

# Exosomal and Ectosomal Noncoding RNAs in Cancer—More Than Diagnostic and Prognostic Markers



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## Abstract

The release of exosomes and ectosomes carrying noncoding RNAs is addressed in the context of cancer, with focus on microRNAs and long noncoding RNAs as well as differences in RNA cargos produced by tumor and nontumor cells. The differential appearance of ncRNAs can be used for diagnostic and prognostic purposes. Beyond these possibilities, the spreading of pathological and beneficial messages deserves particular attention and will gain future importance. Especially the use of exosomes released by cells that overexpress ncRNAs with antitumor properties appears to be a promising strategy.

## Introduction

The research of noncoding RNAs (ncRNAs) represents one of the actually most dynamic and expanding fields. It started with a lot of surprises:

- The overall ncRNA transcriptome exceeds considerably that of hnRNAs, the mRNA precursors [1].
- Numerous previously unknown types of RNA were discovered, such as, in addition to the earlier detected microRNAs (miRNAs), the long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), piRNAs (PIWI-interacting RNAs), and small nucleolar RNAs (snoRNAs) [2].
- A remarkable functional diversity was discovered especially among lncRNAs, which comprise (a) anti-sense transcripts (asRNAs) that can either down- or upregulate the expression of the corresponding coding transcripts, (b) enhancer RNAs (eRNAs), which may be either unidirectionally (1D type) or bidirectionally (2D type) transcribed, and (c) the unidirectionally transcribed super-enhancer RNAs (= super RNAs), which target several enhancers [3].

An additional function of both lncRNAs and circRNAs was identified as the sponging of miRNAs [4,5]. These ncRNAs have gained additional relevance by the discovery of exosomes and ectosomes, i.e., vesicles that are released by cells, found in all body fluids and participate in intercellular communication. Exo- and ectosomes are distinguished by their biogenesis. While exosomes

are intracellularly formed from multivesicular bodies, ectosomes are produced by budding at the plasma membrane [4] and are, therefore, also referred to as shed microvesicles (sMV) [6] or microvesicles. Especially in older literature, the term microvesicle has been applied to both ecto- and exosomes. Sometimes, exosomes are also distinguished with regard to the cellular site of release as apical and basolateral exosomes, which differ in the primary appearance in body spaces and, importantly, in the composition of their contents [6]. All three types of extracellular vesicles contain various ncRNAs, but also functionally active proteins, often with regulatory properties, mRNAs and not rarely DNA [4]. The vesicular membrane protects the exo- and ectosomal contents against degradation and allows specific attachment to target cells that are influenced by the regulatory components. Therefore, regulatory messages can be transmitted over short or long distance within the body.

## Cancer Changes Exo- and Ectosomal Contents

Meanwhile, numerous studies have shown that the contents of exosomes and ectosomes, which are not generally distinguished in all studies, are changed by malign transformation. Most of the respective investigations have dealt with changes in miRNAs, i.e., molecules that mostly act by targeting mRNAs and lead to their destruction. Sometimes, a single miRNA species may target more than a hundred mRNAs. This may even be increased by RNA editing of miRNAs [5]. Additionally, increasing evidence shows that the composition of exosomal lncRNAs and circRNAs is also

changed in tumor cells, which should have consequences for spongeable miRNAs, but is also of importance with regard to the direct regulatory properties of these longer RNAs. The differences between exo- or ectosomes released from nontumor and tumor cells has been perceived as a chance for diagnosing cancer by testing body fluids, in particular, blood or cerebrospinal fluid, for miRNAs and other ncRNAs, without the need of collecting and identifying circulating cancer cells. Additionally, the composition of miRNAs, lncRNAs and circRNAs in the extracellular vesicles provides information concerning proliferation, metastasis and cancer progression [7-10], angiogenesis [11,12] and even drug resistance [12,13] and is, therefore, of considerable prognostic and therapeutic value.

### A Few Mechanistic Examples of Exo- or Ectosome-Mediated Changes

Many studies have focused on the tumor-promoting properties of ncRNAs, mostly of miRNAs. For instance, exosomal miR-93-5p was shown to stimulate the proliferation of esophageal cancer cells by downregulating the tumor suppressor PTEN (phosphatase and tensin homolog) [14]. Exosomes released by glioma cells promote proliferation and metastasis of glioblastoma by miR-148a, which downregulates CADM1 (cell adhesion molecule 1). In colon cancer patients, exosomal miR-200c and miR-141 were shown to be associated with poor survival, findings that may also apply to other members of the miR-200 family [15]. In head and neck cancer, miR-196a was found to inhibit the expression of the antitumor factor ANXA1 (Annexin A1) [16]. In a study on malignant mammary epithelial cells, numerous exosomal miRNAs were shown to influence various oncogenic networks [17]. microvesicular miR-106a/b was reported to promote malign transformation of hematopoietic cells [18]. Similar results on leukemic transformation were obtained with miR-146b-5p in microvesicle from chronic myelogenous leukemia cells [19]. Tumor promoting properties in prostate cancer were also described for the lncRNA MYU, which is the antisense RNA of the VPS9D1 (vacuolar protein sorting-associated protein 9 domain containing 1) gene. Its action was concluded to result from binding to miR-184 [20]. These few examples may be regarded as being representative for a considerably longer list of findings. For further details on exosomal lncRNAs in cancer see ref. [12].

However, additional information of potentially higher importance exists for ncRNAs with tumor suppressing properties. However, not all of these findings are easily compatible with some publications on tumor promotion. For instance, miR200a was reported to inhibit microvesicle release by hepatocellular carcinoma cells and, thereby, to reduce proliferation [21], results that appear to be at variance with data in ref. [15]. Other studies do not seem to be controversial. In gastric carcinoma, microvesicular miR-29a/c was reported to inhibit growth and vascularization [22]. In endometrial cancer, miR-148b acted as a suppressor of metastasis by downregulating its target gene, DNMT1 (DNA

cytosine-5-methyltransferase 1), obviously by modulating DNA methylation at regulatory sites [23]. Moreover, miR-148b was shown to be strongly reduced in cancer-associated fibroblasts, which release tumor-promoting exosomes [23]. Other cytosine-5-methyltransferases, DNMT3a and 3b, were upregulated by an lncRNA, lincPOU3F3 (linc = long intergenic noncoding), perhaps by sequestering the procarcinogenic miR-106a/b [18]. By virtue of this property, lincPOU3F3 delayed the malign transformation of hematopoietic cells [18]. Moreover, numerous miRNAs with tumor suppressing properties have been identified, as summarized elsewhere [5]. Although their presence in exosomes or ectosomes has not been demonstrated in any case, their transmission by these extracellular particles is highly likely.

### Spreading of Pathological and Beneficial Signals

As shown above, exosomes and ectosomes carrying ncRNA cargos can spread pathological messages from cancer to other cells and even seem to participate in processes of transformation [18,19]. Obviously, they also influence cell types different from those from which the tumor cells originated. This may lead to vascular outgrow and to prevent immunological actions against the tumor. A cell receiving dysregulating miRNAs released by cancer cells may, in fact, become dysregulated itself, but it will not necessarily turn into a real tumor cell, as long as no carcinogenic mutation has occurred. However, the existence of ncRNAs with tumor suppressing properties, which can also be transmitted by exosomes and ectosomes, implies the possibility of spreading and amplifying beneficial signals, too. This may include preventive properties of exo- and ectosomal cargos from cells in a healthy state. Moreover, signaling by protective molecules may elevate the levels of beneficial cargos. As an example, a study on in vitro differentiated macrophages shall be mentioned, which were exposed to exosomes released by hepatocellular carcinoma cells. When these tumor cells were pre-treated with melatonin, a hormone known for its oncostatic properties [24,25], the exosome cargos downregulated in these macrophages the proinflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , whereas they were upregulated by exosomes from untreated tumor cells [26]. Unfortunately, the responsible cargo molecules, which may not necessarily be RNAs, have not been identified. Nevertheless, similar effects may be expected in future studies that may reveal roles of ncRNAs. In the context of pathologies other than cancer, various beneficial effects of ncRNAs have already been described, as summarized elsewhere [5,27,28].

### Conclusion

The identification of ncRNAs, especially miRNAs, lncRNAs and circRNAs, in exosomes and ectosomes for diagnostic and prognostic purposes is, without any doubt, of high value. However, the applicability of these particles and their RNA contents goes much beyond this objective. Measurements of extracellular RNAs in exosome-containing supernatants of blood or in fractions of

isolated vesicles is comparably easy. However, future research should more strongly focus on the curative potential of exosomes and ectosomes. This would include a more ample identification of ncRNAs with antitumor properties. This has to be followed by the development of procedures of generating exosomes or ectosomes containing higher amounts of these components. Strategies that were suggested earlier were based on the idea of preventing the spreading of cancer-promoting vesicles by eliminating them or inhibiting their docking to target cells by antibodies [29]. It would be a more promising strategy to collect exo- and ectosomes from cultured cells that overexpress beneficial ncRNAs and test their suitability as curative vehicles. This has already been done using microvesicles from cells overexpressing miR-29a/c to reduce angiogenesis and tumor growth in gastric cancer [22]. This kind of research should be more consequently followed, with the aim of ultimately developing suitable methods for application in humans.

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