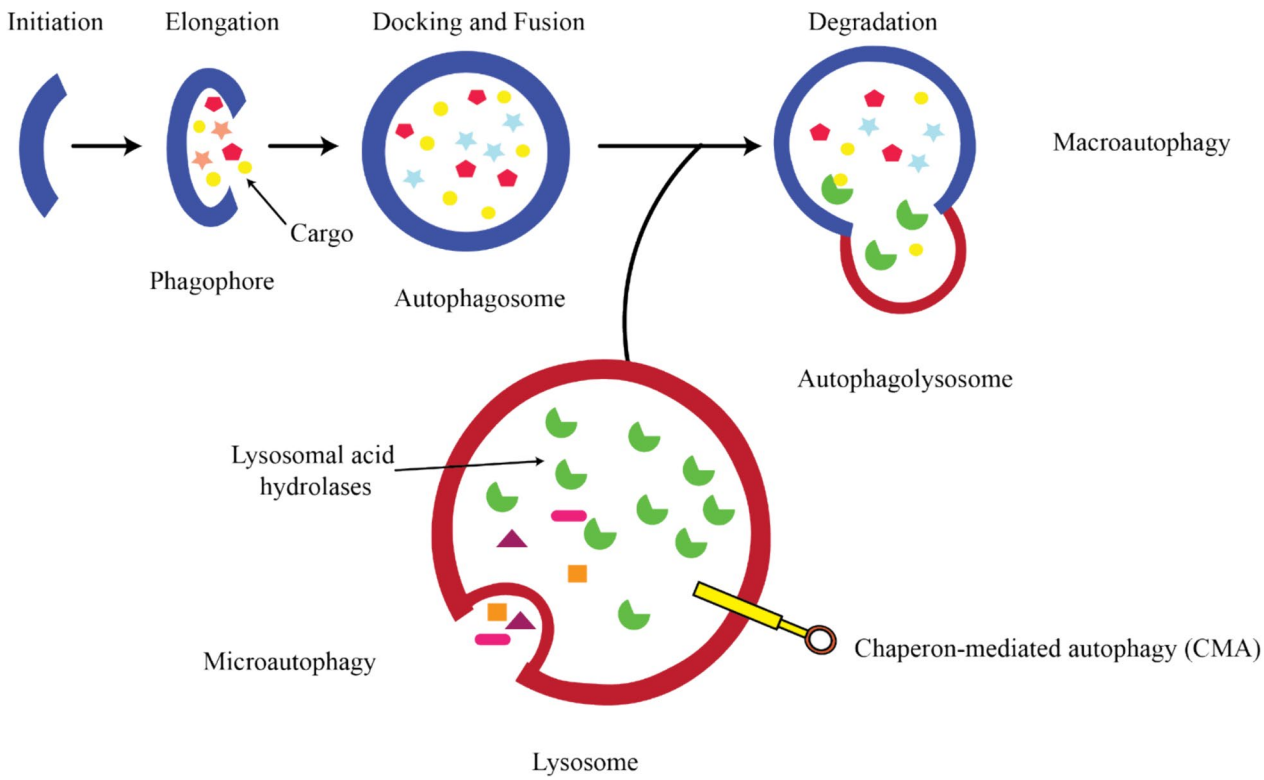

Fig. 3 There are three primary forms of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). In macroautophagy, an isolation membrane called the phagophore surrounds a section of cytoplasm, creating a double-membraned structure known as an autophagosome. This autophagosome then merges with a lysosome to form an autophagolysosome, where lysosomal enzymes break down the cytoplasmic materials. In contrast, microautophagy involves the direct invagination of the lysosomal membrane to facilitate cargo delivery

components for destruction. These ATGs make sure that autophagy is carried out correctly by coordinating the several stages that are involved [40]. In response to cellular stress or nutritional restriction, autophagy is triggered by blocking the mTOR pathway, which typically inhibits autophagy. The recruitment and assembly of protein complexes such as ULK1 and PI3K nucleates the phagophore, which functions as the precursor structure of the autophagosome, subsequent to termination. These complexes synchronize the development of the phagophore assembly site (PAS), which serves as the production platform for autophagosomes. Later, other protein complexes such as ATG12-ATG5-ATG16L1 help the phagophore lengthen and grow into the autophagosomal membrane by facilitating the conjugation of LC3 to phosphatidylethanolamine (PE). The autophagosomal membrane's elongation and closing depend on LC3-II, the lipidated form of LC3. Autophagosomes selectively engulf particular cellular components, including intracellular infections, protein aggregates, and damaged organelles, resulting in the identification of specific cargo. Cargo is sequestered into the expanding autophagosome with the help of autophagy receptors such as p62/SQSTM1, NBR1, and NDP52, which bind to both the cargo and LC3-II on the autophagosomal membrane. After autophagosomes are generated, they develop by merging with lysosomes to become autolysosomes. The HOPS complex and proteins like SNAREs interact during this fusion process. The breakdown of the trapped cargo by lysosomal enzymes is made possible by the union of autophagosomes and lysosomes. Autophagosome production is a tightly controlled process that depends on the synchronization of many protein complexes and signaling pathways. Any abnormalities in regulation of this process's steps might impair autophagy and exacerbate a number of pathological ailments, including as cancer, neurological illnesses, and metabolic problems.

The dual regulatory roles of autophagy in CRC

Autophagy is thought to play a crucial role in preserving the integrity of the intracellular environment, and a variety of human illnesses are linked to irregularities in autophagy. This is supported by a wealth of data. Furthermore, the development of cancer and its resistance to treatment are both dynamically influenced by autophagy (Fig. 4). Still, there has long been disagreement concerning the particular functions of autophagy in different kinds of cancer [41].

Tumor-suppressive role of autophagy in CRC

Autophagy is well acknowledged as a system that impedes the growth of tumors by averting the buildup of damaged proteins and organelles, preserving cellular equilibrium, and thwarting genetic instability in CRC (Table 1) [42, 43]. Beclin1 suppresses tumor growth in CRC by promoting autophagy-mediated apoptosis and preventing cell division. It has been demonstrated that overexpressing Beclin1 increases autophagy flux, which causes a decrease in CRC cell survival and an increase in the breakdown of cellular constituents [44]. Based on real-world data, an investigation has shown that autophagy may contribute to the effectiveness of cetuximab, a targeted treatment for CRC. The study discovered that in patients with advanced CRC, higher expression of Beclin1, a crucial autophagy regulator, and lower levels of 4E-binding protein 1 (4E-BP1) were independently linked to prolonged overall survival. The results imply that autophagy—which is suggested by elevated Beclin1 expression—may have a role in improving the response to cetuximab therapy in CRC. Given that Beclin1 expression is linked to the stimulation of autophagy, high expression levels of this protein may enhance the anti-tumor effects of cetuximab [45]. CRC patients with microsatellite instability have been shown to contain frameshift mutations of the ultraviolet irradiation resistance-associated gene (UVRAG), ATG2B, ATG5, and ATG9B. ATG2B, ATG5, ATG9B, and UVRAG are among the autophagy-related genes that experience frameshift mutations as a result of mistakes in the mismatch repair machinery, which is compromised in CRC cases with microsatellite instability [46].

Tumor-promoting role of autophagy in CRC

Although autophagy is typically acknowledged as a tumor suppressor process, there are instances where it can actually facilitate tumor progression. Autophagy has the potential to contribute to the survival, proliferation, and resistance of tumor cells to treatment in the setting of established CRCs (Table 1.). Autophagy can be triggered as a response to different anti-cancer treatments, such as chemotherapy and targeted therapies. In certain instances, the activation of autophagy can aid tumor cells in surviving these treatments, resulting in resistance to therapy and the potential for tumor recurrence. Blocking the activity of ATG4B could potentially decrease autophagy, leading to increased sensitivity of CRC cells to therapeutic agents [47]. According to a clinical study, normal cells in advanced cancer patients exhibited significant downregulation of the ATG4D gene compared to CRC cells [48]. Another important gene linked in autophagy, ATG7, is essential in avoiding CRC cell death. In CRC, ATG7 suppression or knockdown can cause apoptosis and improve the efficacy of treatment [49]. According to new research, CRC cells' radiosensitivity can be significantly increased by a combination treatment that includes the autophagy inhibitor chloroquine

Fig. 4 The roles of autophagy in promoting and suppressing tumors in colorectal cancer

and the mTOR inhibitor tesirolimus. This synergistic treatment method holds potential for enhancing radiotherapy's therapeutic effectiveness in CRC [50] (Tables 2, 3).

LncRNAs control signaling pathways in CRC

More and more research is identifying lncRNAs as critical modulators of CRC development. They may have an impact on the onset, growth, invasion, metastasis, and responsiveness to therapy of the tumor, among other aspects of CRC development and progression. Certain lncRNAs act as tumor suppressors, inhibiting CRC progression [42, 43]. Examples include lncRNA MEG3, which suppresses CRC cell growth and induces apoptosis, and lncRNA GAS5, which inhibits CRC cell proliferation. Conversely, several lncRNAs function as oncogenes in CRC. For example, lncRNA HOTAIR stimulates the invasion, migration, and multiplication of CRC cells. Among the ways that lncRNAs control CRC pathogenesis are as follows:

Epigenetic regulation

LncRNAs can influence CRC pathogenesis through epigenetic mechanisms [51]. Various mechanisms have been proposed to explain how lncRNAs regulate gene expression at the transcriptional level. LncRNAs are increasingly recognized for their role in mediating epigenetic modifications of DNA through their influence on chromatin status and structure [52]. At the human HOX loci, numerous lncRNAs are involved in regulating gene expression through their interactions with RNA polymerase and histone modification enzymes. LncRNAs can assist RNA polymerase in the transcription of HOX genes. By binding to specific regions, they help stabilize the transcription machinery, facilitating effective gene expression. LncRNAs can recruit histone-modifying

Table 1 The role of lncRNAs in colorectal cancer, with a focus on its autophagy

LncRNAs	Dysregulation in CRC	Autophagy in CRC	Role	CRC pathogenesis	Target	Model (human in vitro, in vivo,)	Cell lines	Refs.
LncRNA GAS5	↓	Inhibition	Suppressesor	Suppress	miR-34a, SIRT1, mTOR	Human, in vitro, in vivo	FHC, HT29, HCT116, SW480, SW620	[42]
LncRNA HOTAIR	↑	Promotion	Oncogene	Enhance	miRNA-93/ATG12	Human, in vitro, in vivo	FHC,HT29, SW20, HCT116, SW480	[84]
LncRNA EGOT	↑	Inhibition	Oncogene	Enhance	LC3II/I, Beclin1, P62	Human, in vitro, in vivo	SW480, SW620, SW1116, LoVo, CaCo2,NCM460	[96]
LncRNA LINC00858	↑	Inhibition	Oncogene	Enhance	WNK2	Human, in vitro, in vivo	HCT116	[98]
LncRNA CPS1-IT1	↓	Promotion	Oncogene	Enhance	LC3-II, HIF-1α	Human, in vitro, in vivo	SW620, LS174T, LoVo, HCT116, HT29, SW480, HUVEC	[85]
LncRNA NEAT1	↑	Promotion	Oncogene	Enhance	P 62, LC3-II/LC3 miR-138, SLC38A1	Human, in vitro, in vivo	HCoEpiC, SW480, SW620	[74]
LncRNA NEAT1	↑	Promotion	Oncogene	Enhance	miR-34a	Human, in vitro	FHC, HT29, HCT8, HCT116, SW480, SW620	[75]
LncRNA POU3F3	↑	Inhibition	Oncogene	Enhance	SMAD4	Human, in vitro	LOVO, SW480	[91]
LncRNA UCA1	↑	Promotion	Oncogene	Enhance	AKT/mTOR	in vitro	293T, LoVo, HT29, HCT116, Caco-2	[117]
LncRNA UCA1	↑	Promotion	Oncogene	Enhance	miR-23b-3p, ZNF281	Human, in vitro	SW480,SW620, 293T	[118]
LncRNA UCA1	↑	Promotion	Oncogene	Enhance	miR-185-5p, WISP2	in vitro, in vivo	CCD-18Co, HIEC-6, SW620,HT29	[56]
LncRNA SNHG6	↑	Promotion	Oncogene	Enhance	miR-26a-5p,ULK1	Human, in vitro, in vivo	RKO,HT29, HCT116	[83]
LncRNA SNHG8	↑	Promotion	Oncogene	Enhance	ATG7, miRNA-588	In vitro	HCT116, FHC, HCT8, HT29, SW480	[76]
LncRNA SNHG14	↑	Promotion	Oncogene	Enhance	miR-186, ATG14	Human, in vitro, in vivo	SW620, SW480, NCM460, 293 T	[77]
LncRNA CASC2	↓	Inhibition	Oncogene	Enhance	miR-19a, NF-κB	In vitro	HT29, SW620, SW480, NCM460	[62]

Table 1 (continued)

LncRNAs	Dysregulation in CRC	Autophagy in CRC	Role	CRC pathogenesis	Target	Model (human in vitro, in vivo,)	Cell lines	Refs.
LncRNA CASC2	↓	Inhibition	Oncogene	Enhance	miRNA-214,TRIM16	Human, in vitro	CCD-18Co, HT-29, SW-948, RKO, SW480	[78]
LncRNA CASC9	↑	Inhibition	Oncogene	Enhance	mTOR	Human, in vitro	DLD1, HT-29, SW480, HCT-116, CCD-112CoN	[90]
LncRNA SP100-AS1	↑	Promotion	Oncogene	Enhance	miR-622, ATG3,	Human, in vitro, in vivo	HCT116, SW480, LS174T, CT26, HT29, LoVo	[79]
LncRNA SLCO4A1-AS1	↑	Promotion	Oncogene	Enhance	miR-508-3p,PARD3	Human, in vitro and in vivo	HT29, SW620, LOVO, DLD-1, HCT116, SW480, RKO, NCM460	[80]
LncRNA MALAT1	↑	Promotion	Oncogene	Enhance	miR-101, p62/SQSTM1 and LC3	Human, in vitro	FHC, HT29, HCT116, SW480, SW620	[81]
LncRNA MALAT1	↑	Promotion	Oncogene	Enhance	miR-26a-5p, BMP2, Smad1, ATG5	Human, in vitro, in vivo	HT29, SW1116	[82]
LncRNA H19	↑	Promotion	Oncogene	Enhance	miR-194–5p,SIRT1	Human, in vitro	HCT8, HCT8Fu, SW1116, HCT116, HT29, Lovo, SW480, CCD-18Co SW620	[85]
LncRNA LINC01871	↓	Promotion	Oncogene	Enhance	miR-142-3p, ZYG11B	Human, in vitro	SW480, HCT116, HT29,SW620, FHC	[85]
LncRNA FIRRE	↑	Promotion	Oncogene	Enhance	PTBP1, BECN1	Human, in vitro	RKO, HCT116, HT-29, FHC,293T, SW480,SW620	[102]
LncRNA 1p36.3	↓	Inhibition	Oncogene	Enhance	BECN1, p62	In vitro and in vivo	HCT116DKO, HCT116	[156]
LncRNA TUG1	↑	Promotion	Oncogene	Enhance	miR-195-5p, HDGF, DDX5,β-catenin	Human, in vitro, in vivo	FHC,LS513, HT-29, HCT15, LoVo, DLD-1	[86]
LncRNA LARP6	↓	Inhibition	Oncogene	Enhance	ZNF267/SGMS2	Human, in vitro, in vivo	NCM460, SW480, DLD1, RKO, LOVO, CACO2, HCT116, SW620	[105]
LncRNA LINRIS	↑	Inhibition	Oncogene	Enhance	IGF2BP2/MYC	Human, in vitro, in vivo	CCD841, HCT116, DLD-1	[106]
LncRNA RP4	↑	Inhibition	Suppresse-sor	Suppress	miR-7-5p, SH3GLB1,PI3K/Akt	In vitro	SW480 cells	[43]
LncRNA CKMT2-AS1	↑	Promotion	Suppresse-sor	Suppress	LC3II/LC3I	In vitro	SW480, HCT116	[43]

Table 1 (continued)

LncRNAs	Dysregulation in CRC	Autophagy in CRC	Role	CRC pathogenesis	Target	Model (human in vitro, in vivo,)	Cell lines	Refs.
LncRNA CERS6-AS1	↑	Promotion	Oncogene	Enhance	miR-6838-5p, RUBCNL	Human, in vitro, in vivo	HTC116, SW620, DLD1,HT29, FHC	[87]
LncRNA CTA-941F9.9	↓	Inhibition	Oncogene	Enhance	LC3-II	Human, in vitro	HCT116,HT29,RKO	[107]
LncRNA KcnQ1OT1	↑	Promotion	Oncogene	Enhance	miR-34a/ATG4B	Human, in vitro, in vivo	HCT116,SW480	[88]

Table 2 Autophagy-related lncRNAs that regulate tumor drug resistance and radiation resistance

LncRNA	Dysregulation in CRC	Autophagy	Mechanisms of Autophagy	Drug	Drug resistance	Radiation resistance	Refs.
LncRNA CKMT2-AS1	↑	Promotion	LC3II/LC3I	5-FU	Suppress	–	
LncRNA HOTAIR	↑	Promotion	miRNA-93/ATG12	–	–	Promote	[84]
LncRNA NEAT1	↑	Promotion	miR-34a	5-FU	Promote	–	[75]
LncRNA UCA1	↑	Promotion	miR-23b-3p/ZNF281	5-FU	Promote	–	[118]
LncRNA SNHG14	↑	Promotion	miR-186, ATG14	Cisplatin	Promote	–	[77]
LncRNA LINC01871	↓	Promotion	miR-142-3p, ZYG11B	5-FU	Promote	–	[85]
LncRNA SNHG6	↑	Promotion	miR-26a-5p,ULK1	5-FU	Promote	–	[83]
LncRNA SP100-AS1	↑	Promotion	miR-622, ATG3	–	–	Promote	[79]
LncRNA RNA H19	↑	Promotion	miR-194–5p,SIRT1	5-FU	Promote	–	[85]
LncRNA TUG1	↑	Promotion	miR-195-5p, HDGF, DDX5,β-catenin	Cisplatin	Promote	–	[86]
KcnQ1OT1	↑	Promotion	miR-34a/ATG4B	Oxaliplatin	Promotes	–	[88]

enzymes, such as methyltransferases and acetyltransferases, to the HOX loci [52]. This recruitment leads to specific histone modifications that alter chromatin structure. Through these interactions, lncRNAs play a crucial role in modifying chromatin status, transitioning between open (active) and closed (inactive) configurations. This dynamic change influences the accessibility of DNA for transcription. Dysregulation of lncRNAs at HOX loci can lead to aberrant gene expression patterns, contributing to developmental disorders and cancers. LincRNAs are a subset of lncRNAs that are transcribed from regions between protein-coding genes. They play distinct regulatory roles in gene expression [53]. LincRNAs are often associated with specific histone modifications, particularly trimethylation of lysine 4 (H3K4me3) and lysine 36 (H3K36me3) of histone 3. These marks are indicative of active transcription and are crucial for the regulation of lincRNA expression. LincRNAs can interact with polycomb repressive complexes (PRCs), a key complex involved in gene silencing [53]. This interaction helps lincRNAs recruit PRC2 to specific genomic regions. When bound to PRC2, lincRNAs facilitate the trimethylation of histone H3 at lysine 27 (H3K27me3). This modification is associated with transcriptional repression and contributes to the establishment of a repressive chromatin environment. The recruitment of PRC2 and associated proteins by lincRNAs leads to changes in chromatin structure. This alteration can compact the chromatin, making it less accessible to the transcriptional machinery. By varying the histone modifications and chromatin architecture, lincRNAs help suppress transcriptional activity of target genes, effectively silencing them [53]. HOTAIR is one of the most well-studied lincRNAs and transcribed from the homeobox C gene cluster. HOTAIR recruits PRC2 to specific genomic regions, leading to the trimethylation of histone H3 at lysine 27. This modification is associated with transcriptional repression. The overexpression of HOTAIR has significant implications for epithelial cancer cells, particularly related to polycomb proteins and metastatic behavior. In CRC, studies have shown that patients with overexpression of HOTAIR tend to have a poorer prognosis compared to those with low levels of this lincRNA [54].

Signaling pathways

LncRNAs have become significant modulators of gene expression and biological processes, encompassing the control of signaling pathways in diverse illnesses, such as CRC. Dysregulation of many signaling pathways involved in cell invasion, proliferation, differentiation, and death characterizes CRC, a complicated disease.

Wnt/β-catenin signaling pathway

The development, advancement, and spread of CRC are associated with the aberrant stimulation of the Wnt/β-catenin signaling system [55]. LncRNAs can modulate this pathway by interacting with key components [56, 57]. In CRC, β-catenin nuclear localization is suppressed by lncRNA TUG1 knockdown, which limits cell proliferation. LncRNA CRNDE promotes cell division and chemoresistance by inhibiting β-catenin expression, reducing its accumulation, and reducing the activity of the Wnt/β-catenin pathway.

Notch signaling pathway

It's been shown that the RNA FOXD2-AS1 modifies the Notch signaling pathway, which promotes the growth of CRC tumors. In CRC, the Notch pathway can be rendered inactive by downregulating FOXD2-AS1 expression, which will prevent invasion and migratory activities as well as the epithelial–mesenchymal transition (EMT) [58]. A ncRNA called FAM83H-AS1 might

Table 3 The role of exosomal lncRNAs in colorectal cancer, with a focus on its autophagy

Cargo	Dysregulation in CRC	Target	Model (in vitro, in vivo, human)	Type of cell lines	Regulation of autophagy	Ref.
LncRNA FAL1	↑	Beclin1	In vitro, in vivo, human	SW480, HCT116	Inhibition	[150]

be an oncogene in CRC. It is associated with Notch1 and Hes1, and it is upregulated in CRC. FAM83H-AS1 suppression inhibits the development of CRC cells, however this inhibitory impact may be overridden by activating the Notch signaling system [59].

PTEN signaling pathway

Tumor suppressor PTEN is involved in the initiation and progression of cancer by blocking PI3K/AKT activation and controlling cellular processes as proliferation, survival, energy consumption, and motility [60]. LncRNA by inducing apoptosis and rearranging the cell cycle, Linc02023 efficiently restricts the development of CRC cells. It could interact with the tumor-suppressing protein PTEN, blocking its breakdown by WWP2 ubiquitination and therefore stopping the tumor-suppressive protein's destruction [61].

NF-κB signaling pathway

Nuclear factor-κB, or NF-κB, is extensively linked to the development of CRC and is involved in a number of events, including angiogenesis, apoptosis, cell proliferation, and metastasis. It was discovered that the effects of lncRNA CASC2 on the production of Bcl-2 and Bax were reversed in CRC cells by overexpression of miR-19a. The activation of the NF-κB signaling pathway caused this reversal [62].

PI3K/AKT signaling pathway

In CRC patients, the PI3K-AKT signaling pathway is shown to be dysregulated. This dysregulation involves reduced expression of PIK3CG, a gene encoding a PI3K subunit, as well as elevated levels of cyclin D1, EIF4E, and FOS. Important biological functions in CRC, including as cell survival and proliferation, are disrupted by these alterations [63]. By controlling the fucosylation of sLeX-CD44, an E-selectin ligand, the HOTAIR/miR326/FUT6 axis promotes the growth of CRC by altering α1,3-fucosylatedCD44 and triggering the PI3K/AKT/mTOR pathway [64]. GALNT7 is a glycosyltransferase associated with the carcinogenesis of CRC, and miR-34a interacts with SNHG7 to promote its expression. Through PI3K/AKT/mTOR signaling, this relationship encourages cell division and metastasis [65].

JAK/STAT signaling pathway

The development and progression of CRC are substantially influenced by the JAK/STAT signaling pathway, which is comprised of Janus kinases and signal transducers and activators of transcription. Variations in the JAK/STAT pathway's activity are seen in a variety of tumor forms, including CRC [66]. LncRNA RP11-468E2.5 targets STAT5 and STAT6, which suppresses the JAK/STAT signaling pathway in CRC. This leads to a reduction in cell division and an increase in apoptosis, which AG490 may be able to reverse [67]. Through upregulating LINC00174 expression and encasing miR-1910-3p, STAT1 contributes to the progression of CRC. Tumorigenesis may be aided by the LINC00174/miR-1910-3p/TAZ axis, which involves WWTR1 and the PDZ-binding motif [68]. The interplay between HOTAIR, miR-214, and ST6GAL1 forms a crucial axis that significantly contributes to the malignant characteristics of CRC. Through the process of sialylation, this axis modifies the c-Met receptor, which then triggers the JAK2/STAT3 signaling cascade [69].

VEGF signaling pathway

One of the most important angiogenesis regulators, VEGF, is essential to the growth and metastasis of malignancies. Reduction of VEGF-A expression has an inverse relationship with the invasion, migration, and proliferation of cancer cells [70]. NcRNA TPT1-AS1 interacts with NF90 to improve cell secretion and stability of VEGFA mRNA, which is linked to angiogenesis and liver metastases in CRC. This implies that it would be advantageous to attack this axis with anti-CRC treatment [71].

TGF-β signaling pathway

Phosphorylation of SMAD proteins and dysregulated activation of TGF-β receptors are important factors in the development of CRC's malignant features. Unfavorable prognosis is closely associated with these anomalies [72]. The study found that inhibiting the ncRNA short nucleolar RNA host gene 6 (SNHG6) can reduce the amount of phosphorylated SMAD2 and SMAD3 produced by the UPF1/TGF-β signaling pathway, which can reduce CRC cells' ability to invade and proliferate [73]. According to a research by Javanmard et al. [71], the lncRNA LOC646329 acts as a miR-29b-1

sponge, which inhibits the growth of CRC. This suppression is attributed to the regulation of TGF-β signaling pathways and the control of cyclin D1 expression.

MicroRNA regulation

LncRNAs have the ability to sequester miRNAs and inhibit their association with target mRNAs, therefore functioning as competitive endogenous RNAs (ceRNAs). Through changing the expression of miRNA target genes, this ceRNA interaction can impact the pathophysiology of CRC [42, 43, 56, 62, 74–89].

Metastasis and invasion

LncRNAs play important roles in CRC metastasis and invasion. They can regulate processes like EMT, migration, and invasion-related signaling pathways [85, 90, 91].

Immune response and inflammation

LncRNAs have a key role in the development of CRC due to their ability to regulate the immune system and inflammation. One such instance is the lncRNA NEAT1, which actively promotes CRC development. This is accomplished by NEAT1, which is implicated in the pathophysiology of CRC, by encouraging the polarization of tumor-associated macrophages and enhancing inflammatory signaling [92].

Drug resistance

LncRNAs can also influence CRC response to therapy and contribute to drug resistance. LncRNA H19 has been implicated in chemoresistance in CRC by regulating the expression of drug efflux pumps and promoting cancer stemness [93]. The varied functions of lncRNAs in CRC pathogenesis are demonstrated by these instances. They can affect epigenetic alterations, modify immunological response and inflammation, function as oncogenes or tumor suppressors, control important signaling pathways, and contribute to drug resistance. Gaining knowledge of the functional roles of lncRNAs in CRC may help identify new indicators for the disease's diagnosis and potential treatment targets.

LncRNAs and autophagy in CRC

The impact of lncRNAs on autophagy and their role in CRC pathogenesis are indeed complex [94]. The functions of lncRNAs in autophagy regulation can be context-dependent. Some lncRNAs can serve as both positive and negative regulators of autophagy, with their effects varying depending on the cellular context and stage of CRC progression. Signaling mechanisms such as AMPK and mTOR control autophagy, and lncRNAs can interact with these pathways to modify autophagy in an indirect way. Important autophagy-related proteins, including as those in the mTOR complex and AMPK, can be affected in terms of expression and function. Moreover, lncRNAs have the ability to function as ceRNAs, sequestering miRNAs and influencing the expression of miRNA target genes that are implicated in autophagy. Autophagy in CRC is intricately regulated, in part due to the interaction of lncRNAs, miRNAs, and autophagy-related genes. Long-lasting impacts on autophagy regulation and CRC development might result from lncRNAs' interactions with chromatin-modifying complexes, which affect the expression of genes relevant to autophagy. Epigenetic processes also play a part in this. Numerous biological processes, such as apoptosis, inflammation, and metabolism, are linked to autophagy. Through their influence on these processes, lncRNAs can modify autophagy, which in turn can affect autophagy's effect on lncRNA expression and function. This complicated interaction shapes the pathophysiology of CRC through a complex regulatory network.

Autophagy inhibition by autophagy-related lncRNAs in CRC

Autophagy-related lncRNAs inhibit autophagy and suppress CRC pathogenesis

lncRNA GAS5

Growth arrest-specific transcript 5, or lncRNA GAS5, has been investigated in relation to CRC and has been linked to a number of biological processes, including autophagy. According to a number of studies, colon cancer cells' autophagy can be regulated by the lncRNA GAS5. By preventing autophagy in colon cancer, GAS5 has been demonstrated to function as a tumor suppressor. It interacts with and sequesters important autophagy-related proteins or miRNAs involved in autophagy control to produce its inhibitory action on autophagy. For instance, one study showed that via interacting with the ATG5, GAS5 suppresses autophagy and induces death in colon cancer cells. Autophagy is suppressed as a result of this interaction, which hinders the production of the ATG5-ATG12 conjugate that is required for autophagosome formation. Furthermore, it has been discovered that GAS5 controls autophagy via interacting with certain miRNAs that control autophagy. As an example, it has been demonstrated that GAS5 snoops on miR-23a, which targets the gene ATG12 associated to autophagy. GAS5 stimulates ATG12 expression and encourages autophagy suppression in colon cancer cells via sequestering miR-23a. GAS5, on the other hand, served as miR-34a's molecular sponge. miR-34a had a role in controlling the mTOR/SIRT1 pathway's induction of apoptosis and GAS5's regulation of CRC cell macroautophagy. The inhibitory impact of GAS5-mediated macroautophagy on CRC cell apoptosis persisted [42]. Furthermore, GAS5

has also been connected to the control of other signaling pathways, such the PI3K/AKT/mTOR pathway, that are involved in the modulation of autophagy. Colon cancer cells may experience autophagy suppression as a result of GAS5's inhibition of this route.

LncRNA RP4

According to bioinformatics research, several solid tumors have higher levels of lncRNA RP4 than the equivalent normal tissues [95].Liu et al. [43] focused on investigating the functional role of lncRNA RP4 in CRC. The results showed that in SW480 cells, RP4 had a suppressive impact on early apoptosis, tumor development, and cell proliferation. Further investigation revealed that RP4 interacts with miR-7-5p and sequesters it as a ceRNA. The SH3GLB1 gene eventually expressed itself more as a result of this interaction. As a result, in vivo, this interaction relieved the inhibition of PI3K and Akt phosphorylation in CRC cells and activated the autophagy-mediated cell death pathway [43].

Autophagy-related lncRNAs inhibit autophagy and enhance CRC pathogenesis

lncRNA CASC9

By triggering signaling pathways linked to autophagy, CASC9 can increase autophagy in colon cancer cells, which may support tumor cell survival, growth, and resistance to treatment. Researchers discovered that inhibiting CASC9 decreased cell migration and proliferation, suggesting that it encourages characteristics of cancer. Moreover, CASC9 knockdown changed the expression of EMT marker proteins, increased AMPK phosphorylation, suppressed the mTOR and AKT signaling pathways, and stimulated autophagy. This implies that CASC9 may impact mTOR signaling, which in turn may impact autophagy in colon cancer cells [90].

LncRNA EGOT

The intriguing lncRNA known as lncRNA EGOT, often referred to as lncRNA-EGOT or EGOT, has been connected to a number of biological processes, including cancer. The findings demonstrated that EGOT had a strong diagnostic value and was substantially expressed in CC patients. It was discovered that overexpressing EGOT enhanced the cells' capacity for invasion and proliferation while lowering their rate of apoptosis. Furthermore, EGOT was discovered to stimulate cell proliferation and prevent autophagy in CC cells. In mice, tumor development was significantly reduced by EGOT knockout. Additionally, the scientists hypothesized how EGOT and miRNAs would interact and discovered putative binding sites for EGOT and miR-33a-5p and miR-33b-5p [96].

LncRNA LINC00858

Several studies have linked the autophagic process and CRC to the lncRNA LINC00858. lncRNA LINC00858 has been shown to be dysregulated in a number of malignancies, including CRC [97]. Numerous investigations have proposed that LINC00858 might be involved in the control of autophagy, a cellular mechanism that breaks down and recycles biological components. Dysregulated autophagy has been noted in the setting of CRC and is thought to have a role in the initiation and spread of the disease. According to some research, LINC00858 may alter CRC cells' autophagy. In the study conducted by Wu et al. [98], they observed an increase in LINC00858 expression and a decrease in WNK2 expression in both CRC tissues and cells. These findings suggest that LINC00858 and WNK2 may contribute to the aggressive characteristics of CRC cells. WNK2 has been shown to play a positive role in the maturation of autophagosomes [99]. Consequently, LINC00858 could potentially function as an oncogenic lncRNA in colon cancer by suppressing the expression of WNK2.

LncRNA FIRRE

Limited research has been carried out to investigate the direct influence of FIRRE on the development, progression, or treatment of cancer [100–102]. In the context of colon cancer, studies have suggested a link between FIRRE expression and autophagy regulation. By stabilizing BECN1 mRNA and promoting autophagy through PTBP1 (Polypyrimidine tract-binding protein 1)-mediated means, FIRRE functions as an oncogenic factor in CRC. There is a discernible increase in the expression of PTBP1, or hnRNP I, in those with CRC. There is a correlation between this hnRNPs family member and poor outcomes in patients with CRC [102]. PTBP1 functions as an inducer of the autophagy process. For PTBP1 to have a functional role, its subcellular location must be appropriate. For several facets of mRNA metabolism, including mRNA transport and stabilization, which include every phase of this process, PTBP1 must be located in the cytoplasm [103]. PTBP1 moved from the nucleus to the cytoplasm as a result of overexpression of FIRRE. PTBP1 deletion, on the other hand, caused FIRRE to delocalize from the nucleus to the cytoplasm. The mRNA of BECN1 was directly bound by the cytoplasmic FIRRE-PTBP1 complex. Functional studies with Actinomycin D treatment shown that FIRRE stabilizes BECN1 mRNA in a PTBP1-dependent manner, which contributes to autophagy [102].

1p36.3 lncRNA

Tumor suppressor genes are known to be located at region 1p36.3, and they are commonly deleted in a

variety of cancer types. TP73, PRDM16, and CHD5 are among the tumor suppressor genes that have been found by researchers in this area. In Li et al. [50] study, the researchers conducted an analysis of CpG methylation patterns and made a surprising discovery. It was discovered that the KIAA0495 gene, which was previously thought to be a lncRNA, actually encodes a small protein known as SP0495. Due to promoter CpG methylation, it was discovered that the expression of KIAA0495 was repressed in a number of tumor cell lines and primary tumors, including colorectal, esophageal, and breast malignancies. The downregulation and methylation of KIAA0495 were associated with poorer survival outcomes in cancer patients. SP0495 acts as a tumor suppressor and exerts its effects by inducing autophagy, cell cycle arrest, senescence, and apoptosis. By promoting the accumulation of BECN1 and controlling the levels of p62, SP0495 helps to maintain proper autophagy function [50].

LARP6

Tumor growth and progression have been found to be significantly correlated with LARP6, a protein belonging to the LARP family [104].The role of LARP6 in autophagy and colon cancer has been investigated. It was discovered by Long et al. [105] that CRC had down-regulated LARP6 expression. The researchers found that autophagy activity in CRC cells was impacted by changed LARP6 expression. Moreover, the research demonstrated that the reduction of SGMS2-mediated sphingomyelin production was at least largely responsible for the action of LARP6 on autophagy. The control of autophagy has been linked to SGMS2, the gene that encodes sphingomyelin synthase 2. According to the research, sphingomyelin levels in CRC cells are unbalanced because LARP6 suppresses the expression of SGMS2. This mismatch thus plays a role in the increased autophagy activity that is seen [105].

LINRIS

Research has looked into how LINRIS functions in autophagy and CRC. Yun Wang et al.'s [106] study concentrated on the function of a particular lncRNA termed LINRIS in accelerating the development of CRC and its potential as a target for therapy. In CRC tissues, LINRIS was shown to be elevated in individuals who had a low overall survival rate. When LINRIS was inhibited, the growth of CRC cell lines was impaired. It was shown by the researchers that LINRIS interacts with a protein known as insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), which has a role in identifying N6-methyladenosine (m6A) on RNA molecules. LINRIS prevents the degradation of IGF2BP2 by blocking a process called ubiquitination, which normally leads to protein degradation, thus maintaining the stability of IGF2BP2. As a result, the autophagy-lysosome pathway (ALP), responsible for cellular degradation, is inhibited, and IGF2BP2 is protected from degradation. Through this mechanism, the downstream effects of IGF2BP2 are diminished, particularly the stimulation of glycolysis in CRC cells, which is mediated by the protein MYC. The study also showed that GATA3, a transcription factor, can prevent CRC cells from producing LINRIS. Inhibition of LINRIS was observed to reduce tumor growth in in vivo tests employing patient-derived xenograft (PDX) models and orthotopic models of CRC [106].

lncRNA CTA-941F9.9

Recently, it was discovered that chromosome 22 is the source of the lncRNA CTA-941F9.9 (ENSG00000238120). It consists of 548 nucleotides and is categorized as a novel lncRNA. The findings of the experiment demonstrated a substantial downregulation of CTA-941F9.9 in CRC tissues [107]. Based on the provided information [107], it appears that the results suggest a role for lncRNA CTA-941F9.9 in promoting autophagy at the protein level. It is specifically claimed that CTA-941F9.9 stimulates the production of LC3-II, a crucial protein involved in autophagy. This implies that rather than having direct impacts on these cellular processes, CTA-941F9.9's participation in the genesis and progression of CRC may be more directly linked to its involvement in autophagy control [107].

LncRNA POU3F3

Linc-POU3F3 is a lnc intergenic RNA that has been connected to CRC. Studies have shown that linc-POU3F3 is elevated in CRC tissues in comparison to normal tissues, suggesting a potential function for this protein in the start and development of CRC [91]. The expression levels of POU3F3 and linc-POU3F3 in CRC specimens show an inverse connection, meaning that when POU3F3 expression is low, linc-POU3F3 levels are high. All things considered, the research suggests that linc-POU3F3 may be a useful biomarker for diagnosis or a possible target for treatment in CRC [108]. Multiple functional functions of linc-POU3F3 in CRC have been identified by research. It has been linked to encouraging CRC cell invasion, migration, proliferation, and metastasis. Furthermore, it has been discovered that linc-POU3F3 controls the EMT, a critical mechanism in the spread of cancer. By modulating EMT-related genes and signaling pathways, linc-POU3F3 contributes to the acquisition of invasive and metastatic properties in CRC cells [91]. SMAD4, a significant component of the BMP pathway, plays a role in numerous physiological and pathological

processes, including metastasis [109, 110]. According to the findings of Shan et al.'s study [91], LOVO and SW480 cells exhibited elevated expression levels of SMAD4 and pSMAD1, 5, 8, following linc-POU3F3 suppression. The suppression of linc-POU3F3 led to an increase of BMP signaling, which was linked to a decrease in the migratory and invasive potential of CRC cells. SMAD4 is critical in the signaling pathways that lead to autophagy. The activation of autophagy-related proteins mediated by TGF-β is eliminated when SMAD4 expression is reduced [111, 112]. The results indicate that linc-POU3F3 knockdown produced a strong and long-lasting activation of autophagy, perhaps via SMAD4 overexpression [91]. This elucidates the molecular pathways that underlie the control of autophagy in CRC and identifies linc-POU3F3 as a putative target for therapeutic intervention to regulate autophagy activity in CRC cells.

lncRNA CASC2

Tumor suppressor CASC2 has been found in a number of cancer types. It is known that various malignancies, particularly CRC, have downregulated CASC2 [62, 78]. According to a research by Ju et al. [78], the regulatory activity of miR-214 suppresses the production of TRIM16, which is one of the functional impacts of lncRNA CASC2. The protein TRIM16, which is involved in a number of cellular functions, including the control of autophagy, is suppressed by CASC2. According to these results, TRIM16 repression-mediated CASC2-mediated autophagy activation may represent a viable therapeutic approach for preventing the proliferation of colon cancer cells. In Zhang's work [62], it was shown that overexpression of miR-19a via the NF-κB signaling pathway reversed the effects of lncRNA CASC2 on Bcl-2 and Bax expression. Additionally, the study discovered that lncRNA CASC2 suppressed the expression of p62 and LC3-1 while boosting the expression of LC3-2, two important proteins involved in the autophagic process, hence inhibiting autophagy. MiR-19a was found to be increased in cancer cell lines, and it was hypothesized that this protein would bind to the lncRNA CASC2. MiR-19a may be involved in processes connected to cancer because of its overexpression, which may also cause autophagy to be dysregulated and Bcl-2 and Bax to express differently [62].

Autophagy promotion by autophagy-related lncRNAs in CRC

Autophagy-related lncRNAs activate autophagy and enhance CRC pathogenesis

lncRNA SNHG8

He et al.'s [76] study revealed that SNHG8 expression is upregulated in primary tumor tissues from CRC patients. In CRC cells, it was discovered to promote autophagy and cell growth. Additionally, the study discovered the connection between SNHG8 and ATG7, which controls autophagy [76]. Research by Slam Khan et al. [113] demonstrated that inhibiting SNHG8 expression decreased the development and multiplication of CRC cells. The AKT/AMPK/mTOR signaling axis was linked to the activation of autophagy in this result.

LncRNA SLCO4A1-AS1

The primary players in the start of autophagy, particularly in response to energy signaling and amino acid sensing, are AMP-activated protein kinase (AMPK) and the mechanistic target of rapamycin complex 1 (mTORC1). The coordination of cellular responses to energy status and nutrition availability is greatly aided by these signaling pathways. When there is an enough supply of nutrients and energy, mTORC1 is triggered, which prevents autophagy. On the other hand, mTORC1 activity is inhibited in nutrient-deficient or energy-stressed environments, which permits the start of autophagy. When cellular energy levels are low, as they are during nutritional deprivation or periods of elevated energy demand, the cellular energy sensor known as AMPK is triggered. Through the promotion of catabolic processes like autophagy, which produces energy by breaking down biological components, activated AMPK aids in the restoration of energy balance. PARD3 recognizes and reacts to signals pertaining to energy and amino acids via acting downstream of mTORC1 and AMPK [114]. Research by Wang et al. [80] discovered that in CRC tissues, SLCO4A1-AS1 expression was positively correlated with PARD3 (partition-defective 3) expression. By specifically targeting PARD3, knocking down SLCO4A1-AS1 was found to reduce cytoprotective autophagy and impede cell proliferation through both in vitro and in vivo investigations. PARD3 was upregulated and CRC cell proliferation was encouraged by the mechanistic action of SLCO4A1-AS1 acting as a sponge for miR-508-3p [80].

LncRNA MALAT1

MALAT1 has been reported to modulate autophagy through its interaction with miRNAs in colon cancer. It can act as a ceRNA by sponging specific miRNAs, thereby regulating their availability and influencing downstream targets involved in autophagy. By binding to miR-101, expression dropped when Malat1 levels were lowered. In CRC cells, overexpressing miR-101 negatively affected autophagy, which resulted in decreased cell division, increased apoptosis, and changes in the expression of autophagy-related proteins such as p62/SQSTM1 and LC3 [81]. MALAT1 eliminated the inhibitory effects of miR-101 on proliferation, autophagy, and apoptosis

in CRC, the researchers showed [81]. It has been demonstrated that miR-26a directly targets and regulates a number of genes related to the autophagy system. It can specifically target two proteins that are necessary for the production of autophagosomes and the beginning of autophagy: ATG16L1 and ULK1 (Unc-51-like autophagy-activating kinase 1). Autophagy can be inhibited by miR-26a via downregulating the expression of these genes. The researchers discovered that by upregulating the expression of ATG5, Smad1, a crucial effector of bone morphogenetic protein (BMP)-Smad signaling, causes autophagy in CRC cells. Additionally, they showed that BMP2, a BMP family member, promotes autophagy in CRC. Smad1 overexpression has been demonstrated to promote CRC cell migration and carcinogenesis, whereas ATG5 knockdown partially reversed the pro-migratory and pro-proliferative effects of Smad1 [82]. In a research, Zhou et al. [82] discovered that by directly targeting and inhibiting Smad1, elevated levels of miR-26a can prevent autophagy in CRC cells. On the other hand, by encouraging the overexpression of Smad1, miR-26a inhibition improved autophagy activation. It has been suggested that MALAT1 binds to miR-26a-5p competitively to perform the role of a ceRNA. Because of this interaction between MALAT1 and miR-26a-5p, miR-26a-5p is unable to bind to its target mRNA, which derepressed Smad1, the downstream target. MALAT1 may alter Smad1 expression and function by sequestering miR-26a-5p, which might have an impact on cellular activities that the Smad1 pathway regulates [82].

CERS6-AS1

Well-known transcription factor MYC is essential for controlling the expression of certain genes. It is frequently dysregulated in many kinds of malignancies and has been connected to the abnormal expression of several lncRNAs. MYC plays a crucial role in the initiation and advancement of cancer by acting as a transcription factor [115]. It has been shown that in CRC, downregulating MYC expression can repair disturbed metabolic pathways and reduced cell proliferation [116]. MYC acts as a transcription factor inside CRC, stimulating CERS6-AS1 transcription and increasing CERS6-AS1 expression (89). According to studies, CERS6-AS1 expression is dysregulated in CRC [89]. Evidence exists to support the theory that CERS6-AS1 promotes tumor growth in CRC. According to experimental research, CERS6-AS1 downregulation in CRC cell lines can cause cell cycle arrest, impede cell division, and encourage apoptosis. These results point to a possible function for CERS6-AS1 in inhibiting the onset and spread of CRC. Chen et al. [87] showed that miR-6838-5p uses the lncRNA CERS6-AS1 as a molecular sponge. The expression of Rubicon-like autophagy enhancer (RUBCNL), which in turn affects a number of CRC cell functions such migration, apoptosis, and cell proliferation, is impacted by this relationship.

lncRNA UCA1

Numerous facets of cancer biology, particularly colon cancer, have been linked to the lncRNA UCA1 (urothelial carcinoma-associated 1). When comparing colon cancer samples to nearby normal tissues, the researchers discovered that UCA1 expression was elevated in the former [56, 117, 118]. A significant correlation between UCA1 and LC3 levels were found in the Song et al. research [78], indicating that UCA1 may be involved in the control of autophagy. Additionally, the researchers found that decreasing UCA1 expression prevented autophagy from being activated, which in turn caused CRC cells to proliferate less rapidly and undergo more apoptosis. The investigation also showed that in Caco-2 cells, UCA1 knockdown led to an increase in p62 expression and a decrease in the levels of the proteins LC3-II and ATG5. This suggested that autophagy activation was suppressed by UCA1 knockdown. The distribution of cells throughout the cell cycle was also seen to be impacted by downregulated UCA1, with fewer cells in the G1 phase and more in the G2 phase. As a result, there was a decrease in cell division and an increase in apoptosis [117]. UCA1 was shown to function as a molecular sponge for miR-185-5p in a different investigation by Liu et al. [56]. UCA1 and miR-185-5p were interacting, inhibiting the expression of UCA1. The inhibitory effects of miR-185-5p on CRC cell proliferation and autophagy were reversed by UCA1's inhibition of the protein. It was discovered that this connection may lead to the activation of the WISP2/β-catenin signaling pathway and the overexpression of WISP2 (WNT1-inducible signaling pathway protein 2) expression. The UCA1-miR-185-5p-WISP2-Wnt/β-catenin axis was postulated by the researchers as a possible regulatory route involved in the onset and progression of CRC. Gaining knowledge about this route may help in CRC diagnosis and therapy [56].

LncRNA NEAT1

One well-known lncRNA that contributes to the development and operation of nuclear paraspeckles—subnuclear structures involved in the control of gene expression—is NEAT1. However, emerging research suggests that NEAT1 can also influence autophagy. According to some research, NEAT1, autophagy, and colon cancer are related. Dysregulation of autophagy has been implicated in colon cancer pathogenesis, and NEAT1's potential role in modulating autophagy may contribute to tumor progression. The specific mechanisms through which NEAT1 affects autophagy in colon cancer are still under

investigation. Potential interactions between NEAT1 and other autophagy-regulating molecules or proteins might affect their expression or function. In the Wang et al. [71] study, it was demonstrated that CRC tissues and cells had significantly higher levels of NEAT1 and Solute carrier family 38 (SLC38A1). The protein-coding gene SLC38A1, also known as sodium-coupled neutral amino acid transporter 1, is a part of SLC38. Among other organs, the liver, colon, and brain are where it is most expressed. This transporter facilitates the passage of amino acids through cell membranes [119, 120]. The development and progress of cancer have been related to SLC38A1's aberrant activity [121]. In fact, studies have demonstrated that CRC tissues have high levels of SLC38A1 expression (74). This increased expression of SLC38A1 has been connected to its role in promoting tumor development by inducing increased migration and proliferation of cells in CRC [122]. In CRC cells, NEAT1 knockdown or SLC38A1 downregulation decreased cell invasion and proliferation but increased autophagy and autophagic death. Additionally, it was shown that NEAT1 acted as a sponge for miR-138 to control the expression of SLC38A1 in vivo and in vitro [74].

LncRNA CPS1-IT1

Research has indicated that CPS1-IT1 expression is commonly disrupted in CRC, with decreased expression observed in CRC samples compared to normal colorectal tissue [85, 123]. This decrease in expression implies a potential tumor-suppressive function for CPS1-IT1 in CRC [123]. Furthermore, studies have proposed that CPS1-IT1, an lncRNA, has the ability to regulate autophagy in colon cancer cells. Studies have demonstrated that CPS1-IT1 knockdown can cause colon cancer cells to undergo autophagy, which lowers their viability and increases their apoptosis. This implies that in colon cancer, CPS1-IT1 may function as a negative regulator of autophagy. Hypoxia has a complex effect on several elements of tumor biology, including the angiogenesis of the tumor, increased aggressivity, higher recurrence rates, and the emergence of treatment resistance [124]. Research has demonstrated that the HIF-1α signaling pathway may initiate autophagy in hypoxic environments. Additionally, it has been discovered that hypoxia promotes tumor cell invasion and metastasis [125, 126]. Zhang et al. [85] have examined the connections between lncRNA CPS1-IT1, EMT, CRC metastasis, hypoxia-induced autophagy, and the inactivation of HIF-1α. According to studies, the lncRNA CPS1-IT1 can prevent CRC spread and EMT. The inactivation of HIF-1α in CRC inhibits hypoxia-induced autophagy, which is one way that CPS1-IT1 suppresses EMT and metastasis [85].

Autophagy, autophagy-related lncRNAs, and therapeutic resistance in CRC

Autophagy-related lncRNAs activate autophagy to suppress tumor drug resistance

LncRNA CKMT2-AS1

Chromosome 5 contains the CKMT2-AS1 gene locus, which is the source of transcription. In CRC tumor tissues and CRC cell lines, CKMT2-AS1 expression levels were shown to be lower [127, 128]. According to Zhuang et al. [127], CKMT2-AS1 may play a role in the reduced survival of CRC cells. The study observed that the expression of CKMT2-AS1 was significantly increased in 5-fluorouracil (5-FU)-treated SW480 and HCT116 cells, and suppressing CKMT2-AS1 expression resulted in a decrease in apoptosis of cancer cells. It is believed that CKMT2-AS1 works by focusing on the AKT/mTOR signaling pathway, which is necessary for cell survival, growth, and proliferation.

Autophagy-related lncRNAs activate autophagy to promote tumor drug resistance

In CRC, deregulation of lncRNAs and autophagy may be a factor in treatment resistance. Because enhanced autophagy helps cancer cells survive under stress circumstances brought on by chemotherapy and targeted therapies, it has been linked to resistance to these treatments in CRC. Similarly, several lncRNAs have been linked to the promotion of therapeutic resistance by their impact on processes associated with autophagy or their modulation of gene expression relevant to drug response. Developing ways to overcome resistance and enhance treatment results in CRC requires an understanding of the complex interactions between autophagy, lncRNAs, and therapeutic resistance. It is promising that targeting certain dysregulated lncRNAs and autophagy pathways might be a therapeutic strategy to overcome resistance mechanisms and make CRC cells more susceptible to therapy.

lncRNA NEAT1

The research conducted indicates that NEAT1 contributes to the development of chemoresistance to 5-FU in CRC [75]. A protein with a variety of roles in both healthy and pathological circumstances, HMGB1, often referred to as High Mobility Group Box 1, is involved in many different chemical reactions. It is categorized as a non-histone chromosomal protein and is a member of the high mobility group (HMG) protein superfamily. HMGB1 functions as a DNA-binding protein and interacts with chromatin to regulate gene expression in the nucleus of cells, where it is mostly located. Strong evidence has connected HMGB1 to cancer cell invasion, growth, and metastasis. Higher levels of HMGB1 have

been found in several cancer types and have been linked to more aggressive tumor features [129]. The cellular process known as autophagy, which is in charge of breaking down and recycling cellular components, can be induced by HMGB1. Through HMGB1-induced autophagy activation, cancer cells are able to withstand chemotherapy-induced apoptosis as a defense mechanism [130]. The researchers discovered that CRC cells and tissues had higher levels of NEAT1 expression [74, 75]. NEAT1 downregulates miR-34a to enhance autophagy in CRC cell lines, according to research by Liu et al. [75]. NEAT1 knockdown reduced CRC cell growth and increased their susceptibility to 5-FU. Additionally, the researchers found that NEAT1 knockdown inhibited the production of certain autophagy-related proteins as well as the development of autophagy puncta. Overexpression of miR-34a showed similar effects as NEAT1 knockdown. After conducting more research, it was shown that miR-34a specifically targeted binding sites in the 3′-untranslated regions of the autophagy-activating genes HMGB1, ATG9A, and ATG4B. The increased 5-FU sensitivity brought on by NEAT1 knockdown was reversed by inhibition of miR-34a or overexpression of HMGB1. Furthermore, the researchers discovered that in HT29 cells, NEAT1 overexpression-induced resistance to 5-FU could be restored by blocking autophagy with a substance known as 3-MA [75].

lncRNA UCA1

Xian et al.'s study [118] found that autophagy and UCA1 expression are positively correlated with 5-FU resistance in CRC. Facilitating autophagy and blocking apoptosis, UCA1 enhances 5-FU resistance. The study also discovered that miR-23b-3p is a target of UCA1, and that inhibiting its expression promotes death in CRC cells by counteracting the inhibitory effects of UCA1 interference on 5-FU resistance and autophagy. Additionally, it was shown that ZNF281 is a binding partner of miR-23b-3p. In CRC cells, miR-23b-3p increases 5-FU sensitivity by downregulating ZNF281. The transcription factor ZNF281 is a member of the zinc finger protein family. It affects a number of biological functions, including as the formation and control of genes. ZNF281 is linked to oncogenic characteristics in a number of cancer types, including CRC, and has been involved in the advancement of cancer. ZNF281 promoted the proliferation and spread of CRC cells through its control of the Wnt/β-catenin signaling pathway. ZNF281 contributed to Wnt/β-catenin pathway activation, which in turn promoted CRC cell proliferation and dissemination [57]. ZNF281 has been shown by Xian et al. [113] to contribute to CRC cells' resistance to the chemotherapeutic medication 5-FU. The study found a correlation between the downregulation of LC3II and Beclin1 and the reduction in ZNF281 expression. These modifications imply a possible connection between declining ZNF281 levels and CRC cell autophagy. Together, these in vivo studies showed that UCA1 promoted autophagy and inhibited apoptosis via the miR-23b-3p/ZNF281 axis, which helped CRC acquire a resistance to 5-FU [118].

lncRNA SNHG14

Research has revealed that a specific gene called SNHG14 has elevated expression in colon cancer tissues and cell lines. Increased proliferative, migrating, and invading potential of CRC cells has been linked to this overexpression of SNHG14. These results clearly suggest that SNHG14 is an oncogene that advances CRC [131]. Research has demonstrated that elevated SNHG14 expression is linked to resistance to chemotherapy medications, such as 5-FU and cisplatin, which are often used to treat CRC [131]. In CRCs, SNHG14 has also been demonstrated to alter autophagy. For the development of autophagosomes and the advancement of autophagy, it has the ability to control the expression of genes and proteins linked to autophagy, such as Beclin-1 and LC3. By sponging miRNAs and inhibiting their action, SNHG14 can operate as a ceRNA. SNHG14 can control the expression of genes linked to autophagy indirectly by sequestering certain miRNAs. It was noted that the levels of SNHG14 and ATG14 in CRC tumor tissues were substantially higher than in normal tissues in the investigation carried out by Han et al. [131]. The findings of the study suggest that ATG14, miR-186, and SNHG14 might be potential therapeutic targets for the treatment of CRC as they have been found to have a role in the development of CRC and drug resistance. Increased expression of SNHG14 encourages cell invasion, migration, and proliferation, while miR-186 decreases these processes. ATG14 overexpression, which encourages CRC cell growth while blocking apoptosis, facilitates treatment resistance.

LncRNA LINC01871

It has been documented that LINC01871 is dysregulated in a number of malignancies, including colon cancer [132, 133], but its functional role and mechanism of action are not well characterized. Scientists looked at the function of a lincRNA known as LINC01871 in CRC chemoresistance and the molecular mechanism behind its effects in the work carried out by Duan et al. [85]. According to the study's conclusions, CRC tissues and cell lines both showed low levels of LINC01871. Significantly worse survival rates were seen in patients with low LINC01871, indicating the possibility of this marker serving as a prognostic indicator. In order to study LINC01871's functional significance in CRC, the researchers overexpressed

LINC01871 in CRC cells. LINC01871 overexpression was shown to result in decreased cell viability and heightened susceptibility to 5-FU, a chemotherapy medication frequently used for the treatment of CRC. Furthermore, downregulating the expression of autophagy-associated proteins, LINC01871 overexpression suggests that it plays a role in the control of autophagy. Subsequent mechanistic studies showed that LINC01871 serves as a "sponge" for miR-142-3p. This implies that miR-142-3p binds to LINC01871, blocking its ability to regulate target genes. One of the genes involved in cellular processes, ZYG11B, was shown to be one of miR-142-3p's targets. The researchers changed the expression levels of ZYG11B or miR-142-3p in order to confirm the functional significance of the LINC01871/miR-142-3p/ZYG11B axis. The effects caused by LINC01871 overexpression were reversed when miR-142-3p or ZYG11B expression was changed, indicating that the LINC01871/miR-142-3p/ZYG11B axis is important in mediating the observed cellular responses [85].

lncRNA SNHG6

It has been discovered that CRC considerably upregulates the lncRNA SNHG6. The stimulation of CRC cell proliferation, invasion, and migration has been linked to this SNHG6 overexpression [73]. By preventing 5-FU-induced apoptosis and fostering autophagy, SNHG6 was demonstrated to enhance CRC cells' resistance to 5-FU. Subsequent investigation showed that miR-26a-5p, which controls gene expression, uses SNHG6 as a sponge. A protein called ULK1, which is linked to the initiation of autophagy, was produced higher when SNHG6 was able to suppress the expression of miR-26a-5p. This suggests that by inducing autophagy through the SNHG6/miR-26a-5p/ULK1 axis, SNHG6 helps CRC cells become more resistant to chemoresistance [83].

LncRNA RNA H19

The human chromosome 11 contains the maternally expressed imprinted LncRNA H19 gene, which is essential to mammalian development [134]. Despite extensive research on H19's epigenetic properties, the pathogenic role of this non-coding RNA in tumors is just now being determined. There is a lot of evidence that H19 is overexpressed in CRC [135, 136]. H19, a protein associated with a poor prognosis for CRC, has been shown by Han et al. to attract and bind to eIF4A322, which stimulates tumor development [137]. The function of lncRNA H19 in CRC and its correlation with resistance to the chemotherapeutic medication 5-FU were investigated by Wang et al. [85]. The analysis showed that recurrent samples from CRC patients had a significant increase of H19 expression. Furthermore, a substantial association was found between poor recurrence free survival outcomes and increased H19 expression in CRC tissues. Functional experiments provided evidence that H19 played a role in promoting resistance to the chemotherapy drug 5-FU in colorectal cells. The underlying mechanism involved H19 triggering autophagy through the participation of SIRT1, a protein involved in cellular stress response pathways. As a result, H19 helped cancer cells become more resistant to chemotherapy. Moreover, computational research revealed that H19 could sequester the suppressive miR-194-5p, which is known to operate as a ceRNA. Additionally, the investigation revealed that in CRC cells, SIRT1 was a direct target of miR-194-5p [85].

lncRNA TUG1

Tumor drug resistance heavily relies on the critical function of the lncRNA known as taurine upregulated 1 (TUG1) [138]. IGF2BP2 assumes pivotal functions in the processes of cancer formation and the resistance to chemotherapy. Its impact on ncRNAs, including their stability, translatability, or localization, is instrumental in these roles [139]. Xia et al. [99] demonstrated that in CRC tissues, the levels of both TUG1 and IGF2BP2 are elevated. Furthermore, it was discovered that in CRC cells, IGF2BP2 increased TUG1 expression. TUG1 in turn promotes autophagy, which contributes to CRC cells' resistance to the chemotherapeutic medication cisplatin. Additionally, the study showed that miR-195-5p interacts with HDGF (Hepatoma-derived growth factor) and TUG1 interacts with it. A heparin-binding protein called HDGF expresses itself atypically in various cancer forms [140]. It is an important regulator of the angiogenesis, metastasis, and apoptosis of malignant cancer cells. These results suggest that HDGF has a role in controlling the growth of cancer and the virulence of tumors. The excessive expression of HDGF has the ability to hinder the apoptosis of CRC cells induced by nordihydroguaiaretic acid (NDGA) and promote tumor growth. As a result, this enhances the resistance of CRC to the effects of NDGA [141]. DDX5, also known as DEAD-box helicase 5, is a protein that has been linked to CRC and can interact with β-catenin. Studies have suggested that DDX5 can modulate β-catenin activity and downstream signaling in CRC cells. The suppression of DDX5 has been seen to diminish the responsiveness of cetuximab-resistant colon cancer cells to cetuximab therapy [142]. By inhibiting autophagy through the HDGF/DDX5/β-catenin pathway, overexpression of miR-195-5p neutralizes TUG1's carcinogenic effects. Further evidence that IGF2BP2 has a role in CRC cell proliferation comes from in vivo investigations conducted on mice [99].

KcnQ1OT1

KcnQ1OT1 is a lncRNA that has been connected to several biological processes, such as medication resistance and the development of cancer. The research carried out by Li et al. [143] revealed that the tumor tissues of individuals with colon cancer had an increased expression level of KCNQ1OT1.The association between the overexpression of KCNQ1OT1 and a bad prognosis implies that individuals with colon cancer may have greater expression levels of KCNQ1OT1, which might be a sign of poor outcomes. In colon cancer, KcnQ1OT1 contributes to chemoresistance to oxaliplatin. By focusing on the miR-34a/ATG4B pathway, it does this. MiR-34a suppresses tumors and controls a number of biological functions, including autophagy. One gene implicated in the control of autophagy is ATG4B. The evidence presented indicates that KcnQ1OT1 targets the miR-34a/ATG4B pathway, which may cause deregulation of autophagy and increased chemoresistance in colon cancer cells treated with oxaliplatin. According to mechanism, KcnQ1OT1 may facilitate the establishment of resistance in colon cancer patients to oxaliplatin-based chemotherapy regimens by boosting protective autophagy [143].

Autophagy-related lncRNAs activate autophagy to promote tumor radioresistance

lncRNA SP100-AS1

It was discovered that radioresistant CRC tissues have higher levels of SP100-AS1, a lncRNA that targets the SP100 gene's complementary region. Additional research using the suppression of SP100-AS1 demonstrated its function in lowering radioresistance, preventing cell division, and stifling the growth of tumors in both animal models and lab cell cultures. Mechanistic analyses of its mechanism of action showed that SP100-AS1 uses the ubiquitination-dependent proteasome pathway to bind with and stabilize the ATG3 protein, an essential part of the autophagy system. Furthermore, miR-622, a miRNA that typically targets ATG3 mRNA and affects autophagic activity, uses SP100-AS1 as a "sponge". These results imply that SP100-AS1 regulates both RNA and protein levels, which plays a role in radioresistance in CRC [79].

LncRNA HOTAIR

LncRNA called HOTAIR has attracted a lot of interest in the study of cancer. It functions as a crucial regulator of gene expression and is transcribed from the human genome's HOXC locus. It is well recognized that HOTAIR interacts with epigenetic regulators and chromatin-modifying complexes to alter patterns of gene expression (51). HOTAIR has been linked to poor clinical outcomes and carcinogenic features in a variety of cancer types, such as breast, kidney, and nasopharyngeal carcinoma [144]. HOTAIR expression is elevated in CRC, and this elevated expression has been associated with a poor prognosis for patients and resistance to treatment [145]. It has been determined that HOTAIR is a gene expression regulator that promotes the development of cancer by interacting with certain miRNAs and altering their activity. Studies have shown that lowering HOTAIR levels in CRC cells can lead to increased susceptibility to radiation, decreased viability of the cells, apoptosis start, and autophagy inhibition. As a ceRNA for miR-93, HOTAIR has been found to regulate the expression of ATG12. The upregulation of ATG12 expression was seen upon reduction of miR-93 levels; however, the opposite impact was observed upon depletion of HOTAIR. Depletion of HOTAIR also increased radiosensitivity in CRC xenograft tumors by influencing the miR-93/ATG12/LC3 II -mediated autophagy. The miR-93/ATG12 axis may be a major contributor to CRC resistance to radiation treatment, as our data indicate that HOTAIR regulates this axis. It could be possible to increase the efficacy of radiation therapy for CRC by focusing on this axis as a therapeutic [84].

Exosomal lncRNAs and tumor drug resistance

Treatments for cancer are frequently rendered less effective by malignancies that have developed drug resistance. An increasing amount of research has demonstrated that exosomes, via a variety of pathways, are essential in promoting drug resistance. Exosomes, which are small vesicles released by cells including tumor cells, have the ability to influence both the tumor microenvironment and recipient cells, thereby contributing to drug resistance [146, 147]. Several mechanisms have been identified through which exosomes promote drug resistance. Exosomes play a role in one process by transporting drug efflux pumps, such P-glycoprotein, from resistant cells to susceptible cells [147]. The amount of drug that accumulates inside the sensitive cells is reduced as a result of this transfer. Additionally, exosomes have the ability to transport certain molecules, including lncRNAs, which might alter the recipient cells' expression of genes linked to drug sensitivity or resistance. Through a number of processes, exosomal lncRNAs have been linked to the development of treatment resistance in malignancies. Recipient cells may acquire resistance to anti-cancer medications through the transmission of genetic information linked to treatment resistance via exosomal lncRNAs. Studies have found that a human non-small cell lung cancer (NSCLC) cell line that is resistant to the drug gefitinib expresses elevated levels of lncRNA called H19. This is an example of how lncRNA H19 interacts specifically with hnRNPA2B1 to be packed into exosomes. By transferring lncRNA H19 to non-drug-resistant NSCLC

cells, these exosomes can cause the establishment of gefitinib resistance. According to this process, NSCLC may acquire treatment resistance as a result of lncRNA H19 being transferred by exosomes [148]. Glioma cells that are resistant to the chemotherapy drug temozolomide have been found to secrete exosomes containing lncRNA SBF2-AS1. These exosomes have the ability to alter the tumor microenvironment and cause nearby cells to become resistant to chemotherapy. Although the precise processes by which lncRNA SBF2-AS1 alters the microenvironment and imparts resistance are unknown, it is suggested that lncRNA SBF2-AS1 transfer via exosomes contributes to the promotion of resistance to temozolomide, a medication that is frequently used to treat glioblastoma [149].

Autophagy can have two contrasting effects when it comes to tumor cells' resistance to drug treatments. Autophagy can either amplify the drug-induced death of tumor cells or, conversely, help the tumor cells survive and become resistant to the drug. Through modifying the expression of genes linked to autophagy, such as those involved in the production or destruction of autophagosomes, exosomal lncRNAs can control autophagy. Exosomal lncRNAs can modify the autophagy apparatus, which in turn affects how sensitive tumor cells are to anti-cancer medications. Furthermore, exosomal lncRNAs have the ability to synchronize the regulation of autophagy and drug resistance. For example, some exosomal lncRNAs can suppress autophagy in tumor cells, which can increase treatment resistance. These lncRNAs support lower drug sensitivity and cell viability by inhibiting autophagy. On the other hand, some exosomal lncRNAs could increase drug sensitivity by triggering autophagy-mediated cell death in reaction to anti-tumor medications.

Role of exosomal lncRNAs in chemotherapy resistance via autophagy modulation in CRC

Exosomal lncRNAs have become well-known for their role as regulators of several cellular functions, such as autophagy. Exosomal lncRNAs have been implicated in the regulation of autophagy, according to recent research [150, 151]. Exosomal lncRNAs have the ability to directly interact and modify the actions of proteins involved to autophagy. Their roles in autophagic activity can entail scaffolding, decoying, or regulating protein–protein interactions that are part of autophagy signaling pathways [151]. Research has examined the function of FAL1 in connection to autophagy in the setting of colon cancer. The contribution of exosomal FAL1 to chemoresistance to oxaliplatin in CRC was examined by Zhu et al. [150]. According to the research, there is a strong expression of the lncRNA FAL1 in CRC samples, and individuals with CRC who have greater levels of FAL1 may have poorer survival results. The results showed that in both cellular and animal models of CRC, exosomal FAL1 contributes to the promotion of resistance to the chemotherapeutic medication oxaliplatin. Furthermore, the investigation demonstrated that exosomal FAL1 and its overexpression prevent CRC cells treated with oxaliplatin from undergoing autophagic induction. Mechanistically, Beclin1 and TRIM3 interact more easily thanks to the scaffolding function of FAL1. This interaction encourages TRIM3 to polyubiquitinate Beclin1, which leads to its breakdown. FAL1-mediated suppression of autophagic cell death plays a role in CRC patients' development of oxaliplatin resistance [152].

LncRNA-targeted approaches

Researchers are looking at the dysregulated expression of several lncRNAs and their functional involvement in CRC. By understanding the molecular mechanisms through which specific lncRNAs contribute to the development and progression of CRC, it may be possible to develop new therapeutic approaches. Small interfering RNAs (siRNAs), antisense oligonucleotides, and other RNA-based tactics can be used in these interventions to modify the expression and function of certain lncRNAs. In HCT116/5-FU and HT29/5-FU cells, it has been shown that inhibiting the lncRNA colon cancer-associated transcript 1 (CCAT1) significantly suppresses CCAT1 expression and reverses the resistance to the chemotherapeutic medication 5-FU. The resistance of these CRC cell lines to 5-FU therapy can be overcome by decreasing the levels of a particular form of lncRNA called CCAT1. Based on this discovery, it appears that CCAT1 is involved in mediating the 5-FU resistance. By increasing the susceptibility of these cells to 5-FU, targeting CCAT1 expression suppression may be a viable strategy to improve the efficacy of chemotherapy in the treatment of CRC [153]. In CRC, miR-31-5p is sucked up by the long intergenic nonprotein-coding RNA 689 (LINC00689), which suppresses tumor development, metastasis, and treatment resistance. By upregulating the expression of large tumor suppressor kinase 2 (LATS2) and blocking the β-catenin/yes-associated protein (YAP) signaling pathway, this approach is achieved. The lncRNA LINC00689 functions as a ceRNA by binding to and sequestering miR-31-5p. This prevents miR-31-5p from interacting with and repressing its other target mRNA transcripts. At higher levels, the lncRNA LINC00689 indirectly leads to increased expression of the LATS2 tumor suppressor kinase. LATS2 is known to hinder cancer cell proliferation and metastasis. Moreover, YAP/β-catenin signaling pathway blocking by LINC00689 is linked to medication resistance and tumor progression in

CRC. By regulating the expression of LATS2 and blocking the YAP/β-catenin signaling pathway, LINC00689 regulates CRC through its ceRNA activity. As a result, there is a decrease in treatment resistance, metastasis, and tumor growth. The previous findings emphasize the potential therapeutic significance of targeting the lncRNA LINC00689 and its related signaling pathways for the management and treatment of CRC [154]. It has been shown that elevated expression of the lncRNA MIR600HG, a tumor suppressor in CRC, limits tumor invasion and increases susceptibility to treatment. To do this, ALDH1A3, which codes for the enzyme aldehyde dehydrogenase, is the particular target. lncRNA MIR600HG works by modifying the expression of ALDH1A3, a gene linked to chemotherapy resistance and cancer progression. The increased levels of MIR600HG prevent tumor invasion and enhance the response to chemotherapy in CRC via interacting with ALDH1A3. The findings imply that MIR600HG has a tumor-suppressive function in CRC, and that increasing the expression of this RNA molecule may represent a therapeutic strategy to inhibit tumor infiltration and improve the effectiveness of chemotherapy. MIR600HG's regulatory impact on ALDH1A3 highlights its importance as a crucial mediator in these processes [155]. As was previously mentioned, autophagy affects tumor cell proliferation, survival, and responsiveness to therapy in a complicated way in CRC. Targeting certain autophagy-related proteins or signaling pathways, as well as using autophagy inducers or inhibitors, can all be used to modify autophagy. Scientists want to improve treatment efficacy by utilizing autophagy manipulation in conjunction with lncRNA-targeted strategies to take advantage of the interaction between autophagy and lncRNA-regulated activities. Combination therapies, which include autophagy regulation and lncRNA-targeted techniques, can also be used in addition to the current conventional treatments for CRC, which include surgery, chemotherapy, and targeted therapies. The objective is to concurrently target various pathways involved in the development of CRC in order to synergistically increase the effectiveness of existing treatments. This approach acknowledges the complex and heterogeneous nature of CRC and aims to develop customized treatment plans tailored to the unique features and needs of individual patients.

Conclusions

lncRNAs and exosomal lncRNAs have emerged as important players in CRC. Their involvement in several facets of CRC initiation and advancement has been shown, encompassing tumor growth, metastasis, and resistance to treatment. In oncology, especially CRC, autophagy—a cellular mechanism important in preserving cellular homeostasis—has been identified as a possible therapeutic target. Current treatment options based on autophagy in oncology are being explored in the context of CRC. Modulating autophagy can impact tumor cell survival, response to therapy, and overall treatment outcomes. Several strategies are being investigated, such as autophagy inhibition to sensitize cancer cells to chemotherapy or radiation therapy, or autophagy induction to trigger cell death in cancer cells. Targeted therapy development in CRC requires an understanding of the interaction between lncRNAs, exosomal lncRNAs, and autophagy. Exosomal lncRNAs can modify autophagy-related activities in the tumor microenvironment and are engaged in cell-to-cell communication. By targeting specific lncRNAs or manipulating exosomal lncRNA cargo, it may be possible to influence autophagy and enhance therapeutic responses in CRC. Clinical trials and preclinical studies are ongoing to investigate the potential of targeting autophagy and lncRNAs for improving outcomes in CRC patients.

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