Transcribed Ultraconserved Regions (T-UCR) as a Missing Puzzle in Cancer Research

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Independent research

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ABSTRACT

The ultraconserved regions (UCRs) of the DNA are highly similar across different organisms due to the negative selection of these DNA regions. The UCRs are transcribed into non-coding RNAs, named transcribed UCRs (T-UCRs). The current review on T-UCRs has identified the most significant T-UCRs for cancer, and it argues that there should be a focus on these T-UCRs to better understand their molecular mechanism in different cancers. Most of T-UCRs have an oncogenic role, with uc.63+, uc.338, uc.339, and uc.147 being the most commonly mentioned. At the same time, uc.160 and uc.454 have a tumor suppressor role. Uc.138 and uc.238+A have dual roles depending on the cancer type, probably through the modulation of different molecular pathways. Interestingly, there are T-UCRs with high specificity, such as uc.300A in neuroblastoma or uc.112 in B-ALL. Future research should acknowledge the current limitations and further improve the scientific approach.

Keywords: Ultraconserved regions, Noncoding RNAs, Cancer development, miRNA sponging, Oncogenic roles

Highlights

- T-UCRs affect cancer development and progression.
- Uc.63+ is the most common pro-carcinogenic T-UCR.
- Uc.160 is the most common tumor suppressor T-UCR.
- Most often, T-UCRs act by suppressing the activity of microRNAs.

Introduction

The ultraconserved regions (UCRs) of the DNA are genomic sequences that bear high similarity across multiple species, from sea anemones to humans.[1–5] Moreover, UCRs are not randomly distributed in the genome. They form approximately 61 gene clusters. These clusters are often flanked by coding genes involved in the formation of ion channels, transporters, and transcription factors.[1] The UCRs are transcribed into non-coding RNAs (ncRNAs), called transcribed UCRs (T-UCRs). Presently, it is considered that there are 481 T-UCRs in humans.[3] They have a length between 200 bp and 779 bp.[6] Hence, they are classified as long non-coding RNAs (lncRNAs). However, while lncRNAs have low similarity (0.3–3.9%) across multiple vertebrate species,[7] the conservation of T-UCRs[1,4,8] is comparable to that of protein-coding genes, which exhibit 40–90% sequence similarity across multiple vertebrate species.[7] This high level of conservation has led to the recognition of T-UCRs as a unique class of ncRNAs, with significant potential implications for advancing our understanding of human physiology and pathology.[8] This is because sequence conservation is attributed to biological significance and by extension to pathological state. T-UCRs are predominantly involved in embryonic development,[3] though their full functional roles remain to be fully elucidated. Their expression profiles vary across different pathological conditions,[9] with the majority of research focusing on cancer.[2,8,10–13]

A 2023 review identified 297 T-UCRs exhibiting differential expression between cancerous and normal tissues. These T-UCRs are linked to different clinical outcomes, such as: overall survival, disease-free survival, tumor size, lymph node involvement, and the presence of distant metastases.[10] In cancer, the T-UCRs go through a variety of changes that disrupt their function. In normal tissue, the ultraconserved elements rarely develop copy number variations (CNVs), while, in cancer cells the CNVs in UCRs are more common.[14] Also, in cancer cells versus normal cells, the methylation status of UCRs is changed.[15–17]

The understanding of the role of these lncRNAs is continuously evolving, driven by an increasing volume of studies on this topic. This review focuses on the role of T-UCRs in cancer development, categorized by cancer type. It provides an overview of their expression patterns and the molecular mechanisms underlying their tumor-suppressive or tumor-promoting effects. This review offers a comprehensive summary of the current data, providing a foundation for future research that focuses on T-UCRs of particular relevance to cancer.

Genetic and Molecular Mechanisms of T-UCRs

The pathological implications of T-UCRs come from their conserved sequences across species. The high conservation level is due to negative selection during evolution.[18] The ultraconserved elements rarely develop SNPs, duplications, or CNVs,[18–21] even in the context of pathology. For instance, in the European population with hereditary non-polyposis colorectal cancer the mutability is higher in regions flanking UCRs than inside the UCRs in both tumor tissue and normal adjacent tissue.[22] The low mutation rate of UCR was confirmed by another study on the general Caucasian population (n = 95). In this instance, 28 UCRs were sequenced, and six SNPs were found. This rate is lower (1/1572 nucleotides) than the general randomly selected human regions (1/279 bp).[23] However, lately due to a rapid growth of the human population and weak selection pressure, the rare single nucleotide variations in UCRs are becoming more frequent.[24]

The UCRs are grouped based on the Homo sapiens (human) genome assembly NCBI36 (hg18)[25] as: exon containing (4.2%), exonic (5%), partly exonic (5%), multiple (3.9%), intergenic (38.7%) and intronic

(42.6%). The exon containing means that the T-UCR contains the whole exon as well as part of the intron from a gene. The exonic UCR has one exon from the protein-coding gene. The partially exonic UCR contains one part of an exon and one part of the adjacent intron. Multiple UCR means that its genomic annotation depends on the splice variant of their gene of origin. Intergenic UCR is located between the genes. Intronic UCR has the intronic region of one protein-coding gene.[26]

As can be observed, the sequence of UCRs is many times contained inside protein-coding genes, which would once again explain their high conservation level. However, at the transcription level T-UCRs are many times independently expressed from their host mRNA: uc.63+ and Exportin 1 (XPO1);[27] uc. 147 and the LPS Responsive Beige-Like Anchor Protein (LBRA) gene[28] and uc.285+ and Cell Division Cycle and Apoptosis Regulator 1 (CCAR1).[29]

Some T-UCRs have a bidirectional transcription. They are transcribed in the same direction as the flanking gene or in the opposite direction. The frequency of generating a type of transcript specific for one direction is tissue-specific. For instance, uc.450+ is largely expressed in the nervous system, while uc.450– is specific for the respiratory system.[30] The direction of transcription affects the downstream molecular interactions of UCRs. In the general population, uc.276 with the [G] at 335 position, if it is transcribed in the sense orientation, can interact with miR-125a, but if it is transcribed in the antisense orientation, it can bind to miR-638.[23]

At the molecular level, T-UCRs are involved in several processes such as primary microRNA (pri-miRNA) processing,[31,32] miRNA sponging,[33] splicing regulation of mRNA, nonsense-mediated decay,[34] binding to mRNA, and inhibiting translation[35] (Figure 1). The interactions between T-UCRs and miRNAs are the most studied because they are highly relevant to the pathological mechanisms of T-UCRs.[36] For instance, uc.283+A has an 11 nucleotide sequence complementarity with pri-miR-195 in the Drosha binding area. In a normal cell line, uc.283+A is expressed at a normal level and represses the processing of miR-195. In a cancer cell, the transcription of uc.283+A is repressed through the methylation of the CpG island. This T-UCR is no longer bound to pri-miR-195. Thus, this miRNA is processed and can exert its pro-tumoral effects.[37] It is worth considering that T-UCRs might have higher stability than miRNAs. A study demonstrated that uc.339 has a higher stability than miR-339, miR-663b, and miR-95. At the same time, uc.339 has a relatively low expression when compared generally with miRNAs.[38]

Digestive System

Currently, the malignancies of the digestive system are the most studied in regard to dysregulation of T-UCRs. Due to the abundance of data this chapter was divided into tumor-promoting T-UCRs, tumor-inhibiting T-UCRs, and DNA mutations in UCR regions with carcinogenic consequences.

Tumor-Promoting T-UCRs

The most common T-UCRs with elevated expression in cancers of the digestive system are: uc.338, uc.285+, uc.339, uc.158–, uc.145, uc.345, and uc.189. Further details regarding their specificity for different organs and their biological/molecular effects are detailed in the following paragraphs.

The level of uc.338 was found to be elevated in cancer tissue, and it is directly correlated with tumor progression.[39,40] It causes increased cell viability, cell growth, self-renewal capacity,[40] and cell migration and invasion.[39] In HCT-116 cells specifically, uc.338 inhibition caused cell cycle arrest in the G1 phase.[40] P21 impairs cell cycle progression by inhibiting the activity of cyclin-dependent kinases (CDKs).[41] P21 is inversely correlated with the expression of uc.338. Moreover, this lncRNA exerts its oncogenic effects by activating the PI3K-Akt pathway,[40] a cancer-promoting pathway.[42] Uc.338 also targets TIMP Metallopeptidase Inhibitor 1 (TIMP-1) by binding in its 3'UTR and inhibiting its expression. TIMP-1 is reported as a tumor

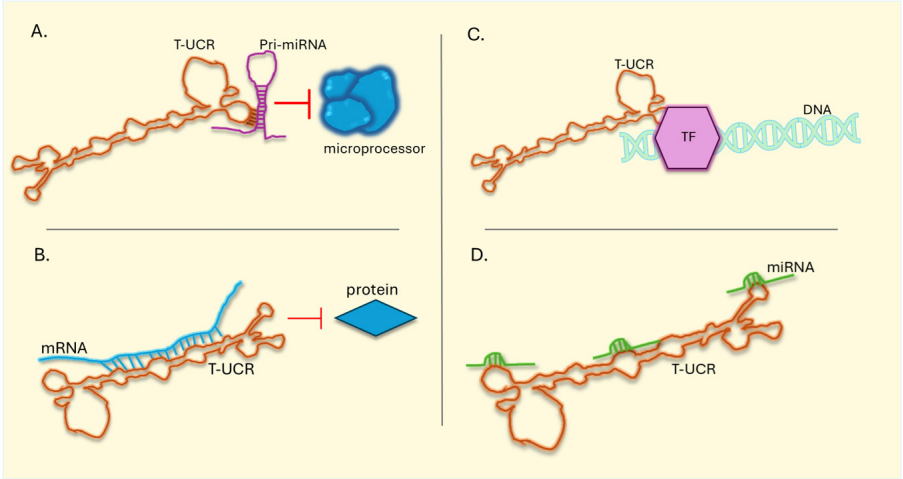

Fig 1 | The main molecular interactions established by T-UCRs. (A) T-UCR interacts with pri-miRNA and it inhibits its further processing by the microprocessor. (B) T-UCR also interacts with the mature miRNA. (C) T-UCR interacts with transcription factors and affects their activity. (D) T-UCR interacts with mRNA and inhibits its translation

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inhibitor in this study,[39] although others mention TIMP as having an oncogenic role in colon cancer.[43] Uc.338 was also increased in hepatocellular carcinoma (HCC) tissue as opposed to normal tissue. Uc.338 is involved in HCC cell cycle progression and cell proliferation.[44,45] It increases the expression of proteins involved in the cell cycle progression to the S phase: Cyclin-dependent kinase 4 (CDK4), Cyclin-dependent kinase 6 (CDK6), and cyclin D1.[44] At the same time, uc.338 suppresses Cyclin-Dependent Kinase Inhibitor 1A (*CDKN1A*) gene by recruiting BMI1 proto-oncogene, polycomb ring finger (BMI1) to its promoter region.[45] BMI1 is a central component of the polycomb repressive complex 1 (PRC1), which is involved in gene silencing through histone H2A ubiquitination.[46] In HCC, uc.338 also interacts with genes involved in cell proliferation: E2F1, Ribosomal Biogenesis Factor (BOP1), Syntaxin-61, epidermal growth factor receptor, Excision Repair Cross-Complementation Group 1, Forkhead box C1 protein, Oncostatin M, Sonic Hedgehog Signaling Molecule, and Zinc Finger E-Box Binding Homeobox 2.[47]

Another T-UCR with an oncogenic role in colon cancer is uc.285+. This T-UCR originates from the pre-CCAR1 gene. The mRNA of Cell Division Cycle 42 (CDC42) shared 10 bases with uc.285+. CDC42 is a member of the Ras-related GTPase family, which affects cytoskeletal organization and cell cycle progression. Uc.285+ overexpression increases the stability of CDC42.[29]

The cell-to-cell communication through extracellular vesicles (EVs) is necessary for tumor formation and survival.[48,49] These vesicles contain: proteins, peptides, RNAs, lipids, and DNA fragments[50] intended to keep the tumor-promoting phenotype of tumor-associated cells[48, 49, 51] or prepare a distant environment for metastasis formation.[50,52] A total of 290 T-UCRs were identified in the EVs of HCC cells. From these, 24 T-UCRs were specifically enriched in the EVs compared with the intracellular environment. The most up-regulated T-UCR was uc.339. Anchorage-independent growth and colony formation were reduced after si.uc.339 treatment of Hep3B and PLC/PRF/5 cells.[53]

The effects of T-UCRs are also dependent on the mutation status of their target protein. HepG2 is an HCC cell line with a mutation in the Catenin Beta 1 (*CTNNB1*) gene. Huh-7 is another HCC cell line with the wild-type (WT) form of *CTNNB1*.[54] *CTNNB1* encodes for β-catenin, a protein part of the Wnt/β-catenin pathway.[55] In the HepG2 cell line, the inhibition of uc.158– causes reduced cell viability and cell cycle arrest in sub-G0/G1 phases, while in Huh-7, it had no significant effect.[54]

Uc.145 plays an oncogenic role in gastric cancer. The enhancer of the zeste 2 polycomb repressive complex 2 subunit (EZH2) is a protein involved in DNA methylation through histone modification. Uc.145 stimulates the increased level of EZH2 protein. This protein has a binding site in the promoter region of the Dickkopf-1 (*DKK1*) gene.[56] *DKK1* is a suppressor of the Wnt/β catenin pathway.[57] As follows, uc.145 exerts its tumor-promoting activity in gastric cancer by increasing the methylation of the *DKK1* gene. The Wnt pathway is released from the inhibition of *DKK1* and begins to be overexpressed.[56] The Wnt/ β-catenin overexpression is involved in the progression of gastric cancer.[58]

Uc.345 is overexpressed in pancreatic cancer. Patients with high expression of uc.345 have a lower overall survival rate in comparison with patients with low expression of uc.345. The *in vitro* tests gave contradictory results. The exogenous overexpression of uc.345 in PANC-1 and Patu 8988 cells did not affect the cell viability and cell cycle progression, but it stimulated the self-renewal capacity. The proportion of cancer stem cells ($CD44^+$ and $CD24^+$) was also increased in the uc.345 overexpressing tumors.[59]

Lastly, the esophageal cancer was analyzed. Uc.189 is overexpressed in esophageal squamous cell carcinoma (ESCC)[35,60] and peritumoral lymphatic vessel[35] as opposed to normal tissue.[35,60] The overexpression of this miRNA increases with the tumor stage (TNM), formation of metastasis, and overall survival rate of the patients.[60] The exosomes from two ESCC cell lines, KYSE-150 and EC9706, contained high levels of uc.189. Uc.189 binds to the 3'UTR of Ephrin type-A receptor 2 (*EPHA2*) mRNA and inhibits its translation. *EPHA2* is an inhibitor of lymphangiogenesis. Thus, by inhibiting this receptor, uc.189 promotes the *de novo* formation of new lymph vessels.[35]

Tumor Inhibiting T-UCRs

Following the literature research, uc.77–, uc.73, uc.160, and uc.346 have antitumoral effects on malignancies of the digestive system. Further particularities of their expression regulation in specific cancers are provided below.

The expression of uc.77– has an antitumor effect in CRC. Uc.77– competes with F-box and WD repeat domain-containing 8 (*FBXW8*) for the binding of miR-4676-5p. If miR-4676-5p is bound to uc.77– then the level of *FBXW8* protein increases. This causes the ubiquitination of CDK4 and its down-regulation. The low level of CDK4 halts the cell cycle in G0/G1 phases.[61]

Uc.73 was found to be down-regulated in CRC tumor tissue compared with normal tissue, and it is positively correlated with the overall survival rate of patients.[62] However, uc.73 is up-regulated in hypoxia-exposed CRC cells, along with uc.63, uc.106, uc.134, and uc.475.[63]

Uc.283+A is inhibited through CpG island methylation in the colon cancer cell line HCT 116. Uc.283+A binds to the primary transcript of miR-195 and prevents the formation of the mature miR-195.[31] MiR-195 is a tumor suppressor in colon cancer by suppressing the Wnt/β-catenin pathway.[64] It also targets Insulin-like growth factor 1 and represses the PI3K/AKT pathway by controlling the phosphorylated forms of PI3K and Akt.[65]

The methylation of uc.160, uc.238, and uc.346 gradually increases from hyperplastic polyps to adenoma and then to *in situ* adenocarcinoma. However, their methylation decreases in invasive adenocarcinoma. HT-29 cells that developed resistance to 5-fluorouracil

or oxaliplatin had decreased expression of uc.283 and uc.346. The expression of uc.160 was also decreased in HT-29 cells resistant to fluorouracil but not for oxaliplatin.[66]

In gastric normal tissue, uc.160+ has a tumor-inhibiting effect by increasing the expression of phosphatase and tensin homolog (PTEN) and suppressing the phosphorylation of Akt. In gastric cancer, the expression of uc.160+ is impaired,[67,68] probably through the methylation of the promoter region.[67] The exogenous overexpression of uc.160 in SGC-7901 and AGS cell lines induces decreased viability and proliferation, as well as an increased apoptosis rate. In SCID mice, it leads to the formation of smaller tumors.[68]

A general view of the T-UCRs dysregulated in cancer from the digestive system is presented in Table 1.

Table 1 | Transcribed ultraconserved regions with differential expression in tumors from the digestive system

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.285+	CRC	Up	TT versus NT, • Higher in stage III and IV	**Promotes:** • Viability • Migration • Cell cycle **Inhibits:** • Apoptosis	**Increases:** • Tumor volume • Tumor weight	• Positive correlation with pre-CCAR1 • Binding to CDC42 mRNA and protein to increase its stability • Positive regulation of cyclin D1	29
uc.77–	CRC	Down-	TT versus NT	**Inhibits:** • Proliferation • Colony formation	**Decreases:** • Tumor size • Proliferation rate of cells inside the tumor	• uc.77– suppresses miR-4676-5p • miR-4676 inhibits FBXW8	61
uc.166–	CRC	Down		NA	NA	NA	
uc.160+	CRC	Down (TT versus TN)	TT versus NT	**Inhibits:** • Cell proliferation • Migration • Invasion	NA	NA	69
uc.346	CRC				NA	NA	
uc.283	CRC	Down					
uc.73	CRC	Down	TT versus NT	NA	NA	NA	62
uc.388	CRC	Down		NA	NA	NA	
uc.138	CRC	Up	TT versus NT	**Promotes:** • Cell growth • Cell cycle progression (G2/S) • Cell migration	**Increases:** • Tumor size	• Indirect increase of CDK1, cyclin A and cyclin B, CCNA1, CCNB2 • Indirect decrease of p21	70
uc.338+	CRC	Up	TT versus NT • Overall survival, larger tumor size, deeper tumor invasion, and increased lymph node metastasis	**Promotes:** • Viability • Colony formation • Cell cycle progression	**Increases:** • Tumor volume • Tumor weight	• Down-regulation of p21 • Up-regulation of cyclin-D1 • Phosphorylation of PI3K and Akt	40
uc.306	Liver cancer	Down	In M2 macrophage versus M1 macrophage*, TT versus NT	NA	NA	• Inhibition of β-TrCP protein	71
uc.147	Liver cancer	Up	Higher tumor grade versus lower tumor grade	**Promotes:** • Colony formation • Viability	NA	• TEAD4 binds to and positively regulates the expression of uc.147	30
uc.158–	Liver cancer	Up	CTNNB1 mutated HCC tissue versus in WT CTNNB1	**Promotes:** • Cell growth • 3D spheroid formation • Spheroid-based cell migration **Inhibits:** • Apoptosis	• Mice develop tumors after activation of Wnt pathway • Higher expression of uc.158– in these tumors	• Inhibition of miR-193b	54
uc.339	Liver cancer	Up	Extracellular vesicles from HCC cell lines versus cells of origin	**Promotes:** • Anchorage-independent growth • Colony formation	NA	• si.uc.339 led to 374 up-regulated genes and 469 down-regulated genes	53
uc.338	Liver cancer	Up	TT versus NT	**Promotes:** • Proliferation • Cell cycle progression	NA	• uc.338 recruits BMI1 to the promoter region of CDKN1A (p21), and it represses its transcription	45
uc.190	Pancreatic cancer	Up	TT versus NT/benign tissue	**Promotes:** • Viability (uc.233)	**Increases:** • Tumor formation in KRAS mutated mice	• EGR1 influences the transcription of uc.190, uc.233, uc.270	72
uc.233							
uc.270							

(Continued)

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Table 1 | Continued

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.345	Pancreatic cancer	Up	TT versus NT, initial stages versus late stages of the disease	**Promotes:** • Colony formation	• Tumor growth • Cancer stem cells	Correlated with the expression of hnRNPL	59
uc.63+	Gastric cancer	Up	TT versus NT, initial stages of the disease versus late stages	**Promotes:** • Proliferation	NA	• Causes overexpression of *PNLDC1*, *RARRES1*, *UGT1A8*, *EREG*, *ANGPTL2*, *BST2*, *SERPINB9*, *NNMT*, *STEAP4*, *MEST*, *TNS4*, *MYHAS*, *SAA4*, *SAA1*, *ZFP57*, *SEMA3A*, *ME3*, *IL6*, *CCL2*, *CCL1*, *IL-1B*, *p65* and *RELA*	73
uc.145	Gastric cancer	Up	TT versus NT, poor survival rate	**Promotes:** • Proliferation • Colony formation • Cell cycle arrest • Migration **Inhibits:** • Apoptosis	NA	• uc.145 interacts with *EZH2* and affects the methylation of the *DKK1* gene • It also has a reverse effect with *PRKG1-AS1* • *PRKG1-AS1* increases the expression of the *DKK1* gene • Increased N-CAD and Snail expression • Decreased E-Cad expression	56
uc.160+	Gastric cancer	Down	TT versus NT/tubular adenoma	NA	NA	• Suppression of AKT phosphorylation	67
	Gastric cancer	Down	TT versus NT, increased in stage III	**Inhibits:** • Proliferation • Viability **Promotes:** • Apoptosis	**Decreases:** • Tumor size • Tumor weight	• miR-155 binds to uc.160 • uc.160+ induces the overexpression of PTEN	68

* M2 inhibits the local immunity in the tumor and are tumor promoting, M1 = anti tumor effect, by stimulating local immunity; they also identify the cancer cells and kill them.
CRC = colorectal cancer, TT = tumor tissue, NT = normal tissue, NA = not available, CCAR1 = Cell Division Cycle and Apoptosis Regulator 1, CDC42 = Cell division control protein 42, FBXW8 = F-box and WD repeat domain-containing 8, CDK1 = Cyclin-dependent kinase 1, CCNA1 = Cyclin A1, CCNB2 = Cyclin B2, PI3K = Phosphoinositide 3-kinase, AKT Serine/Threonine Kinase 1 = AKT, β-TrCP = Beta-transducin repeats-containing proteins, TEAD4 = TEA domain transcription factor 4, Catenin beta-1 = CTNNB1B Lymphoma Mo-MLV Insertion Region 1 Homolog = BMI1, CDKN1A = cyclin-dependent kinase inhibitor 1A, EGR1 = Early Growth Response 1, hnRNPL = Heterogeneous Nuclear Ribonucleoprotein L, PNLDC1 = PARN Like Ribonuclease Domain-Containing Exonuclease 1, RARRES1 = Retinoic Acid Receptor Responder 1, UGT1A8 = UDP Glucuronosyltransferase Family 1 Member A8, EREG = Epiregulin, ANGPTL2 = Angiopoietin Like 2, BST2 = Bone marrow stromal antigen 2, SERPINB9 = Serpin Family B Member 9, NNMT = Nicotinamide N-Methyltransferas, STEAP4 = Six-Transmembrane Epithelial Antigen of Prostate 4, MEST = Mesoderm Specific Transcript, TNS4 = Tensin 4, MYHAS = myosin heavy chain gene cluster antisense RNA, SAA4 = Serum Amyloid A4, SAA1 = Serum Amyloid A1, ZFP57 = Zinc Finger Protein 57 Homolog, SEMA3A = Semaphorin 3A, ME3 = Malic Enzyme 3, IL6 = Interleukin 6, CCL2 = C-C Motif Chemokine Ligand 2, CCL1 = C-C Motif Chemokine Ligand 1, IL-1B = Interleukin 1 Beta, RELA = REL-associated proto-oncogene NF-kB subunit, EZH2 = Enhancer of zeste homolog 2, DKK1 = Dickkopf-related protein 1, N-CAD = NCadherin, E-Cad = E-cadherin, PTEN = Phosphatase and tensin homolog.

DNA Mutations in UCR Regions

The carcinogenic effects of UCRs extend beyond the dysregulated expression of their transcription. Given the slow evolutionary rate of mutations in these regions, it is unsurprising that certain population variants caused by SNPs in UCRs can have pathological consequences. To date, the risk of cancers in the digestive system, particularly colorectal cancer, has been the most extensively studied in this context. This section reviews the genetic variants within UCRs that either elevate or reduce the risk of developing colorectal cancer.

Rs7849 is in a region located in the Stearoyl-CoA desaturase-1 gene that also contains the uc.298 in the 3'UTR. CRC patients who carry a variant of this SNP ("G" allele) have an increased risk of recurrence of the disease after treatment. rs10211390 is in the LOC7301134 gene, and it is transcribed into uc.54. Individuals with rs10211390 homology (GG) also have an increased risk of recurrence of colorectal cancer. Also, patients with rs2421099 ("T" allele) and rs16983007 ("A" allele) have an increased risk of recurrence. rs2421099 is transcribed from the Sideroflexin 5 (*SFXN5*) gene, and it contains in its intron uc.66, while rs16983007 is in the *FAM48B1* gene that encodes also for uc.465. For stage III CRC, a decrease in recurrence after fluoropyrimidine-based chemotherapy is associated with the rs6124509 variant and the rs11195893 variant.[74]

A study comparing 787 CRC patients with 551 healthy controls found a significant association between CRC risk and SNPs in UCRs of the DNA. Homozygotes for rs7849 (GG) are associated with a reduced risk of CRC compared to GA or AA carriers. Rs.7849 is in the 3'UTR of stearoyl-CoA desaturase, where uc.298 is also transcribed. For rs1399685, there is an increase in the risk of CRC in the case of allele carriers of A, either homozygotes or heterozygotes. Rs.1399685 is in the *LOC728773* gene, and it is also transcribed into uc.81. Moreover, carriers of the rs6124509 variant had a borderline reduced overall risk of CRC and decreased risk of right-sided CRC. Rs6124509 is in the 3'FR of RB transcriptional corepressor-like 1 (*RBL1*) gene, and it is transcribed into uc.455. The major allele is "A," and the minor allele is "G." Subjects carrying rs1399685 TA + AA and rs9784100 GC + CC have the highest risk of developing CRC.[75]

SNP rs6983267 is associated with an increased risk of colorectal cancer. This SNP is located in a UCR of the DNA, named colon-cancer-associated transcript 2, CCAT2. It has a higher expression in colorectal cancer tissue versus normal tissue. Moreover, the ncRNA transcribed from this gene can stimulate *in vivo* tumor growth and metastasis. If the CCAT2 carries the G allele, it will activate the Wnt pathway; if it carries the T allele, it will not activate this pathway.[76]

Excretory System

Having explored the digestive system cancers, we now focus on the role of T-UCRs in the excretory system, where unique patterns of expression emerge. There was less available data on this subject, which is why this chapter was not divided into subchapters.

Uc.63 is up-regulated in bladder cancer tissue versus normal tissue. It increases the viability of UMUC3 cells. In the RT112 bladder cancer cell line, uc.63 offers chemoresistance to cisplatin by activating the androgen receptor (AR).[77]

Olivieri et al. took an in-depth look at the expression of T-UCRs in bladder cancer. They found that uc.8+ is the most up-regulated T-UCR in bladder cancer tissue compared with normal bladder epithelium taken from a control healthy group. However, uc.8+ had a lower expression in tumor tissue than in the pericancerous tissue from bladder cancer patients. In the bladder cancer cell line, J82, the reduced expression of uc.8+ caused reduced cell growth, a lower percentage of cells found in the S phase, and a slower rate of cell invasion/migration. The location of uc.8+ also differs through malignancy progression. It was found that uc.8+ has a nuclear localization in high-grade bladder cancer and in normal tissue, whereas, in low-grade bladder cancer, it has a cytoplasmic localization.[78] These results contradict another study, where uc.8+ was found in the cytoplasm and nucleus in low-grade bladder cancer, while in high-grade bladder cancer, it was localized only in the cytoplasm.[79] Different cellular locations of an RNA often indicate different molecular targets.

Uc.416+A plays a tumor-promoting role in renal cell carcinoma. It stimulates epithelial-to-mesenchymal transition through inhibition of E-Cadherin (E-Cad) and stimulation of Snail and Vimentin. Uc.416+A has a reverse correlation with the tumor-inhibiting miRNA, miR-153.[80] The full list of the T-UCRs and their roles in cancers of the excretory system are presented in Table 2.

Respiratory System

Moving on from the excretory system, the respiratory system was analyzed in terms of dysregulated expression of T-UCRs and the development of tumors. All the findings on this subject were on lung cancer, the most prevalent cancer type worldwide, with over 2.48 million cases.[82,83] Until now, the role of T-UCRs in lung cancer has been related mostly to their increased expression. More details regarding the role of T-UCRs in lung cancer are available in the following paragraphs.

Uc.339 is up-regulated in lung cancer tissue compared with normal lung tissue. Furthermore, patients with overexpression of uc.339 have a shorter overall survival rate.[38,84] The expression of uc.339 is dependent on the expression of ATP Synthase Membrane Subunit C Locus 3 (*ATP5G3*) and p53. Uc.339 is transcribed as an antisense transcript from *ATP5G3*. There is an inverse correlation between the expression of uc.339 and *ATP5G2*. Also, p53 has a binding location of 2963 bp upstream of the uc.339 region. The p53 wild-type lung cancer cells have a decreased expression of uc.339, compared with the p53 mutated cancer cells. Exogenous induced expression of p53 in the p53-null cell line, H1299, lowered the expression of uc.339.[38] At the molecular level, uc.339 acts as a miRNA sponge for miR-339,[38,84] miR-663b, and miR-95. All these three miRNAs target Cyclin E2 (*CCNE2*), a protumor protein. There is also a direct correlation of expression between uc.339 and *CCNE2*.[38] In addition, by inhibiting miR-339, uc.339 allows for the increased expression of solute carrier family 7 member 11 (*SLC7A11*). *SLC7A11* is an inhibitor of ferroptosis, which is a natural process of iron-dependent cell death that impairs tumor formation.[84]

Uc.338 has a carcinogenic effect on lung cancer. It causes the epithelial-to-mesenchymal transition of cells by down-regulating E-cad and up-regulating N-Cad, Vim, and Snail.[85]

Table 2 | Transcribed ultraconserved regions with differential expression in tumors from the excretory system

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.8+	Bladder cancer	Up (control) Down (adjacent)*	TT versus NT (adjacent + control)	**Promotes:** • Invasion • Migration • Viability • Cell cycle progression	NA	• It inhibits miR-596 • miR-596 suppresses MMP9 • CASZ1 (mRNA of origin) is higher in NT versus TT, whereas uc.8 is higher in TT versus NT	78
uc.339		Up (control)	TT versus NT (control)	NA	NA	NA	
uc.195	Bladder cancer	Up	Peri bladder cancer normal tissue versus tumor tissue	NA	NA	NA	
uc.63+	Bladder cancer	Up	TT versus NT	**Promotes:** • Proliferation • Resistance to cisplatin **Inhibits:** • Apoptosis	NA	• Increases expression of AR	77
uc.8+	Bladder cancer	Up	Low grade versus high grade, TT versus NT	NA	NA	• DDX19B and NXF1 stimulate the nuclear exportation of uc.8+	79
uc.213+A uc.455+A	Bladder cancer	Down	TT versus NT, low grade versus high grade	NA	NA	NA	81
uc.283+A uc.339+	Bladder cancer	Up	TT versus NT, low grade versus high grade				
uc.416+A	Renal cell carcinoma	Up	TT versus NT, increased in sarcomatoid tissue	**Promotes:** • Migration • Cell growth	NA	• Direct binding to mir-153 • Indirect induced expression of snail, VIM, and decreased E-Cad.	80

* Control = Normal tissue from healthy donors, Adjacent = Normal peritumoral tissue from bladder cancer patients.
TT = tumor tissue, NT = normal tissue, NA = not available, MMP9 = metalloproteinase 9, CASZ1 = Castor Zinc Finger 1, AR = androgen receptor, DDX19B = DEAD-Box Helicase 19B, NXF1, VIM = Vimentin, E-cad = E-cadherin.

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Uc.83– is another T-UCR with higher expression in tumor tissue compared with normal tissue. Also, the comparison between 4 lung cancer cell lines found that uc.83– was expressed only in H358 and H1299. Uc.83– is transcribed from *LINC01876*. However, their expressions are independent of each other. In H358 and H1299, the silencing of uc.83– caused decreased cell growth and cell cycle arrest in the G0/G1 phase. The overexpression of uc.83– in all the analyzed lung cancer cell lines increased their viability. Uc.83– acts by stimulating the phosphorylation of AKT and ERK1/2.[86]

Uc.454 has a decreased expression in lung cancer tissue compared with normal adjacent tissue. It has an anticancer effect on lung cancer by decreasing the migration and invasion of A549 and H460 cells. This is done by inhibiting the translation of KRAS, which further down-regulates the expression of p63 and MMP9.[87]

The full list of the T-UCRs and their roles in cancers of the respiratory system are presented in Table 3.

Reproductive System and Accessory Organs

The next system where a major part of malignancies is located is the reproductive system and accessory organs. The discussion here was divided between the female reproductive system and the male reproductive system.

Female Reproductive System and Accessory Organs

In women, the most prevalent cancer type is breast cancer, with over 2 million cases worldwide.[82,83] As follows, most studies were focused on breast cancer.

Uc.51 has an oncogenic role in breast cancer. It does so by binding and increasing the stability of non-POU domain-containing octamer-binding protein (NONO).[90] NONO is an oncoprotein in breast cancer by stimulating the activation of the Akt/MAPK/β-catenin pathway and inhibiting the Programmed Cell Death Ligand 1 expression.[91]

Uc.63 is increased in breast cancer tissue[92] and breast cancer cell lines.[93] The siRNA silencing of uc.63 caused cell apoptosis and cell cycle arrest in the G0/G1 phase.[93] In addition, in hypoxic conditions, as specific for almost all solid tumors,[94] Hypoxia-inducible factor 1-alpha is overexpressed. This protein was also found at the promoter regions of uc.63 and uc.475, which led to the overexpression of these T-UCRs in hypoxic conditions.[63]

Uc.246 is elevated in advanced forms of breast cancer. In the double-positive breast cancer cell line, MCF-7, when uc.246 was overexpressed, it caused increased tube formation by HUVEC cells during co-culture.[95]

Uc.147 is specifically up-regulated in luminal A breast cancer.[96,97] The patients with high expression of this ncRNA have a poorer prognosis than patients with low expression. The effects of uc.147 are

Table 3 | Transcribed ultraconserved regions with differential expression in tumors from the respiratory system

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.339	Lung cancer	Up	TT versus NT	**Promotes:** • Invasion • Migration • Proliferation **Inhibits:** • Ferroptosis	**Decreases:** • Animal survival **Increases:** • Metastasis formation • Tumor volume	• uc.339 suppresses miR-339 • SLC7A11 is a target of miR-339	84
uc.339	Lung cancer	Up (especially in $p53^{mut}$)	TT versus NT	**Promotes:** • Viability • Cell cycle progression • Migration	**Increases:** • Tumor growth speed • Tumor volume	• TP53 binds 2963 bp upstream of the DNA region containing uc.339. • uc.339 contains trapping-related elements for miR-339, miR-663b, miR-95. • Cyclin E2 indirect up-regulation	38
uc.63–	Lung cancer	Up	TT versus NT tumor stage	NA	NA	• XPO1, uc002sbh, and uc002sbg are potential targets	88
uc.280+		Up	TT versus NT			NA	
uc.338	Lung cancer	Up	TT versus NT	**Promotes:** • Proliferation • Cell cycle progression • Invasion • Migration	NA	• Stimulation of Snail, VIM, N-CAD, Cyclin B1, Cdc25C • Inhibition of E-CAD	85
uc.338	Lung cancer	Up	TT versus NT, higher TNM, lower overall and disease-free survival	NA	NA	NA	89
uc.83–	Lung cancer	Up	TT versus NT, with various levels in cell lines	**Promotes:** • Viability • Growth • Cell cycle progression	NA	• Increased phosphorylation of AKT and ERK1/1	86
uc.454	Lung cancer	Down	TT versus NT, decreased in metastasis	**Inhibits:** • Migration • Invasion	NA	• Binding to KRAS at the mRNA level and decreased its expression as well as the protein levels of its downstream proteins: P63 and MMP9	87

TT = tumor tissue, NT = normal tissue, NA = not available, SLC7A11 = solute carrier family 7 member 11, XPO1 = Exportin 1, VIM = Vimentin, N-CAD = N-Cadherin, Cdc25C = Cell Division Cycle 25C, E-CAD = E-cadherin, AKT = Serine/Threonine Kinase 1, ERK1 = Extracellular signal-regulated kinase 1, KRAS = Kirsten rat sarcoma virus, MMP9 = Matrix metalloproteinase-9.

cell-line-specific. The si.uc.147 caused cell cycle arrest in G0/G1 in the CAMA-1 cell line but not in BT474. Still, the colony formation capacity was decreased in both cell lines. Uc.147 is an intronic UCR of the LPS Responsive Beige-Like Anchor (LRBA) gene. The siRNA against uc.147 affected only the LRBA mRNA but not the LRBA protein.[96]

MiR-221 is overexpressed in basal-like breast cancer cells and underexpressed in luminal breast cancer when compared to normal tissue. Its overexpression in luminal breast cancer slows the invasion, migration, and colony formation of malignant cells.[98] The overexpression of miR-221 decreases the level of uc.110, uc.84, uc.96, and uc.183. The silencing of these T-UCRs increase the level of pre-miR-221. This is an example of a feedback interaction between the ultraconserved transcripts and the primary miRNA transcript.[99]

In malignant breast tissue, uc.38 is down-regulated when compared with benign breast tumors[92] or normal tissue.[100] The expression of uc.38 decreases even further in stage IV of the disease.[92,100] This ncRNA is specifically bound to Pre-B-cell leukemia transcription factor 1 (PBX1) at the protein level, which increases its stability. PBX is involved in the increased apoptosis of cells through the down-regulation of B-cell lymphoma-2 (BCL2) and up-regulation of BCL2-associated X.[100]

Sometimes, the induction of SNPs in UCRs causes the development of cancer. In the analysis, two SNPs from the cytoplasmic polyadenylation element binding protein 4 that overlap with uc.184, rs17695092 and rs1564823, were found to increase the risk of breast cancer.[101] In another study, it was discovered that the variant of rs8004379 is the most significantly associated with an increased risk of breast cancer. This SNP is in a region that is transcribed into uc.368.[102] Also, the [G] allele from rs2056116 showed an increased frequency in the familial breast cancer cases, whereas rs9572903 showed only a borderline significant association.[103] Rs9572903 is a region of uc.353, and rs2056116 is located in the uc.140 sequence.

Only two studies were found on other organs of the female reproductive system that proved the pro-carcinogenic role of uc.189 and uc.206 in this context.

In cervical squamous cell carcinomas (CSCCs), endometrial adenocarcinomas (EACs), and ovarian cystadenocarcinoma, it was found that in most cases, uc.189 has increased expression, compared with normal tissue. The low expression of uc.189 increases the survival rate of patients with CSCC and EAC.[60]

Uc.206 is up-regulated in cervical cancer tumor tissue and in cervical cancer cells. In the HeLa cell line transfected with uc.206 containing plasmid, the proliferation of cells was stimulated. Uc.206 binds to the 3'UTR of p53. Uc.206 has an inverse association with p53 in cervical cancer tissue ($r = -0.625$). When p53 is overexpressed, the cell proliferation rate of Hela cells is slowed down.[104]

Male Reproductive System and Accessory Organs

The most common cancer of the male reproductive system is prostate cancer, with 1.4 million cases worldwide.[82,83] In prostate cancer, several T-UCRs were found to have dysregulated expression during the initiation and progression of the malignancy. Further details are available below. The last section of this subchapter is dedicated to findings about the UCR mutations in correlation to prostate cancer.

The expression of uc.63+ was directly associated with a higher Gleason score and increased level of prostate-specific antigen (PSA). *In vitro*, when uc.63+ was overexpressed, it stimulated the proliferation of LNCaP and PC3 cells. It does so by overexpressing the AR, independent of dihydrotestosterone.[27] The increased expression of AR is specific for prostate cancer cells that are able to grow continuously under the influence of male hormones.[105] At the molecular level, uc.63+ inhibits the expression of miR-130b.[27] MiR-130b inhibits the metastasis of prostate cancer cells by down-regulating metalloproteinase 2 (MMP2).[106] As follows, uc.63+ also promotes migration by releasing MMP2 from the inhibition of miR-130b.[27]

Uc. 106+ is up-regulated in prostate cancer tumors, but its expression decreases with the advancement of tumors. Uc.106+ has an inverse correlation with the genes involved in the interferon pathway.[15] The interferon pathway has a tumor suppressor role, and it is commonly down-regulated in prostate cancer.[107,108] Si.uc.106+ leads to the up-regulation of genes related to cell death and the down-regulation of genes involved in cell cycle progression and DNA replication.[15] More T-UCRs with up- or down-regulated expression in prostate cancer are provided in Table 4.

The SNP rs8004379 in uc.368 is correlated with the biochemical recurrence of prostate cancer patients. The C variant is associated with decreased biochemical cancer recurrence and prostate-cancer-specific mortality. The replacement of C to A causes a reduction in free energy. This locus affects the RNA structure of uc.368, and it increases the expression of neuronal PAS domain protein 3 (*NPAS3*). NPAS3 expression is significantly associated with reduced recurrence after radical prostatectomy.[109] The full list of the T-UCRs and their roles in breast and prostate cancer are presented in Table 4.

Brain Tumors

Moving on from the reproductive system, the role of T-UCRs in cancers of the nervous system was discussed. The available findings were based on neuroblastoma and glioma, two aggressive forms of cancer.

Neuroblastoma is a malignant disease that develops in the sympathetic progenitor cells that do not differentiate into mature cells. All-trans retinoic acid (ATRA) is a treatment option that helps in the differentiation of progenitor cells into mature cells.[110] In neuroblastoma cell lines, it was discovered that the treatment with ATRA causes a significant change in the expression of T-UCRs, especially the down-regulation of uc.300A. Uc.300A plays an oncogenic role in neuroblastoma, by stimulating cell proliferation and invasion of malignant cells. Uc.300A is transcribed antisense from Paired box 2 (PAX2) gene[111] PAX2 is a gene specifically

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Table 4 | Transcribed ultraconserved regions with differential expressions in breast and prostate cancer

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.51	Breast cancer	Up	TT versus NT	**Promotes:** • Proliferation • Migration • Invasion	**Increases:** • Metastasis formation • Proliferation rate of cells inside the tumor	• Increases the stability of NONO protein	90
uc.38	Breast cancer	Down	TT versus NT, stage I/II versus stage III/IV	**Inhibits:** • Viability • Colony formation **Promotes:** • Apoptosis	**Decreases:** • Tumors size • Tumor weight **Increases:** • Survival rate	• Degrades the PBX1 protein	100
uc.38	Breast cancer	Down	Malignant breast cancer versus benign breast tumors, stage IV versus stage I/II/III	NA	NA	NA	92
uc.63	Breast cancer	Up	Malignant breast cancer versus benign breast tumors, M1 versus M0	NA	NA	NA	
uc.138 uc.311 uc.376 uc.456	Breast cancer	Down	TT versus NT	NA	NA	NA	97
uc.147 uc.193 uc.268 uc.271 uc.378 uc.427		Up	TT versus NT				
uc.268	Breast cancer	Up (patients ‹40 years)	Breast cancer tumors from patients ‹40 years old versus › 40 years old				
uc.84	Breast cancer	Down (metastasis)	Breast cancer tumors from patients with metastasis or without metastasis				
uc.376	Breast cancer	Down (stage IV)	Breast cancer tumor tissue from different stages of the disease				
uc.63+	Prostate cancer	Up	Higher in patients with metastatic PC poor response to docetaxel.	**Promotes:** • Migration • Proliferation	NA	• It enhances the expression of AR and PSA • Interacts with miR-130b and down-regulates MMP2	27
uc.106+	Prostate cancer	Up	TT versus NT, lower in high Gleason score	NA	NA	• Inverse correlation with IRF7, ISG15, ISG20, OAS1-3, PTPN22	15
uc.346+	Prostate cancer	Down	Primary versus metastatic tumor, high versus low Gleason grade			• Inverse correlation with miR-143, miR-27, miR-21, and miR-16 • Direct correlation with miR-373	
uc.34	Prostate cancer	Down	High versus low Gleason grade	NA	NA	NA	
uc.363+A uc.477+	Prostate cancer	UP	TT versus NT	NA	NA	NA	
uc.454+A		Down				• It interacts with RIN and RAB37	
uc.283+A		Up	Before versus after treatment with 5-AzaC and TSA	NA	NA	NA	

TT = tumor tissue, NT = normal tissue, NA = not available, NONO = Non-POU domain-containing octamer-binding protein, PBX1 = Pre-B-cell leukemia transcription factor 1, AR = androgen receptor, PSA = Prostate-specific antigen, MMP2 = Matrix Metallopeptidase 2, RAB37 = Ras-Related Protein Rab-37, PC = prostate cancer, TSA = Trichostatin A, IRF7 = interferon regulatory factor 7, ISG15 = Interferon-stimulated gene 15, ISG20 = Interferon-stimulated gene of 20 kDa protein, OAS1-3 = 2′-5′-Oligoadenylate Synthetase 1, and PTPN22 = Protein Tyrosine Phosphatase Non-Receptor Type 22.

expressed in the nervous system and kidneys. It is crucial for the mid-hindbrain boundary formation during embryonic development. It also helps in the differentiation of GABA precursor neurons.[112] Several RNA species were up-regulated following both si.uc.300A and ATRA treatment. From these, the calcitonin-related polypeptide alpha (*CALCA*) was the most significant.[111] *CALCA* has been previously correlated with pain-related pathologies, such as migraine.[113] Uc.300A might play a significant role in the targeted therapies for brain tumors, considering that it originates from a protein-coding gene expressed specifically in the brain.

Sometimes, several correlations between T-UCRs and miRNAs affect the progression of a malignant disease. In a study of neuroblastoma, which compared the molecular characteristics of removed tumors from short-term survivors versus long-term survivors, a series of correlations were found. In long-term survivors, 10 pairs of up-regulated T-UCRs and down-regulated miRNAs were listed: uc.209-miR-877, uc.272-miR-383,

uc.312-miR-877* and miR-548d-5p, uc.330-miR-548d-5p, uc.371-miR-877, uc.411-miR-33b, uc.421-miR-877*, uc.235-miR-939, and uc.452-miR-383.[114]

Uc.101 has almost no expression in normal brain tissue, but in glioma, its expression increases significantly. It stimulates the viability and invasion of malignant cells. In immunocompromised mice injected with the U251 glioma cell line, the si.uc.101 cells formed smaller tumors and the mice survived longer. Uc.101 has a direct association with the expression of membrane frizzled related protein (MFRP), a member of the Wnt signaling pathway.[115] The Wnt signaling pathway activation maintains the stemness of the glioma cells, thus contributing to the highly aggressive phenotype of this disease.[116,117] At the same time, miR-544 targets both uc.101 and MFRP. The up-regulation of miR-544 in glioblastoma decreases the expression of uc.101 and MFRP and reduces cell accumulation.[115]

The full list of the T-UCRs and their roles in brain tumors are presented in Table 5.

Hematologic Malignancies

Lastly, the analysis of the role of T-UCRs in cancer moved to hematologic malignancies. These tumors originate in the bone marrow and lymph nodes, where a malfunction of the normal hematopoietic function occurs. They have an acute or chronic form.[118]

T-UCRs have differential expressions depending on the type of hematologic malignancy. In a pilot study (9 B-ALL and 9 T-ALL cases) including only pediatric patients, the high expression of uc.112 was associated with T-ALL but not with B-ALL. When the non-tumor precursor cells were compared, uc.112 had no difference in expression between B and T normal cells.[119]

Chronic lymphocytic leukemia (CLL) patients with high expression AC092652.2.202 (an uc.70-related transcript) have a time to treatment (TTT) of 30 months

Table 5 | Transcribed ultraconserved regions with differential expression in brain tumors

Name	Cancer Type	Expression in Cancer	Tissue Samples	*In Vitro* Analysis	*In Vivo* Analysis	Molecular Mechanism	Ref.
uc.160+	Glioma	Down	TT versus TN	NA	NA	• Editing and processing of pri-miR376 • Inhibits RYBP and FOXP2 proteins	17
uc.101	Glioma	Up	TT versus TN	• Invasion • Cell viability	• Tumor size • Survival rate	• Interacts with MFRP and is directly correlated • Inhibits miR-544 -activates the WNT pathway	115
uc.300A	Neuroblastoma	Down (after ATRA treatment)	NA	Neuroblastoma cell lines compared before and after neurite differentiation (ATRA treatment)	NA	CALCA and LOC402199 lower expression after uc.300 siRNA COL1A2 and INPP5D up-regulated after u.300A siRNA	111
uc.396 uc.481a uc.195a uc.49a uc.449 uc.203 uc.48 uc.419a uc.50a uc.300a uc.284 uc.48a uc.243 uc.163 uc.388 uc.97 uc.82a	Neuroblastoma	Down (after ATRA treatment)			NA	NA	
uc.324 uc.127a uc.75 uc.345a uc.409 uc.109 uc.113a uc.465a uc.344 uc.359a uc.198a uc.206 uc.217 uc.451	Neuroblastoma	Up (before ATRA treatment)			NA	NA	
uc.460, uc.279	Neuroblastoma	Up in MYCN amplified tumors	MYCN amplified tumors versus MYCN non-amplified tumors	NA	NA	NA	26

TT = tumor tissue, NT = normal tissue, NA = not available.

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versus patients with low expression who have a TTT of 116 months. AC092652.2.202 affects the gene expression of genes involved in NF-kB, TP53, and apoptosis pathways.[120]

MiR-155 has an up-regulated expression in CLL. This miRNA suppresses the expression of uc.346A and uc.160. MiR-24-1 is also overexpressed in CLL and causes the suppression of uc.160. This further allows for the overexpression of proteins involved in evasion from apoptosis, self-sufficiency in growth signals, and probably dissemination to distant organs.[121]

Discussions

As research on T-UCRs and cancer continues to grow, it is becoming increasingly evident that these ncRNAs play a crucial role in the molecular mechanisms underlying cancer development and progression.

The available literature has provided insights into the molecular mechanisms of T-UCRs in cancer, as summarized in Figure 2, where a general and useful picture is provided. In HCC, at the nuclear level, uc.338 binds to the transcription factors Pax6 and p53, thereby influencing the transcription of various genes (Figures 2C and D).[47] T-UCRs also interact with pri-miRNAs, where they can either inhibit or promote the processing of pri-miRNAs. In colorectal carcinoma, uc.283+A can prevent the binding of the microprocessor to pri-miRNA-195, thereby repressing the formation of mature miR-195; thus, the targeted mRNAs are released from its control (Figure 2A).[47] In contrast, in glioma, uc.160+ stimulates pri-mi-376 processing into pre-miRNA. After processing by Dicer, the mature miR-376 is generated, which then represses the translation of target mRNAs: RING1 And YY1 Binding Protein (RYBP) and Forkhead box protein P2 (FOXP2) (Figure 2B).[17] In the cytoplasm, T-UCRs bind to mRNAs, proteins, and mature miRNAs. In non-small-cell lung cancer, the interaction between WT p53 and uc.339 prevents uc.339 from binding to miR-339-3p, miR-95-5p, and miR-663b-5p. This, in turn, allows these miRNAs to bind to their target mRNA, *CCNE2*, and suppress its translation (Figure 2E). In the case of p53 mutation, uc.339 is no longer capable of interacting with p53, and it binds to these miRNAs, evading their regulatory effects and leading to the translation of the *CCNE2* protein (Figure 2F).[38] Furthermore, in colorectal cancer, uc.285+ binds to the CDC42 mRNA or protein, leading to its repression through inhibition of translation or lower stability (Figure 2G).[38]

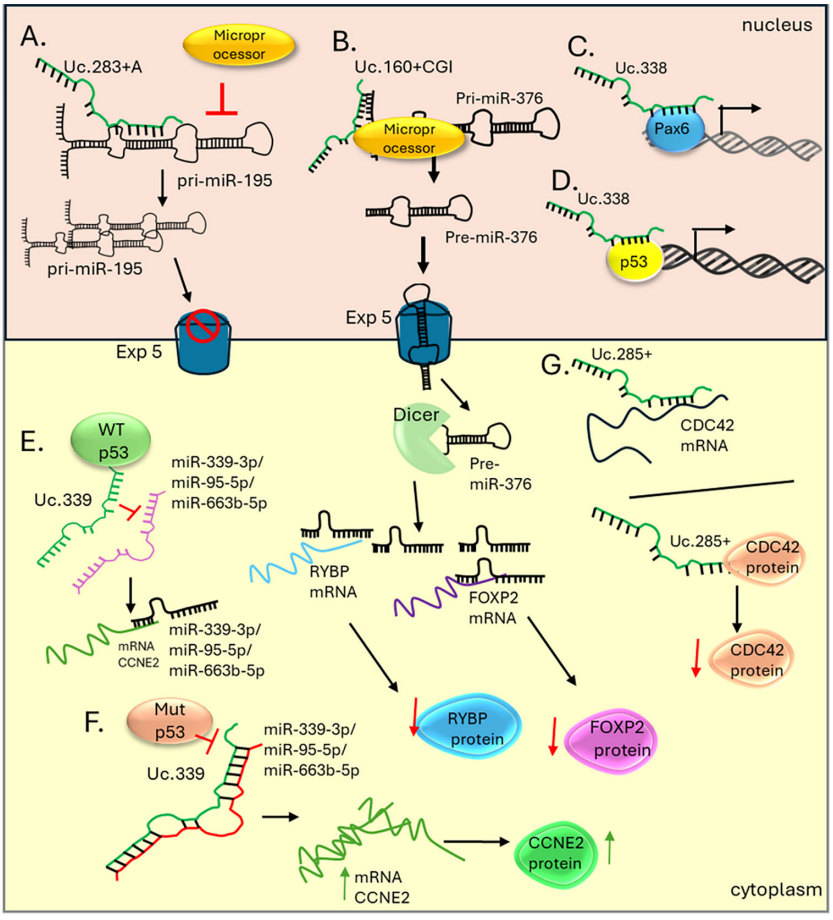

Fig 2 | The T-UCR-based molecular mechanisms that sustain cancer development and progression. (A) uc.283+A interacts with pri-miR-195 and represses its interaction with the microprocessor. (B) When uc.160+CGI interacts with pri-miR-376, its processing is stimulated, which further raises the level of miR-376. This causes the down-regulation of its target mRNAs, RYBP (RING1 and YY1 binding protein) and FOXP2 (Forkhead box protein P2). (C) uc.338 binds to PAX6 (Paired box protein Pax-6) or (D) p53 and regulates gene expression at the DNA level. (E) wild-type p53 interacts with uc.339. Thus, miR-339-3p, miR-95-5p and miR-663b-5p can suppress the translation of *CCNE2* (cyclin E2). (F) The mutated form of p53 does not bind to uc.339 thus uc.339 interacts with miR-339-3p, miR-95-5p and miR-663b-5p. (G) uc.285+ can bind to both CDC42 (Cell division control protein 42 homolog) mRNA and protein

Among these, uc.63+ stands out as the most commonly identified oncogenic T-UCR, showing a tumor-promoting role in gastric, bladder, lung, breast, and prostate cancers. The second most oncogenic T-UCR is uc.338, which has been implicated in colon, liver, and lung cancers. Additionally, uc.339 has been shown to play an oncogenic role in liver, bladder, and lung cancers (Figure 3A). On the other hand, there are fewer tumor-suppressive T-UCRs, with only uc160+ being the most frequently reported tumor suppressor (gastric cancer, glioma, CLL, and colorectal) (Figure 3B). These lists show the scarcity of data and the lack of focus in the current approach. The lists may evolve and change with more studies.

Moreover, there is not a clear line between oncogenic and tumor inhibitor T-UCRs. Some T-UCRs exhibit a dual role, even in the current data, with their effects varying depending on the cancer type. For example, uc.138 is up-regulated in colon cancer,[70] but down-regulated in breast cancer.[97] Similarly, uc.283+A is a tumor suppressor in colon cancer[69] and an oncogene in bladder cancer.[81] The dual role is not specific to T-UCRs. There are many lncRNA with the same characteristics, such as PCAT19,[122] PART1,[123] TINCR.[124] For lncRNAs, the dual role is partially explained by tissue-specific

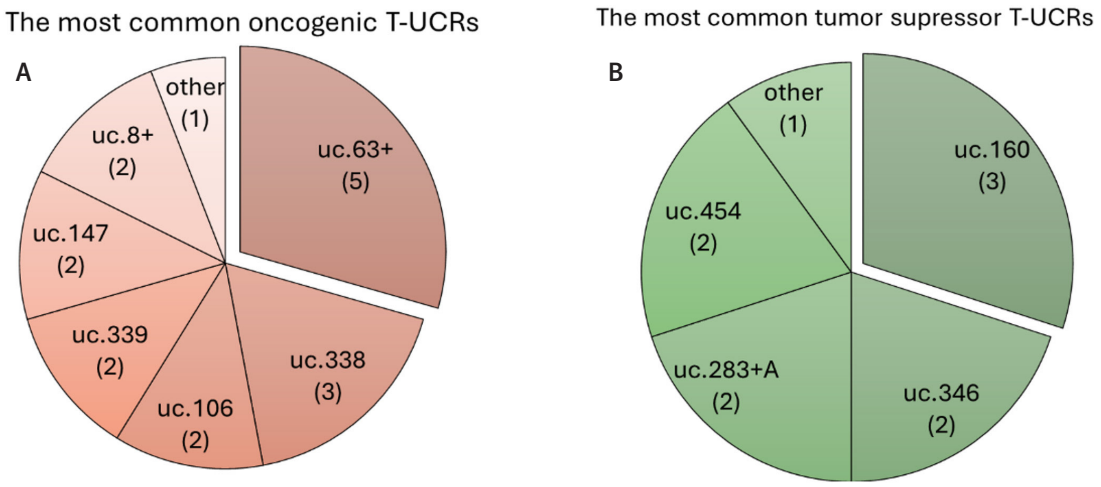

Fig 3 | (A) The most common pro-tumoral T-UCRs and (B) tumor suppressor T-UCRs according to the number of studies where these T-UCRs were studied

molecular modifications, including variations in target miRNAs, interacting proteins (either directly or indirectly via miRNAs), and the subsequent activation or inhibition of specific signaling pathways.[122,124] In the case of T-UCRs, however, the mechanisms behind this dual function remain speculative, as current data is insufficient to draw definitive conclusions. For instance, the molecular targets of uc.138 in breast cancer were not explored in the study,[97] nor were the targets for uc.283+A in colon cancer.[69] These T-UCRs hold potential as powerful diagnostic tools for specific cancer types. Furthermore, they could pave the way for developing targeted therapies that involve exogenous modulation of T-UCR expression and its downstream pathways. Such approaches could enhance treatment specificity, improve therapeutic outcomes, and minimize side effects. Therefore, it is crucial to further investigate the cancer-specific molecular targets of T-UCRs with dual roles to better understand their potential and therapeutic applications.

In addition, researchers should pay attention to several factors when designing their experiments. The selection of cell lines is a critical factor when assessing the role of a specific T-UCR in cancer. For example, silencing uc.83– caused cell cycle arrest in the G0/G1 phase in the H358 and H1299 cell lines (lung cancer), but it had no effect on the A549 and H460 cell lines (also lung cancer).[86] In addition, the regulation of T-UCRs is not consistent across all samples of the same tissue type, and some studies have pointed to this variability. Uc.454 is down-regulated in 63 out of 72 paired normal lung versus lung tumor samples.[87] In this case, the remaining 9 pairs of normal-tumor tissue will not show an uc.454 down-regulation. Future research in this area should focus on validating the presence of elevated T-UCR levels in other diseases and determining the appropriate thresholds for accurate diagnosis.

If T-UCRs are to be developed as diagnostic tools, several other challenges need to be addressed. First, for the discovery of an effective diagnostic marker, it is crucial to analyze the expression of T-UCRs in circulating bodily fluids and compare these levels between confirmed cancer cases, healthy controls, or different stages of the disease. Advanced technologies are necessary due to the limited RNA availability in bodily fluids compared to tissues. One study on prostate cancer used droplet digital PCR to analyze serum levels of uc.63+ in patients with prostatic hyperplasia, primary prostate cancer, and metastatic prostate cancer. This study found that uc.63+ was significantly elevated in the serum of metastatic patients.[27] This might become an essential tumor marker that would allow the clinicians to follow the treatment success and progression of the disease while improving the patients' adherence to periodic medical visits.

Secondly, most studies rely on comparisons with peritumoral tissue, but this may not be the most appropriate model. There are significant differences between normal tissue from healthy controls and "normal" peritumoral tissue.[125] For instance, in one of the bladder cancer studies mentioned earlier, uc.8+ was found to be up-regulated when compared to bladder tissue from healthy individuals but down-regulated when compared to peritumoral tissue.[78] While peritumoral tissue is commonly used in RNA expression studies in cancer due to its availability during surgery and its shared genetic background with tumor tissue, it is not the ideal control. On the one hand, it is easily accessible and often stored in tissue repositories, but on the other hand, it is influenced by tumor-secreted vesicles and humoral mediators that facilitate tumor growth and progression.[125]

The existing limitations in current approaches to studying T-UCRs highlight the need for large-scale longitudinal studies. Tissue and blood samples should be collected from a large cohort of healthy individuals to establish baseline T-UCR expression profiles over a selected period of time (e.g., 5, 10, or 20 years), the development of malignancies in these individuals should be monitored, alongside any changes in T-UCR expression. However, this approach presents challenges, including time and financial constraints, as well as the significant attrition of participants throughout the study. An alternative, more feasible approach would involve tracking

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the levels of T-UCRs in blood samples throughout the progression of a specific malignancy, particularly in individuals at early disease stages. This could provide valuable insights into the personalized dynamics of T-UCR expression in response to treatment, disease regression, relapse, and progression to advanced stages. Such data could offer critical information regarding the molecular factors that differentiate between treatment responses and rates of disease progression.

Another identified gap was that most studies investigating the therapeutic modulation of T-UCR expression have been limited to *in vitro* analyses. For example, in studies of malignancies in the excretory system, there are almost no *in vivo* investigations (Table 2). Furthermore, *in vivo* therapeutic approaches differ significantly. Some studies use transient inhibition of T-UCRs through siRNA,[84] while others opt for permanent deletion of T-UCRs.[40] This variation in methods can contribute to data heterogeneity, as demonstrated by an analysis comparing both approaches. In this study, transient knockdown of uc.339 in lung cancer did not significantly affect tumor growth or animal survival rates. However, when a permanent knockout was performed, a reduction in cancer burden and improved overall survival rates were observed.[84] Additionally, many tumor-suppressive T-UCRs are silenced in cancer through the methylation of their CpG islands. The use of demethylating agents, such as 5-azacytidine, could potentially reverse this repression, thereby reactivating the transcription of tumor-suppressive T-UCRs from their methylated state.[126]

T-UCRs represent an essential missing piece in cancer research, but this field is still in its early stages. While many studies have raised important questions, there is a clear need for larger-scale analyses. At present, the focus should be on the most well-characterized T-UCRs, such as uc.63+, uc.338, uc.339, uc.147, uc.160, and uc.454, to better understand their molecular mechanisms in greater detail. Although the discovery of additional T-UCRs with diagnostic and therapeutic potential is valuable, it would be most beneficial to first gain a more comprehensive understanding of the T-UCRs that are already known.

Conclusion

T-UCRs are a type of ncRNAs that control the molecular landscape of a cell at multiple levels: DNA, through transcription factors, RNAs (mRNAs and miRNAs), and proteins. The best-known mechanisms are related to their interaction with the miRNAs. The possible interaction between T-UCRs and other long ncRNAs is still unknown. Most T-UCRs are listed as tumor-promoting, with uc.63+ being the most common oncogenic T-UCR. The most common tumor suppressor T-UCR is uc.160+. The T-UCRs can differentiate between normal and cancer tissue, and they can affect overall and disease-free survival rates. The *in vitro* studies show that T-UCRs are involved in cell viability, proliferation, growth, invasion, and migration. *In vivo*, T-UCRs influence the migration of tumor cells, invasion of the local tissue, and the survival rate of the animal. However, most studies focus on tumor tissue versus normal tissue and *in vitro* manipulation of T-UCR expression. While providing valuable information, these might be further improved through more 3D cell culture analysis, *in vivo* studies, and large-scale longitudinal studies of circulating T-UCRs in bodily fluids.

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