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Experimed 2025, 15 (2): 101–108

https://doi.org/10.26650/experimed.1623435

Submitted: 20.01.2025
Revision Requested: 24.10.2025
Last Revision Received: 24.10.2025
Accepted: 08.05.2025

Experimed

Review Article

Open Access

The Exosome Complex in Health and Disease: A Multifaceted Regulator of RNA Homeostasis

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Abstract The RNA exosome complex is a multi-subunit ribonuclease complex that participates in RNA degradation, processing, and quality control. In recent years, mutations and dysregulation in the subunits of this complex, which play significant roles in RNA metabolism, have been associated with neurodegenerative diseases, hematological malignancies, and solid tumors. This review discusses the contributions of genes encoding both the catalytic and non-catalytic subunits of the exosome complex to cellular homeostasis, development, and disease pathogenesis. In addition to its roles in RNA homeostasis, the complex also plays a role in maintaining the stability of genomic-resolving DNA:RNA hybrids, regulating telomere integrity, and facilitating homologous recombination. Considering the current literature, this review highlights the potential of RNA exosomes as biomarkers for disease diagnosis and as therapeutic targets for developing new treatment approaches.

Keywords RNA exosome complex · ExosC · RNA degradation · Therapy

Citation: Demirtas EN, & Sozer Tokdemir S The Exosome Complex in Health and Disease: A Multifaceted Regulator of RNA Homeostasis. Experimed 2025; 15(2): 101-108. DOI: 10.26650/experimed.1623435

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INTRODUCTION

The RNA exosome complex (ExosC) is key in regulating RNA metabolism. The system ensures RNA quality by processing and degrading different types of RNA. Located in both the nucleus and cytoplasm, ExosC helps to maintain cellular homeostasis and indirectly supports genome stability by resolving DNA:RNA hybrids (R-loops) and stabilizing telomeres. ExosC functions mainly include quality control of coding and non-coding RNAs, degradation of defective transcripts, and processing of precursor RNAs (1, 2). Although the contribution of ExosC to RNA metabolism is clear, studies on its contribution to disease pathobiology have accelerated in the last decade.

ExosC has been linked to several diseases, including neurodegenerative disorders (3), autoimmune diseases (4), and cancer, and its disruption has been associated with genomic instability (5), uncontrolled proliferation (6), and tumor progression (7). It has been shown that changes detected in exosome subunits in hematological cancers (8, 9) and solid cancers (10) cause them to act as oncogenic drivers or tumor suppressors (10, 11). This review explores the potential of targeting RNA exosome subunits or their specific functions for diagnostic and therapeutic purposes by integrating insights into disease-associated dysfunctions and subunit-specific roles. We aim to inspire further research and novel therapeutic approaches by bridging fundamental biology with clinical implications.

The Structure and Function of the RNA Exosome Complex

ExosC is an 11-subunit protein assembled in the nucleus and cytoplasm (Figure 1). In the nucleus, it facilitates the degradation of RNAs and processes precursors of 5.8S rRNA and other stable RNAs (12). ExosC ensures intracellular homeostasis in the cytoplasm by degrading mRNA (13, 14).

The complex features a unique cap region, the S1/KH ring, comprising exosome components (EXOSC) of EXOSC1, EXOSC2, and EXOSC3 subunits (Figure 1). Below the cap lies the PH-like ring structure, formed by catalytically inactive subunits EXOSC4 to EXOSC9 (collectively called EXO-9). EXO-9 interacts with the two catalytic subunits, EXOSC10 and DIS3, which mediate RNA degradation and processing (15). DIS3, which has three subtypes in humans, is found in the nucleus and cytoplasm, whereas EXOSC10 is enriched in the nucleus (16). RNA enters the ExosC through a gap at the apex of the S1/KH cap and exits via a gap at the base of the PH ring. There are three pathways for RNA interaction: substrates may bypass the channels in the complex body and directly reach EXOSC10 (17, 18), RNA can pass through the channel to reach DIS3 (18–20), or RNA can directly bind to DIS3 without entering the complex (21).

The RNA Exosome Complex in Cellular Stress and DNA Damage Response

The RNA exosome complex plays an important role in maintaining cellular homeostasis by ensuring RNA quality control and preventing the accumulation of toxic RNA species (1, 22). Functional disorders in ExosC cause R-loop formation (23), RNA:DNA hybrid structures that cause transcription-replication conflicts, replication fork stalling, and DNA double-stranded breaks (DSBs) (24). The loss of EXOSC10 function with exoribonuclease activity contributes to tumorigenesis and genomic instability owing to R-loop formation (25). Mutations in the subunit DIS3, which has both endo- and exoribonuclease activity, cause transcriptional stress by preventing the degradation of dysfunctional RNA products (26, 27).

EXOSC plays a critical role in DNA repair. Marin-Vicente et al. showed that during homologous recombination, EXOSC10 localizes at the site of damage and facilitates the uptake of RAD51 into DSBs (28). On the other hand, its depletion makes cancerous cells sensitive to radiation (28, 29).

In addition, EXOSC9 causes stress resistance by promoting the formation of stress granules (30). EXOSC3 upregulation promotes tumor progression by activating pro-inflammatory pathways by stimulating IFNGR1, MYD88, NFκBIA, and STAT3 expression (31). EXOSC is a promising therapeutic target in cancer biology because of its dual roles in genomic stability, stress resistance, and inflammation.

The Roles of RNA Exosome Complex Subunits in Cancer

ExosC subunits play critical roles in various cancers. In colorectal cancer, EXOSC2, EXOSC3, and EXOSC4 are upregulated. The upregulation of EXOSC4 induces metastasis and proliferation, whereas its inhibition leads to cell cycle arrest in the G1 phase (32–34). EXOSC8 disrupts tumor suppressors such as p53 (35), and copy number variation (CNV) gain is associated with poor overall survival (36). In addition, EXOSC10 degrades CYLD deubiquitinase mRNA in colorectal cancer and promotes tumor progression by increasing c-Jun N-terminal kinase (JNK) activity (37). Conversely, EXOSC2 facilitates proliferation, migration, and angiogenesis in breast cancer by activating the Wnt/β-catenin pathway (11). However, EXOSC3 exhibits protective roles against breast cancer by potentially mitigating oncogenic pathways (10), whereas

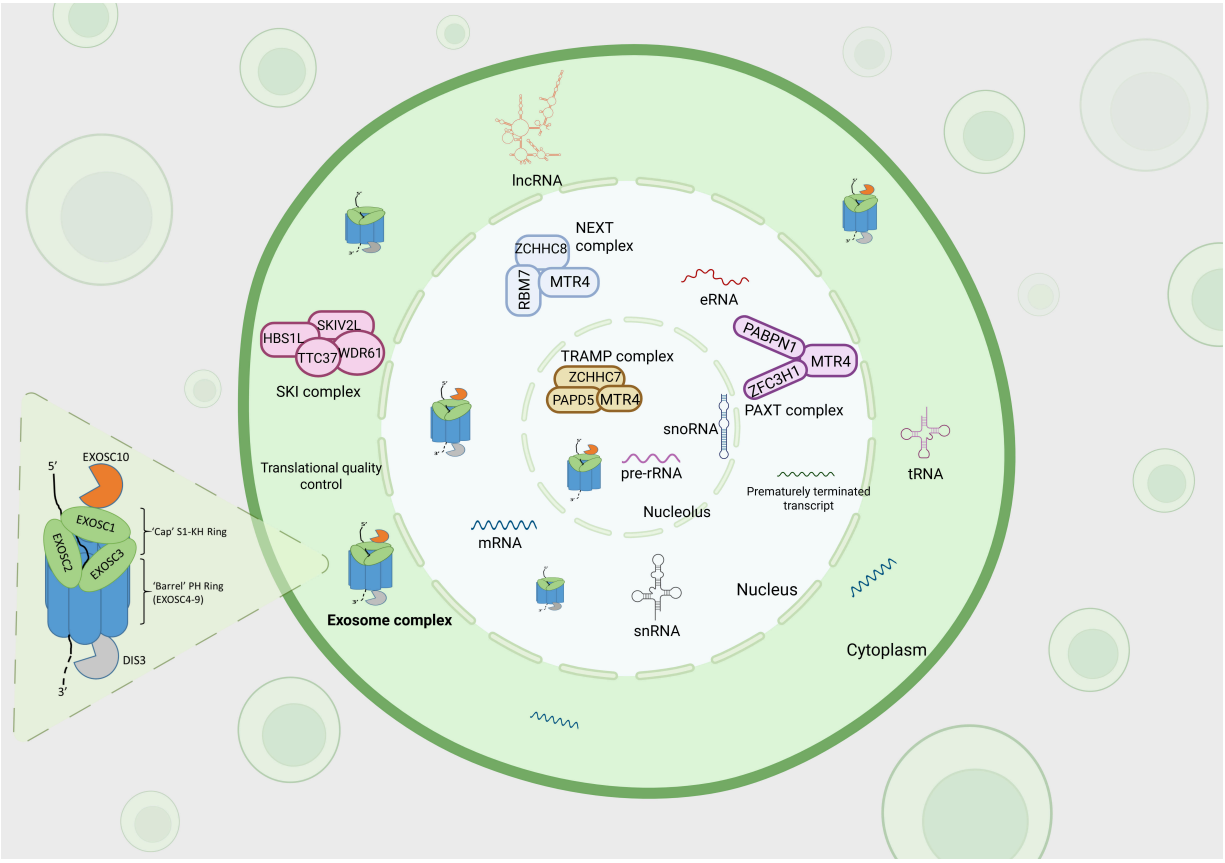

Figure 1. Illustration of the RNA exosome complex inside a cell, including its localization, cofactors, and substrates. The RNA exosome complex is located in the nucleolus, nucleus, and cytoplasm. In the nucleolus, the exosome complex contains the EXOSC10 subunit but lacks DIS3 and interacts with TRAMP complex cofactors, allowing pre-rRNA and snoRNA to bind to the complex. In contrast, the exosome complex located in the nucleus is mediated by the NEXT and PAXT complex for mRNA, snRNA, and eRNA, prematurely terminated transcript binding, and combines with the DIS3. The NEXT complex targets short-lived RNAs, whereas PAXT targets long and polyadenylated RNAs. The SKI complex acts as a cofactor in the cytoplasm, allowing mRNAs to bind to its cap region. The exosome complex is accompanied by DIS3 and DIS3L proteins in the cytoplasm. Abbreviations: TRAMP: Trf–Air–Mtr4 polyadenylation; NEXT: nuclear exosome targeting; PAXT: poly(A) tail exosome targeting; snoRNA: small nucleolar RNA; snRNA: small nuclear RNA; mRNA: messenger RNA; tRNA: transfer RNA; eRNA: enhancer RNA; lncRNA: long non-coding RNA) (Created in BioRender. Demirtaş, E. (2025) https://BioRender.com/g37v632)

EXOSC9 supports metastasis and therapy resistance by degrading telomeric RNAs (38).

In kidney renal clear cell carcinoma, EXOSC1 promotes DNA damage and mutations, thereby contributing to poor patient outcomes (39). EXOSC5 drives tumor proliferation in colorectal cancer (40). In pancreatic cancer, subunits such as EXOSC2 and EXOSC4 support tumor progression by promoting proliferation and survival (41, 42), with EXOSC9 and EXOSC10 playing roles in stress resistance and tumor maintenance (30, 42). In gastric cancer, EXOSC3 and EXOSC5 are associated with poor prognosis (43), with EXOSC3 incorporated into relapse-free survival models (44).

In hematological cancers, multiple myeloma frequently exhibits frequent *DIS3* mutations, disrupting RNA processing and cell proliferation (45), whereas *EXOSC1* is identified as a harmful gene in mantle cell lymphoma (46). In endometrial cancer, EXOSC5 activates c-MYC and enhances cancer stem cell properties (47), while EXOSC10 is linked to aggressive phenotypes (48). Hepatocellular carcinoma shows contrasting roles for EXOSC8, where it acts protectively and improves survival, whereas EXOSC5 supports tumor growth via the STAT3 pathway (49, 50). Other cancers, such as epithelial ovarian cancer, involve EXOSC4, whose over-expression drives aggressive tumor behavior (51). In esophageal squamous cell carcinoma, EXOSC2 prevents malignant progression by degrading oncogenic RNAs (52).

The findings indicate that specific RNA exosome components might function as oncogenes or tumor suppressors, depending on the cancer type and cellular context. The carcinogenic potential of exosome components was demonstrated by the correlation between poor prognosis and over-expression of EXOSC1 in renal cancer (39) and EXOSC10 in hepatocellular carcinoma (53). On the other hand, DIS3 loss-of-function mutations disrupt RNA processing, accumulating abnormal transcripts, and promoting the development of tumors in hematological malignancies like multiple myeloma

(54). The intricacy of RNA exosome biology and the requirement for context-specific research to clarify its roles in oncogenesis are reflected in these dual roles.

The RNA Exosome and Beyond: Connections to Other Diseases

Although primarily studied in the context of cancer, the RNA exosome complex also plays a critical role in the pathogenesis of several non-cancerous diseases, including neurodegenerative disorders, immune dysregulation, and developmental syndromes. Mutations or dysregulation of specific RNA exosome subunits often result in widespread RNA accumulation, toxic RNA species, and disrupted RNA homeostasis, which are hallmark features of these conditions.

Neurodegenerative Diseases

The RNA exosome participates in the degradation of defective mitochondrial RNAs, and any disturbances to this task could disrupt the function of mitochondrial dysfunction, an essential factor in neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (ALS).

Because the RNA exosome complex controls alternative splicing (55), mutations in this complex can cause defective splicing patterns and loss of control of mRNA abundance in neurons (56). Mutations in *EXOSC3* and *EXOSC8* have been strongly associated with pontocerebellar hypoplasia (PCH), spinal muscular atrophy (SMA), and cerebellar hypoplasia, disorders characterized by impaired motor function and progressive neuronal loss (3, 57–60). EXOSC3 loss and mutations contribute to neurodegeneration by causing defective rRNA processing and modulation of R-loop formation (23, 61). In a study of 22 infants, Boczonadi et al. detected a homozygous non-sense mutation in EXOSC8. They showed that the mutation disrupted RNA metabolism in oligodendrocytes, causing them to produce abnormal proteins and to undergo neurodegeneration (3). In ALS and frontotemporal dementia (FTD), accumulation of GGGGCC repeats in the *C9orf72* gene leads to the production of toxic di-peptide repeat proteins (62). By detecting that EXOSC10 and DIS3 cleave these hexanucleotide repeats, Kawabe et al. showed that EXOSC has therapeutic potential to reduce RNA toxicity (63).

Autoimmune and Inflammatory Diseases

ExosC dysfunction triggers immune dysregulation by inducing inflammatory pathways. The disruption of endogenous immunostimulatory genes in the absence of SKIV2L (a cytoplasmic RNA helicase cofactor) leads to the activation of type I interferons, laying the groundwork for systemic autoimmune diseases (64). RNA accumulation causes inflammation and developmental abnormalities in congenital disorders, and similar effects are observed in trichohepatoenteric syndrome, a rare congenital disorder associated with SKIV2L and EXOSC2 deficiencies (65). ExosCs are important for the maintenance of immune homeostasis.

Developmental and Genetic Disorders

ExosC participates in early embryogenesis and differentiation is necessary for normal development (66). EXOSC2 knockout in a zebrafish model disrupted neuronal development by disrupting the mRNA loop. Rapamycin treatment, which modulates mRNA stability through the mTOR signaling pathway, can partially reverse this effect (67). In addition, the downstream effects of modified *EXOSC1* splicing affect vascular pathophysiology and play a role in ischemic stroke (68).

Therapeutic Implications of Targeting the RNA Exosome Complex

The devastating consequences of ExosC dysfunction make it an attractive therapeutic target in diseases. Targeting ExosC subcomponents or cofactors can inhibit the mechanisms that promote tumor formation and render cancer cells susceptible to treatment. Kammler et al. determined that the subunit EXOSC10 with exoribonucleolytic activity is a target for chemotherapeutics such as 5-fluorouracil (5-FU), which induces cytotoxicity by increasing the accumulation of RNA substrates. HeLa cells lacking EXOSC10 became sensitive to 5-FU and showed impaired growth and increased RNA substrate levels (69). Therefore, EXOSC10 expression is critical for enhancing the efficacy of current therapies. Targeting the accumulation of R-loops that trigger replication stress with ribonuclease-active subunits of the complex may reduce genomic instability caused by defective DNA damage repair pathways. Molecules targeting ExosC-mediated R-loop resolution are promising for new drug discovery.

For cancers harboring ExosC dysfunction, a combined treatment approach using PARP and ExosC inhibitors may contribute to the selective death of cancer cells with homologous recombination defects. Marin-Vicente et al. found that EXOSC10 depletion causes RAD51 to be unable to be recruited to the damaged site, disrupting DNA double-stranded break repair, thus making cancer cells susceptible to radiation and DNA-damaging agents (28). Modulation of DIS3 expression provides a different treatment strategy to ensure RNA homeostasis involving enhancer RNAs, promoter upstream transcripts (PROMPTs), and early cleavage and

Table 1. The role of ExosC in cancer, neurodegenerative disease and syndromes.

GENE	DISEASE/CONDITION	POTENTIAL EFFECT	REFERENCES
EXOSC1	Pontocerebellar hypoplasia	Stump protein	(71, 72)
EXOSC2	Short stature, Hearing loss, Retinitis pigmentosa, and distinctive Facies (SHRF)	Impaired RNA metabolism	(73, 74)
		Altered activities in the autophagy pathway	
EXOSC3	Pontocerebellar hypoplasia	Cerebellar and spinal motor neuron development and degeneration.	(75)
	Non-small cell lung cancer	Prediction of NSCLC survival	(76)
	Thrombotic Microangiopathy	Prevention of response to eculizumab treatment	(77)
EXOSC4	Tongue Cancer	biological markers for predicting lymph node metastasis	(78)
	Diffuse large B-cell lymphoma	shorter overall survival and progression-free survival	(79)
	Luminal B/Her2 breast cancer	Colony formation, cell invasion, and mammosphere formation of breast cancer cells	(80)
	Neurodevelopmental defects	Biallelic variant that impairs RNA exosome function	(81)
EXOSC5	Delayed development	Reduced eye/head size, edema, and shortened and curved bodies	(82)
	CABAC syndrome (cerebellar ataxia, brain abnormalities, and cardiac conduction defects)	Thrombotic microangiopathy	(77)
	Prostate cancer	Abiraterone-resistant gene	(83)
EXOSC6	Cerebral amyloid angiopathy	Potential drivers of pathological processes	(84)
EXOSC8	Pontocerebellar hypoplasia	Alterations in mRNA metabolism, hypomyelination with spinal muscular atrophy, and cerebellar hypoplasia	(3)
	Head and neck squamous cell carcinoma	ERS-related biomarkers for predicting immunotherapy response	(85)
EXOSC9	Pontocerebellar hypoplasia	Cerebellar atrophy with spinal motor neuronopathy	(86–88)
	Breast cancer	Support the growth of endocrine therapy-resistant HR+ breast cancer cells.	(38)
		Promising biomarker of response to PARP inhibitors	
EXOSC10	Frontotemporal lobar degeneration (FTLD) and Amyotrophic Lateral Sclerosis (ALS)	Degradation of pathogenic C9orf72-derived repeat RNA	(63)
	Oocyte development	depletion of the ovarian reserve by EXOSC10 inactivation	(89)
DIS3	Premature ovarian insufficiency	Aberrant ovarian development and egg chamber degeneration	(90)
	Male fertility	Disruption of early germline cell development	(91)
	Breast cancer	Target gene to increase major histocompatibility complex I (MHC-I) expression	(92)
		High DIS3 expression leads to cancer cell survival	
		Poor prognosis of breast cancer	

polyadenylation products (PCPA) to prevent the degradation of tumor suppressor RNAs and target oncogenic RNAs.

In addition, the non-catalytic subunits of ExosC can serve as diagnostic and prognostic biomarkers. Elevated levels of EXOSC1 and EXOSC4 subunits were associated with poor renal cell carcinoma (39) and colorectal cancer (33), respectively. These findings provide important tools for patient stratification and treatment response monitoring.

In addition to traditional chemotherapy and radiotherapy treatment methods, synthetic lethality approaches targeting DNA repair and ExosC function can be applied, which may help combat therapeutic resistance.

Therapeutic Insights Across Diseases

ExosC is a potential target for neurodegenerative and inflammatory diseases because it balances RNA metabolism and maintains cell homeostasis. Results from cancer studies targeting EXOSC10 to eliminate toxic RNA species have shown

that this complex is also promising for diseases other than cancer. In ALS and frontotemporal dementia (FTD), Bush et al. designed repetitive RNA-targeted small molecules to target the destruction of unwanted RNAs by ExosC. In the C9ALS/FTD mouse model, these small molecules crossing the blood-brain barrier also prevented the production of di-peptide repeat proteins, thus alleviating disease pathology (70). Likewise, the subsequent development of therapeutic strategies to prevent the generation of pathogenic repeat sequence-containing RNA forms by targeting ExosC function improvement could be implemented in other repeat sequence diseases, like Huntington's disease, myotonic dystrophy, Fragile X syndrome, spinocerebellar ataxia, and Friedreich's ataxia. These results indicate that ExosC is associated with diverse biological processes and diseases other than cancer. Additional studies are required to clarify the potential contribution of ExosC to neurodegeneration, immune dysregulation, and developmental disorders. An improved understanding of how ExosC contributes to the pathogenesis of these conditions may provide vital insights into both disease mechanisms and the development of new therapeutic strategies.

DISCUSSION

ExosC is classified as a ribonuclease complex and can facilitate RNA processing and degradation to maintain RNA homeostasis and genomic stability; thus, ExosC plays an instrumental role in minimizing replication stress by ensuring that R-loop structures are resolved and contributing to the repair of DSBs via the process of homologous recombination. If defects in EXOSC10 or DIS3 impair ExosC function, unresolved R-loops accumulate, causing replication stress and inadequate DNA damage repair. The involvement of the complex in homologous recombination (HR) makes it a promising target in tumors with HR deficiencies, particularly in combination with PARP inhibitors. Cancer and neuroscience studies have shown that mutations and expression changes in ExosC subunits are associated with transcriptional stress, genomic instability, inflammation, cancer cell growth, proliferation, and metastasis processes (Table 1). In addition, the fact that it promotes the formation of stress granules can increase the stress resistance of cancer cells and maintain their survival. Therefore, ExosC subunits are important targets of targeted therapies. The most important difficulty in ExosC studies is that the specific and non-canonical roles of each subunit in the disease remain unclear.

CONCLUSION

ExosC is a vital RNA regulatory mechanism for cancer and other diseases. The disruption of ExosC causes loss of homeostasis and can serve as a potential therapeutic target. Detailed studies will delineate the roles of specific subunits and identify treatments that modulate complex dysfunction. In conclusion, ExosC subunits represent an exciting potential biomarker and therapeutic target and may be a pioneer for novel therapies, particularly in the fields of oncology and neurodegeneration.

Peer-review: Externally peer-reviewed.
Author Contributions: Conception/Design of Study – E.N.D.; Data Acquisition – E.N.D.; Data Analysis/Interpretation – E.N.D., S.S.T.; Drafting Manuscript – E.N.D., S.S.T.; Critical Revision of Manuscript – E.N.D., S.S.T.; Final Approval and Accountability – E.N.D., S.S.T.
Conflict of Interest: The authors declare no conflict of interest.
Financial Disclosure: The authors declare that they received no financial support for this study.

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