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Decoding epigenetic signatures of extracellular RNA in ovarian cancer through artificial intelligence

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Highlights:

- Artificial intelligence enables the integration of epigenetic and post-transcriptional regulatory information to generate biologically interpretable hypotheses from EV-associated RNA signatures.
- Extracellular vesicle-associated RNA signatures are influenced by coordinated regulatory processes, including alternative splicing, RNA editing, epi-transcriptomic modifications, and selective RNA loading into EVs.
- AI-driven integrative models support the generation of mechanistic hypotheses from liquid biopsy-derived EV-associated RNA profiles.
- Integrative multi-omics approaches may support biomarker discovery, patient stratification, and dynamic disease monitoring through the analysis of EV-associated RNA signatures.

Abstract: Artificial intelligence (AI) is redefining the interpretation of epigenetic regulation in RNA biology by enabling the integration of complex, multi-layered datasets spanning genomic, epigenomic, and transcriptomic levels. These improvements are relevant for non-coding RNA associated with extracellular vesicles (EV-ncRNA), whose content may offer a minimally invasive readout of the molecular programs defining cancer cell states. In cancer, epigenetic modifications affect RNA editing, epi-transcriptomic changes, alternative splicing, and circular RNA (circRNA) biogenesis, also modulating the EV-ncRNA content. AI models can propose regulatory activity from sequence context and to integrate chromatin accessibility. These advances offer an opportunity to associate regulatory programs with EV-ncRNA signatures, moving beyond descriptive profiling toward biologically interpretable models. AI can then integrate multimodal data and apply these models to deduce specific cancer cell states from EV-ncRNA obtained by liquid biopsy. This perspective outlines a conceptual framework for understanding EV-ncRNA signatures in ovarian cancer (OC) and for exploring their potential roles in biomarker discovery, patient stratification, and dynamic disease monitoring. The major challenges that may delay effective implementation are also discussed, including data heterogeneity, the absence of standardized EV multi-omics datasets, and the limited interpretability of deep learning models.

Keywords: extracellular RNA (exRNA); extracellular vesicles (EVs); artificial intelligence (AI); non-coding RNA (ncRNA); circular-RNA (circRNA); epigenetic mechanism

1. Introduction

Epigenetic regulation constitutes a central mechanism of gene expression control, orchestrating transcriptional and post-transcriptional processes through DNA methylation, chromatin organization, histone modifications, and RNA-based mechanisms [1]. In cancer, epigenetic regulatory networks are frequently dysregulated, contributing to transcriptional plasticity and onset of dynamic cancer cell phenotype that promote adaptation to environmental and therapeutic pressures. These alterations extend beyond transcriptional control, and influence multiple post-transcriptional processes such as alternative splicing, RNA editing, and RNA modification, thereby increasing transcriptomic diversity and functional complexity [2,3]. Emerging evidence suggests that these processes may also modulate extracellular vesicles (EV-ncRNA) composition, linking intracellular regulatory programs to extracellular molecular signals [4,5]. Consequently, EV-associated RNA (EV-RNA) may provide a molecular readout of the regulatory programs underlying tumor progression, adaptation, and phenotypic plasticity [6]. As a major carrier of extracellular RNA (ExRNA), EVs facilitate the transfer of molecular information between cells and contribute to intercellular communication [7,8]. These membrane-bound particles transport, between cells, proteins, lipids, DNA and RNA molecules, including non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), piwi-RNAs, and circular RNAs (circRNAs), influencing recipient cell behavior and contributing to disease progression [9–12]. Since the first evidence that EVs mediate the intercellular transfer of functional RNA molecules [13–17], growing evidence has highlighted their role in cancer biology and the association of EV-ncRNA composition with both physiological and pathological cellular states [18,19].

Although recent studies have associated distinct EV-ncRNA signatures with clinically relevant cancer phenotypes, including progression, metastasis, chemoresistance, and recurrence, these outcomes result from the interplay of multiple regulatory processes rather than a single molecular mechanism. Consequently, EV-ncRNA cargo should be interpreted as a composite molecular readout of complex regulatory networks. This perspective provides the rationale for developing models to link EV-ncRNA profiles and regulatory programs that define specific cancer cell phenotypes. The proposed framework is summarized in Figure 1. AI, in particular deep learning, has emerged as a tool to address this challenge; recent studies demonstrated that convolutional neural networks could predict regulatory activity directly from DNA sequence, highlighting the importance of sequences in chromatin-state regulation [20,21]. These approaches were expanded to genome-wide prediction of chromatin accessibility and regulatory activity by integrating long-range genomic and epigenomic information [22,23].

AI models have been applied to RNA biology, supporting the prediction of regulatory features linked to RNA processing and ncRNA sorting into EVs [24,25]. EV-ncRNA profiles are considered molecular outputs of interconnected regulatory programs, and AI is proposed as a tool to integrate multimodal data and generate interpretable, testable hypotheses on cancer cell phenotypes. Ovarian cancer (OC) represents a particularly relevant model in which to apply this framework. OC is characterized by marked epigenetic and transcriptional heterogeneity, which contributes to phenotypic plasticity, early dissemination in peritoneal cavity, and a rapid development of therapy resistance [26]. Increasing evidence indicates that post-transcriptional regulatory mechanisms play a central role in these processes [27,28]. Moreover, the absence of early symptoms and the limited accuracy of current biomarkers lead to diagnosis at advanced stages, highlighting the need for minimally invasive

approaches that can detect early molecular alterations. In OC, the proposed framework may support the decoding of EV-ncRNA signatures and their relationship with molecular heterogeneity.

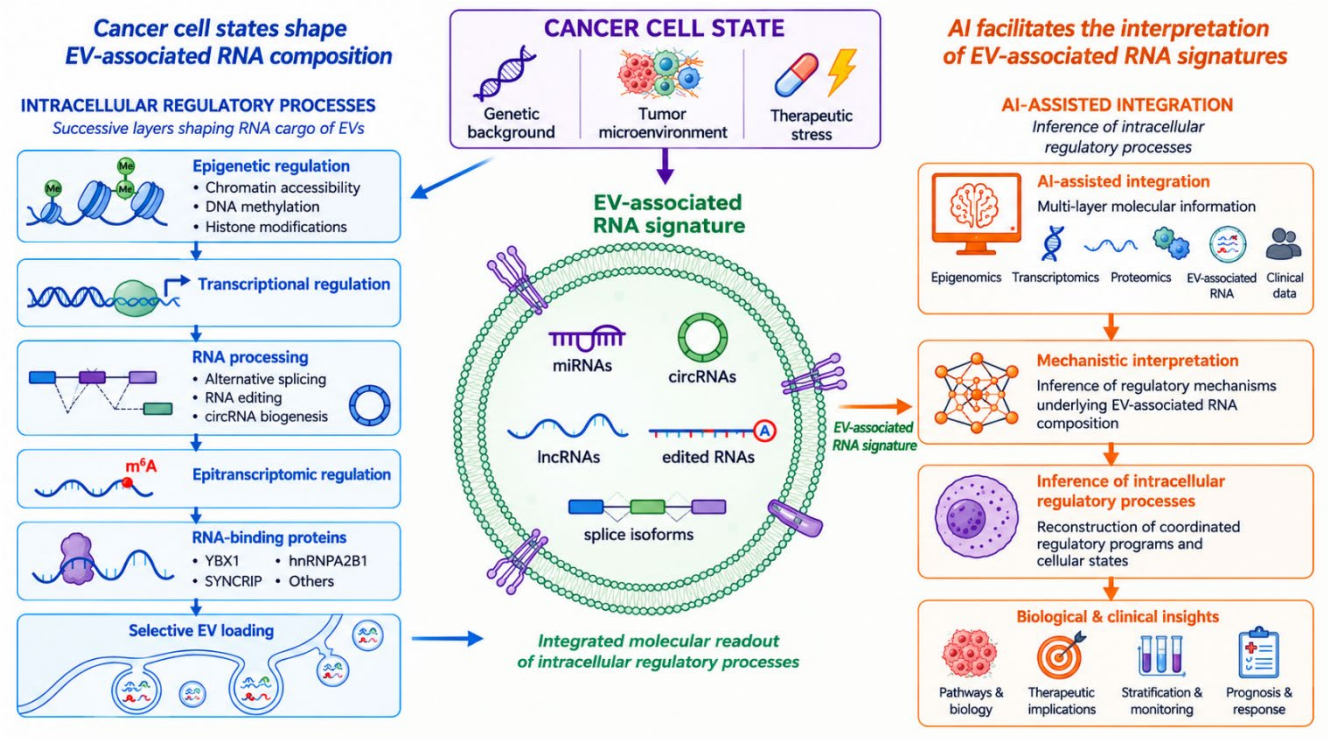

Figure 1. Overview of the framework linking the intracellular regulatory mechanisms to EV-RNA cargo and AI-assisted mechanistic decoding in OC. Graphical rendering supported by Copilot Microsoft. The graphical elements were reviewed by the authors for biological accuracy.

2. AI in epigenetics: from prediction to mechanistic insight

The application of AI to epigenetics has progressed from prediction toward approaches that can identify regulatory patterns and generate experimentally testable hypotheses.

Pioneering studies demonstrated that convolutional neural networks could predict regulatory activity directly from DNA sequence, revealing that sequence context contains sufficient information to accurately predict chromatin states [20]. The Deep Sequence-based Encoder for Regulatory Annotation (DeepSEA) model was trained on hundreds of functional genomics datasets, including DNase I hypersensitivity, transcription factor binding, and histone modification profiles, achieving high predictive accuracy across multiple regulatory layers [29]. Beyond classification performance, a key result was the ability to estimate the functional impact of noncoding genetic variants, showing that single-nucleotide changes could significantly alter chromatin accessibility or transcription factor binding. This provided one of the first concrete demonstrations that deep learning could quantitatively link DNA sequence variation to epigenetic regulation [20]. Successive developments expanded both the scale and interpretative power of these approaches. Models such as Basenji and related architectures extended sequence-based predictions to genome-wide resolution, integrating long-range genomic context and enabling prediction of chromatin accessibility, transcriptional activity, and regulatory element interactions across entire chromosomes [22]. By integrating information from genomic regions, these models highlight the importance of long-range genomic interactions and higher-order chromatin

organization in affecting epigenetic regulation [25]. A critical advance of these models lies in their ability to extract biologically meaningful features that are associated with known regulatory mechanisms. Post hoc interpretability analyses, including saliency mapping and in silico mutagenesis, have revealed that trained networks consistently identify canonical transcription factor binding motifs and combinatorial regulatory patterns [30]. Perturbation of specific nucleotide positions within predicted enhancer regions produces measurable shifts in model output that mirror experimentally observed effects on chromatin accessibility [31]. The ability to simulate the impact of sequence alterations provides a useful framework for in silico hypothesis generation. Motif enrichment analyses further support the biological relevance of model-derived features by identifying known transcriptional regulators active in specific cellular contexts [32]. More recent architectures, including transformer-based and hybrid models, have expanded these approaches through the integration of multiple layers of epigenetic information [33]. The resulting models combine sequence data with chromatin accessibility, histone modification, and DNA methylation profiles, providing a more comprehensive representation of regulatory landscapes across diverse cellular states [34]. Transformer-based architecture has improved the modeling of long-range regulatory interactions in genomics. By capturing relationships between distant enhancers, promoters, and other regulatory elements, they provide a more comprehensive representation of gene regulation, where chromatin interactions frequently influence transcriptional activity [35]. These models have been applied to investigate differences in regulatory landscapes across cell types, developmental stages, and disease conditions, generating insights into how epigenetic programs may be altered in pathological contexts such as cancer [36]. A further advance has been the transition from static prediction to dynamic modeling of regulatory processes. Models trained on perturbation datasets can generate hypotheses regarding how changes in specific regulatory factors may influence chromatin accessibility and gene expression [37]. This is particularly relevant in cancer, where epigenetic states are highly plastic and responsive to microenvironmental signals [38–41]. AI is increasingly used to identify regulatory patterns and generate experimentally testable biological hypotheses. However, experimental validation remains essential to establish causal relationships between predicted interactions and biological function.

3. Modeling RNA editing, splicing, and circular RNA biogenesis

RNA processing represents an important link between epigenetic regulation and transcript diversity. Recent advances in AI have improved the modeling of RNA editing, alternative splicing, and circRNA biogenesis. Adenosine-to-inosine (A-to-I) RNA editing exemplifies how AI can integrate multiple regulatory layers into predictive models. This post-transcriptional process, catalyzed by adenosine deaminase acting on RNA (ADAR) enzymes, involves the deamination of adenosine residues within double-stranded RNA regions, converting them into inosine, which is interpreted as guanosine by cellular machinery. As a result, RNA editing can alter coding sequences, splice sites, RNA stability, and interactions with RBPs or miRNAs. The occurrence and efficiency of editing events are influenced by a combination of factors, including local sequences, RNA secondary structure, and chromatin-dependent transcriptional dynamics. These multilayered dependencies make A-to-I editing particularly well suited for AI-based modeling [42]. Deep learning models trained on transcriptome-wide datasets have demonstrated that incorporating RNA secondary structure predictions alongside sequence features substantially improves the identification of editing sites. Importantly, these models reveal that editing is not uniformly distributed but is dynamically modulated across cellular states [43]. In cancer, including

OC, altered transcriptional programs and chromatin remodeling can shift the editing landscape, producing context-specific patterns that extend beyond intracellular regulation [44]. Edited transcripts, often showing changes in stability or protein-coding potential, have been detected in EV-ncRNA, suggesting that AI-predicted editing hotspots may contribute to circulating signatures associated with tumor adaptation [45]. Alternative splicing represents another important source of transcript diversity, generating distinct isoforms through context-dependent exon inclusion or exclusion.

While early frameworks described a "splicing code" based on sequence motifs, AI-driven models have demonstrated that splicing decisions are influenced by epigenetic context [46]. Chromatin accessibility, histone modifications such as H3K36me3, and RNA polymerase II elongation rates shape splice site selection. For instance, slower elongation rates can promote the inclusion of alternative exons by increasing the temporal window for spliceosome assembly, whereas open chromatin environments associated with active transcription tend to favor canonical splicing patterns [47]. AI models can predict alternative splicing patterns across different conditions, linking transcriptional dynamics to transcript diversity. In cancer, aberrant splicing can generate isoforms that are preferentially represented in EVs, suggesting a potential contribution of splicing regulation to EV-ncRNA composition [48]. CircRNA biogenesis represents another example of the interplay between RNA processing and epigenetic regulation [49]. CircRNAs are generated through back-splicing events [50] and AI models have helped identify factors associated with their formation, including specific sequence features, RBPs, such as QKI RNA-binding protein (QKI) or fused in sarcoma (FUS), and transcriptional dynamics [51,52]. Several of these factors are influenced by epigenetic states. For example, chromatin compaction and transcriptional dynamics can affect back-splicing efficiency and circRNA formation. CircRNAs are also characterized by high stability due to their covalently closed structure, which contributes to their enrichment in EVs and persistence in the extracellular environment [53,54]. AI-based approaches can help identify features associated with circRNA formation and EV enrichment, including sequence characteristics, RBP interactions, and structural stability [55]. Overall, these observations suggest that RNA processing and EV loading are interconnected processes influenced by multiple regulatory layers. Within this framework, EV-ncRNA signatures may provide insight into the regulatory programs associated with different cancer cell states.

4. Epi-transcriptomic regulation and selective RNA sorting into extracellular vesicles

An open question in exRNA biology is how multiple regulatory layers converge to determine the selective packaging of specific RNA molecules into EVs. Figure 2 schematically summarizes the successive regulatory layers that contribute to EV-RNA composition, highlighting the interplay between chromatin regulation, RNA processing, RNA-binding proteins, and selective RNA sorting into EVs. Increasing evidence indicates that this process is regulated and depends on the coordinated action of multiple determinants, including RBPs, sequence and structural features of RNA molecules, and epi-transcriptomic modifications [18,56]. AI enables the integration of these variables, enabling the transition from descriptive cataloging of EV cargo to biologically interpretable models of RNA sorting processes. RBPs represent one of the primary mediators of selective RNA loading into EVs. Proteins such as heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1), Y-box binding protein 1 (YBX1), and synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP) have been shown to recognize specific sequence motifs within RNA molecules and facilitate their incorporation into EVs [57,58].

These interactions are influenced by RNA secondary structure and cellular context; for instance, binding motifs may become accessible or occluded depending on local folding, which in turn can be modulated by transcriptional dynamics and RNA modifications [59]. AI-based models that combine motif discovery with structural prediction have demonstrated the ability to identify composite features that correlate with EV enrichment, suggesting that RNA sorting is driven by combinatorial recognition patterns rather than single determinants. The presence of a canonical motif is necessary but not sufficient; its functional relevance depends on a broader regulatory context that AI models are uniquely suited to capture. Epi-transcriptomic modifications add an additional layer of regulation that directly influences RNA fate. Among these, N6-methyladenosine (m6A) has emerged as a key determinant of RNA stability, localization, and protein interaction [60]. Modified transcripts can be selectively recognized by reader proteins, such as members of the YTH domain family, which modulate RNA turnover and trafficking. Evidence suggests that m6A-marked RNAs may exhibit altered affinity for RBPs involved in EV sorting, thereby influencing their probability of export [60]. AI models trained in sequence features and known modification sites have achieved high accuracy in predicting m6A deposition and have begun to link these predictions to downstream functional outcomes. When integrated with RBP binding profiles, such models can infer how epi-transcriptomic states shape the composition of EV-ncRNA, providing a biological explanation for the selective enrichment of certain transcripts in EVs. The influence of cellular state on RNA sorting becomes evident under conditions of stress, such as hypoxia, which is a hallmark of the tumor microenvironment in OC [59]. Hypoxia induces transcriptional and epigenetic reprogramming, altering chromatin accessibility, RNA processing, and protein localization [61–63]. One consequence is the redistribution of RBPs to stress granules, transient cytoplasmic structures that sequester RNA molecules and regulate their fate. This localization can reduce the availability of RBPs for EV loading or, alternatively, promote the selective export of specific RNA subsets [64]. Hypoxia-associated changes in RNA modification patterns can also influence RNA stability and binding affinity [64]. AI models that incorporate hypoxia-responsive transcriptional signatures alongside RNA sequence features and RBP binding predictions may help model how these combined factors influence EV-ncRNA profiles. Such models support the hypothesis that EV cargo composition may be influenced by both cellular programs and dynamic adaptations to environmental stress (Figure 2) [65,66]. The relationship between RNA processing and EV sorting is particularly evident for circRNAs. Their covalently closed structure confers high stability and resistance to exonuclease degradation, contributing to their persistence in cells and enrichment in extracellular compartments [50]. However, their presence in EVs is not solely a consequence of stability [67]. The interactions with specific RBPs, together with features of circRNA biogenesis and genomic origin, may also influence their selective export. Consequently, circRNA sorting may reflect regulatory processes involved in their formation, linking transcriptional and post-transcriptional regulation to EV-associated ncRNA composition [68]. These observations suggest that RNA sorting into EVs is influenced by multiple interconnected regulatory layers, including sequence features, RNA structure, epi-transcriptomic modifications, RBP activity, and cellular state. AI-based approaches may facilitate the integration of these variables, supporting the identification of RNA features associated with EV enrichment and the generation of testable hypotheses regarding the mechanisms underlying RNA sorting [69].

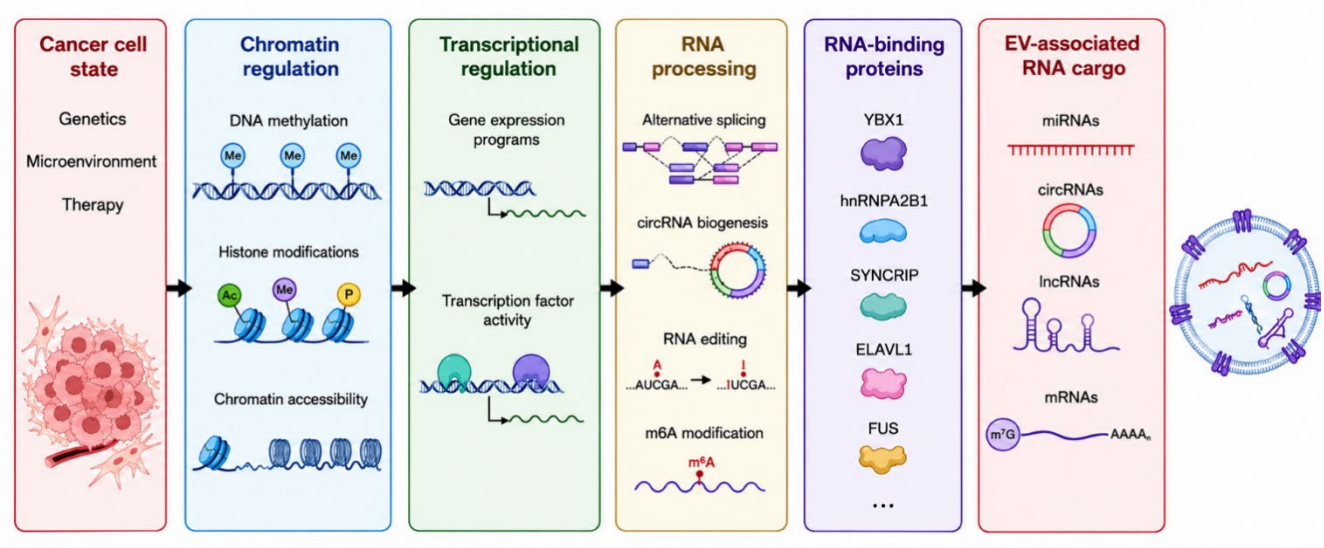

Figure 2. Intracellular regulatory mechanisms contributing to EV-RNA composition. Chromatin regulation, transcriptional regulation, RNA processing and RBPs determine the RNA species loaded into EVs. Abbreviation: Ac: acetylation; m6A: methyladenosine; Me: methylation; P: phosphorylation; TF: transcription; EV: extracellular vesicle Graphical rendering supported by Copilot Microsoft. The graphical elements were reviewed by the authors for biological accuracy.

5. AI-assisted development of integrative mechanistic models

The workflow proposed for developing and validating AI-assisted mechanistic models is outlined in Figure 3. This framework integrates multi-omics datasets, computational analyses, experimental validation, and biological hypothesis testing into an iterative process. A key application of AI in EV-ncRNA biology is the integration of multiple regulatory processes to generate testable hypotheses about their relationships. However, understanding how these processes collectively modulate EV-ncRNA signatures require integrative approaches capable of combining multimodal data into a coherent framework (Table 1).

Integrating multiple regulatory layers may support a more complete interpretation of EV-ncRNA profiles. Sequence features, chromatin accessibility, transcriptional dynamics, RNA modifications, and RBP interactions all contribute to defining RNA fate. When these variables are analyzed independently, their predictive value remains limited; but integrated models can reveal regulatory patterns. For instance, transcripts with specific RBP-binding motifs, and carries epi-transcriptomic modifications may be preferentially exported despite moderate abundance.

AI-based approaches can help identify such complex relationships, identifying combinations of features that would be difficult to detect through conventional approaches [70]. Graph-based approaches enable the integration of multiple molecular interactions and may help identify regulatory modules associated with cancer-related pathways [71]. For instance, circRNAs can modulate miRNA availability by acting as molecular sponges, thereby influencing the expression of downstream target genes [71]. When integrated into AI-derived networks, these interactions may help identify regulatory circuits associated with key oncogenic pathways, including epithelial-mesenchymal transition, angiogenesis, and immune evasion. Such models move beyond simple correlation, providing a structured representation of regulatory dependencies that can be interrogated to generate mechanistic

hypotheses [72]. The interpretative power of these models becomes evident when applied to EV-ncRNA datasets. Rather than treating EV-ncRNA profiles as static signatures, AI-based frameworks enable their decomposition into underlying regulatory components. For example, an observed increase in specific RNA species in EVs may be explained not only by transcriptional upregulation but also by enhanced stability, preferential splicing, or increased affinity for RBPs involved in vesicle loading. By integrating these factors, AI models can generate mechanistic hypotheses linking EV-associated ncRNA changes to specific regulatory mechanisms, thereby facilitating the biological interpretation of descriptive observations [73]. This approach also has important implications for biomarker development. Traditional strategies often rely on identifying individual RNA molecules that are differentially expressed between conditions. However, such markers are frequently limited by biological variability and lack of specificity. In contrast, AI models that integrate multiple features can generate composite signatures that capture the complexity of disease states. For example, combining information on circRNA abundance, RNA editing patterns, and splicing-derived isoforms allows the construction of classifiers that are more robust and informative than single-parameter approaches. These models are valuable in OC, where molecular heterogeneity and overlapping clinical features complicate diagnosis [74]. ExRNA profiles are not static but evolve in response to treatment and disease progression. AI models capable of analyzing longitudinal data may identify trajectories potentially associated with underlying biological processes, such as the development of therapeutic resistance or the activation of compensatory pathways. In this context, subtle shifts in RNA composition, which might be overlooked in cross-sectional analyses, may represent early indicators of disease evolution [75]. This dynamic perspective extends the utility of EV-ncRNA from diagnostic biomarkers to real-time monitoring tools. Overall, integrative AI models provide a framework for developing biologically interpretable models that link molecular features to regulatory mechanisms and specific cancer cell states. Once experimentally validated, these models provide the basis for the subsequent interpretation of patient-derived EV-ncRNA signatures in clinical settings (Figure 3).

Table 1. Representative AI approaches supporting the interpretation of successive regulatory layers.

Regulatory process/input data	Biological application	Representative AI approach	Expected output	Current limitation	Reference
Chromatin accessibility, DNA methylation, histone modifications	Definition of epigenetic regulatory states	Convolutional neural networks (CNNs); transformers	Chromatin accessibility, enhancer activity and transcription-factor binding prediction	Cell-type dependence; incomplete modeling of three-dimensional chromatin organization; large training datasets	[20,76]
Transcriptional regulation	Reconstruction of transcriptional regulatory programs	Regulatory-network inference; ensemble learning; graph-based models	Gene-regulatory networks, regulon activity and predicted responses to transcription-factor perturbation	Context dependence; difficulty distinguishing causal from correlative interactions	[77,78]
RNA sequence and secondary structure	Characterization of RNA sequence and structural determinants	RNA language models; transformers; structure-aware deep learning	RNA structural features, functional motifs and sequence representations	Limited experimentally validated structural data; variable performance across RNA classes and lengths	[79,80]
Alternative splicing	Identification of alternative splicing events and isoform usage	Deep neural networks; sequence-based models	Splice-site usage, variant effects and tissue-dependent splicing predictions	Limited incorporation of chromatin state, RBP dynamics and EV-associated isoform data	[81,82]
RNA editing	Identification of functionally relevant RNA-editing events	Sequence- and structure-aware deep learning	Editing-site probability and functional annotation	False-positive editing calls; dependence on RNA structure predictions; scarcity of EV-associated editing datasets	[48,83]
circRNA biogenesis	Prediction of circRNA formation and back-splicing	Multimodal deep learning; CNNs	circRNA classification, back-splice-site prediction and candidate prioritization	Training-set dependence; limited modeling of cell-state-specific RBP activity and transcriptional kinetics	[84,85]
Epitranscriptomic regulation (m6A)	Characterization of epitranscriptomic RNA modifications	Residual neural networks; CNNs; integrative predictors	Site-specific m6A prediction, sequence determinants and functional annotation	Technology-dependent annotations; limited evidence connecting predicted m6A sites to selective EV loading	[86,87]
RNA-binding proteins	Modeling of RNA–protein interaction networks	Graph neural networks; multimodal deep neural networks	RBP-binding-site prediction, sequence–structure preferences and candidate sorting networks	Contrastive Language–Image Pre-training (CLIP)-derived biases; condition-specific binding; limited OC-specific EV datasets	[88,89]
EV-associated ncRNA signatures	Identification of disease-associated EV-associated ncRNA signatures	Machine learning; Deep Neural Networks	Cancer cell state classification; signature prioritization	Cohort heterogeneity; lack of standardized preprocessing	[24]
Multimodal integration/ explainable AI	Integration of complementary regulatory layers into biologically interpretable models	Latent-factor models; multimodal deep learning; graph neural networks; explainable AI	Integrated molecular representations, cancer-cell-state inference and feature attribution	Scarcity of matched multi-omics datasets; calibration, interpretability and prospective validation	[90,91]

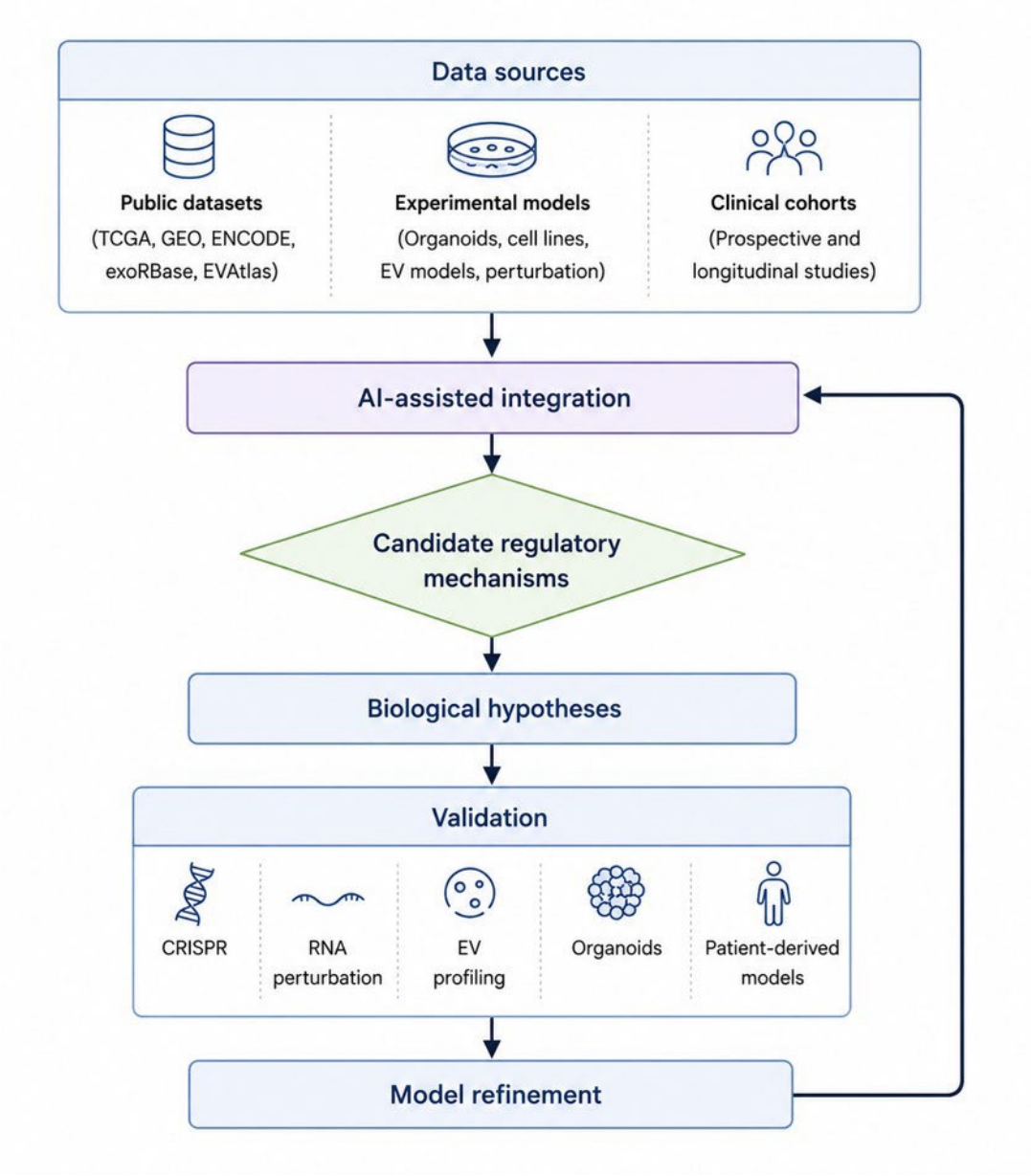

Figure 3. Proposed framework to develop validated AI-assisted mechanistic models via integrated data and experimental validation. Graphical rendering supported by Copilot Microsoft. The graphical elements were reviewed by the authors for biological accuracy.

6. Epigenetic regulation, EV-associated ncRNA and clinical complexity in ovarian cancer

OC remains the most lethal gynecological malignancy, owing to the lack of effective screening strategies and the frequent diagnosis at advanced stages of disease [92]. Despite significant therapeutic advances, recurrence and platinum resistance remain major barriers to long-term disease control [93]. Beyond its clinical aggressiveness, OC comprises a heterogeneous group of diseases with distinct histopathological, molecular, and clinical characteristics. High-grade serous ovarian carcinoma (HGSOC), which accounts for 70% of cases and is responsible for most OC-related deaths, is characterized by nearly ubiquitous TP53 mutations and frequent defects in homologous recombination repair (HRR), including BRCA1/2 alterations [94,95]. Other histological subtypes, including clear cell, endometrioid, mucinous, and low-grade serous carcinomas exhibit distinct mutational landscapes involving genes such as ARID1A,

PIK3CA, KRAS, BRAF, CTNNB1, and PTEN, reflecting different biological mechanisms and therapeutic vulnerabilities [92]. This remarkable inter- and intra-tumoral heterogeneity is further amplified by epigenetic remodeling, transcriptomic plasticity, and dynamic interactions with the tumor microenvironment, generating diverse cancer cell states that influence disease progression, metastatic dissemination, therapeutic response, and patient outcome. Consequently, current diagnostic and prognostic biomarkers, including serum CA125, HE4, and the ROMA algorithm, often show limited sensitivity and specificity, particularly for early-stage disease and for distinguishing malignant tumors from benign gynecological conditions such as endometriosis or benign ovarian cysts, highlighting the need for biologically informed approaches capable of capturing the molecular complexity of OC [96]. OC provides a particularly suitable biological context in which to apply the proposed framework. Growing evidence suggests that regulatory mechanisms such as RNA epigenetic modifications, RNA editing, alternative splicing, circRNA biogenesis, and ncRNA-mediated networks contribute to multiple aspects of OC biology, including tumor progression, metastatic dissemination, and therapeutic resistance [45]. Among these, epi-transcriptomic regulation has emerged as a major contributor to OC biology, implicating m6A writers (METTL3, METTL14, WTAP), erasers (FTO, ALKBH5), and readers (YTHDF and YTHDC family proteins) in the regulation of tumor proliferation, stemness, epithelial-to-mesenchymal transition, immune modulation, and platinum resistance. Likewise, aberrant RNA editing, alternative splicing, and circRNA biogenesis have also emerged as important contributors to OC biology [97]. Dysregulation of the splicing machinery, including spliceosome components such as BUD31, SF3B4, and CTNNBL1, together with the generation of clinically relevant splice variants such as CD44s, CD44v6, KLF6-SV1, ECM1a, and KAI1-SP, has been associated with epithelial-to-mesenchymal transition, metastatic dissemination, angiogenesis, immune evasion, chemoresistance, and poor prognosis [98,99]. Similarly, circRNA biogenesis has attracted increasing attention, with circRNAs such as circWHSC1, circHIPK3, and CDR1as participating in competing endogenous RNA (ceRNA) networks that regulate proliferation, invasion, metastatic dissemination, and platinum resistance [14]. By contrast, although aberrant A-to-I RNA editing mediated by ADAR enzymes has been associated with transcriptomic plasticity and subtype-specific regulatory programs in OC, its functional contribution remains comparatively less well characterized than alternative splicing or circRNA regulation [100]. These observations support the view that post-transcriptional regulation represents a fundamental component of the regulatory networks underlying OC progression. In parallel, the EV-ncRNA signatures associated with multiple clinically relevant features of OC have been identified. The miRNAs contained in EVs (EV-miRNAs) remain the most investigated class of EV-ncRNAs and have been linked to early diagnosis, histological subtype, metastatic dissemination, platinum resistance, recurrence, and patient survival. Recently, EV-associated lncRNAs and circRNAs have also emerged as promising biomarkers, further expanding the spectrum of circulating RNA species associated with OC progression. These studies demonstrate that EV-ncRNA cargo reflects clinically relevant aspects of tumor biology and supports its potential as a minimally invasive source of biomarkers for liquid biopsy (Table 2). Most studies remain based on differential expression analyses and clinical correlations, providing limited insight into the regulatory mechanisms responsible for the selective enrichment of specific ncRNAs within EVs. Consequently, the biological relationship between intracellular RNA regulatory programs and circulating EV-ncRNA signatures remains largely unresolved [101]. While circRNAs and several miRNAs have been linked to EV-mediated communication in OC, much less is known about how RNA epigenetic modifications

influence EV cargo composition. As a result, most EV-ncRNA signatures remain descriptive biomarkers with limited mechanistic interpretation.

Table 2. Representative evidences correlating EV-ncRNA and Regulatory process in OC.

Regulatory process/layer	Representative finding	OC context	Biological implication	Strength of evidence	Reference
circRNA biogenesis/EV-circRNA cargo	EV-associated circWHSC1 promotes OC progression and peritoneal dissemination	OC progression; peritoneal metastasis	Functional evidence that EV-circRNAs contribute to metastatic niche remodeling	Moderate–High	[102]
circRNA biogenesis/EV-circRNA cargo	Exosomal circPUM1 promotes OC proliferation, migration, invasion, and peritoneal metastasis	OC progression; peritoneal metastasis	Supports a mechanistic link between circRNA export and peritoneal dissemination	Moderate–High	[103]
EV-miRNA cargo/immune microenvironment	Plasma-derived exosomal miR-200b promotes macrophage M2 polarization through KLF6 suppression	EOC progression; immune microenvironment	EV-miRNAs may modulate tumor–immune crosstalk	Moderate	[104]
EV-circRNA cargo/therapy resistance	Circulating exosomal circFoxp1 confers cisplatin resistance and is associated with poor outcome	Cisplatin-resistant EOC; prognosis	EV-circRNAs may reflect therapy-resistant cancer cell states	Moderate	[105]
EV-miRNA cargo/diagnostic specificity	Exosomal miR-200 family members have been proposed as diagnostic markers in OC	Diagnosis/ differential diagnosis	Supports clinical relevance of EV-miRNA signatures	Moderate	[106]
EV-miRNA cargo/histotype specificity	Exosomal miR-1290 is elevated in HGSOC and discriminates HGSOC from other histological malignancies	HGSOC; histotype discrimination	EV-miRNAs may capture histotype-specific tumor biology	Moderate	[107]
EV-miRNA cargo/platinum resistance and recurrence	Small EV-associated miRNA profiles, including miR-21-3p/5p and miR-891-5p, are associated with platinum resistance and recurrence	Platinum resistance; recurrent OC	EV-miRNA signatures may reflect treatment-adapted tumor states	Moderate	[108]
EV-mediated transfer/chemoresistance	Stromal exosomal miR-21 suppresses APAF1 in OC cells and confers paclitaxel resistance	Metastatic/recurrent OC; stromal chemoresistance	Functional evidence that stromal EV-miRNAs remodel therapy response	High	[109]

Abbreviations: ceRNA, competing endogenous RNA; OC, ovarian cancer; EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian carcinoma; KLF6, Krüppel-like factor 6; APAF1, apoptotic protease activating factor 1.

7. Challenges and future directions

The available evidence highlights both the potential and limitations of EV-ncRNA analysis. Despite advances in RNA regulation and the growing number of disease-linked EV-ncRNA signatures, establishing causal connections between cellular regulatory programs and circulating EV-ncRNA profiles is still difficult. Addressing this gap will require computational models that generate testable hypotheses and iterative experimental validation. This strategy allows exploration of how upstream regulatory changes affect EV-RNA composition. Integrative can suggest mechanistic links between regulatory events and exRNA profiles, supporting targeted validation. Alternative splicing, circRNA

biogenesis, and epi-transcriptomic regulation represent are ideal systems for this approach. Integrative analyses can suggest mechanistic links between regulatory events and exRNA profiles, supporting targeted validation. Alternative splicing, circRNA biogenesis, and epi-transcriptomic regulation are ideal systems for this approach. Models integrating genomic context, RNA structure, RNA modifications, and RBP interactions can help predict which transcripts enter EVs, while experimental perturbation of key regulatory factors allows experimental validation. Dynamic cancer cell states provide a further setting to study these relationships. Hypoxia, chemotherapy, PARP inhibition, and inflammatory signaling can modulate chromatin, transcription, RNA processing, and RBP localization. Integrative computational approaches can reveal mechanisms stress driven EV RNA changes and generate testable hypotheses on the molecular basis of cancer cells. The successful application of this framework depends on consistent and interoperable molecular datasets. As shown in Figure 4, AI-assisted interpretation should be integrated within a workflow that integrates public multi-omics resources, computational analyses, and experimental validation. Integrated epigenomic, transcriptomic, RNA editing, circRNA, epi-transcriptomic, proteomic, and EV RNA datasets define complementary regulatory layers that could support the development of clinically interpretable AI driven models (Table 3).

Their integration may facilitate the identification of candidate regulatory associations and support the biological evaluation of AI-derived predictions. Methodological challenges reduce the reproducibility and interpretability of AI-driven studies. The lack of standardized workflows for EV isolation, characterization, and RNA analysis remains a major source of variability. Although MISEV2023 guidelines provide recommendations for EV characterization, adherence across studies remains inconsistent. Normalization of EV-ncRNAs is not standardized, and circRNA profiling remains highly method-dependent. As a result, machine-learning models may capture technical noise instead of biological signals. Normalization of EV-ncRNAs is not standardized, and circRNA profiling remains highly method-dependent. Clinical translation will require high-quality datasets with multiple regulatory layers measured in the same samples.

Standardized analytical pipelines and robust validation strategies are essential. and multicenter studies with harmonized workflows can improve reproducibility. Importantly, AI-derived regulatory relationships should be regarded as probabilistic and hypothesis-generating rather than direct evidence of causality. Experimental perturbation and functional validation remain essential for establishing mechanistic links between intracellular regulatory programs and EV-RNA composition. The primary value of AI is to support the biological interpretation of EV-RNA signatures through the integration of complementary regulatory information.

Continued progress will depend on the close interaction between computational modeling, molecular biology, and experimental investigation, supporting the development of next generation of liquid biopsy approaches in precision oncology.

Table 3. AI-assisted workflow for the biological interpretation and validation of EV-ncRNA regulatory mechanisms.

Regulatory process	Representative biological systems and experimental model	AI-assisted analysis	Biological hypothesis	Validation strategy	Contribution to integrative model	Representative database and resource
Chromatin regulation	Patient tissues; patient-derived organoids	Multimodal integration	Epigenetic remodeling generates reproducible EV-ncRNA signatures	ATAC-seq, ChIP-seq, CRISPR perturbation, DNMT inhibition	Epigenetic regulatory states	ENCODE (encodeproject.org); Roadmap Epigenomics (roadmapepigenomics.org); GDC/TCGA (portal.gdc.cancer.gov)
Transcriptional regulation	Bulk RNA-seq; scRNA-seq; patient-derived organoids	Gene regulatory network inference	Coordinated transcriptional programs shape EV-ncRNA composition	CRISPRi/CRISPRa; transcription factor perturbation	Transcriptional regulatory programs	GDC/TCGA (portal.gdc.cancer.gov); GTEx (gtexportal.org); Human Cell Atlas (humancellatlas.org)
Alternative splicing	Long-read RNA-seq; paired tissue–EV samples; 3D spheroids	Splicing prediction	Alternative splicing influences selective EV-ncRNA composition	SF3B1 perturbation; long-read RNA validation	Isoform-specific regulatory information	TCGA SpliceSeq (bioinformatics.mdanderson.org/TCGASpliceSeq); VastDB (vastdb.crg.eu)
RNA editing	RNA-seq; paired tissue–EV samples; patient-derived EVs	RNA editing prediction	ADAR-dependent RNA editing contributes to dynamic remodeling of EV-ncRNA composition	ADAR1/2 perturbation	Transcriptomic plasticity	REDIportal (srv00.recas.ba.infn.it/atlas); REDItools (github.com/BioinfoUNIBA/REDItools)
circRNA biogenesis	circRNA sequencing; patient tissues; EVs	circRNA prediction and prioritization	Back-splicing contributes to circRNA enrichment within EVs	QKI/DHX9 perturbation; RNase R validation	Stable circRNA regulatory components	circAtlas (circatlas.biols.ac.cn); circBase (circbase.org); CircBank (circbank.cn)
Epitranscriptomic regulation (m6A)	MeRIP-seq; direct RNA sequencing; patient-derived EVs	Epitranscriptomic prediction	m6A may contribute to selective EV-ncRNA loading	METTL3/METTL14/FTO/ALKBH5 perturbation	Epitranscriptomic regulatory states	m6A-Atlas (m6aatlas.epomics.org); RMBase (rna.sysu.edu.cn/rmbase)
RNA-binding proteins	eCLIP; RIP-seq; EV proteomics	RBP–RNA interaction prediction	RBPs contribute to selective EV-ncRNA loading	YBX1, hnRNPA2B1 and SYNCRIP perturbation	Selective RNA sorting networks	ENCODE eCLIP (encodeproject.org); POSTAR3 (111.198.139.65/POSTAR3)
EV-ncRNA signatures	Plasma/serum EV cohorts; longitudinal patient samples	Multimodal signature integration	EV-ncRNA signatures reflect intracellular regulatory programs	Independent cohorts; longitudinal validation	Integrated extracellular molecular output	exoRBase (exorbase.org); EVAtlas (evatlas.org); EV-TRACK (evtrack.org)
Multimodal integration/ Explainable AI	Multi-omics datasets; imaging; clinical data	Multimodal deep learning; Graph Neural Networks; Explainable AI	Integration of complementary regulatory layers improves inference of cancer cell states	Prospective validation; feature attribution; multicenter studies	Cancer cell state inference	CPTAC (proteomics.cancer.gov/programs/cptac); GDC/TCGA (portal.gdc.cancer.gov); Human Cell Atlas (humancellatlas.org)

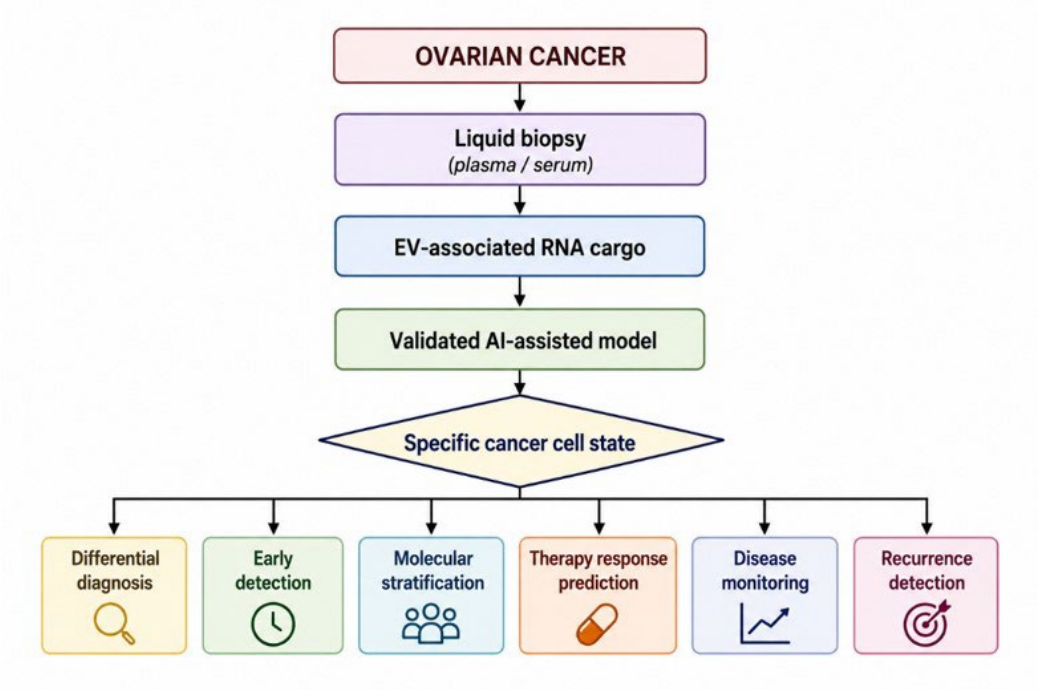

Figure 4. Application of AI-assisted mechanistic models to interpret EV-RNA cargo from liquid biopsy and deduce specific cancer cell states that may support different clinical applications in OC. Graphical rendering supported by Copilot Microsoft. The graphical elements were reviewed by the authors for biological accuracy.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools, specifically Copilot Microsoft, Chatgpt and Grammarly, only to improve language and readability, and the graphical rendering of the figures. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization S.T. and G.C; writing—original draft preparation S.T., A.A., M.G. and G.C.; writing—review and editing, S.T. and G.C.; visualization (figures) S.T. and G.C. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Simona Taverna holds the position of Editorial Board Member for *ExRNA* and has not peer reviewed or made any editorial decisions for this paper. The authors declare no other conflicts of interest.

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