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Review article

Effect of environmental exposures on cancer risk: Emerging role of non-coding RNA shuttled by extracellular vesicles

Paola Monti [a], Giulia Solazzo [a], Valentina Bollati [a,b,c,*]

[a] EPIGET Lab, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[b] CRC, Center for Environmental Health, University of Milan, Milan, Italy
[c] Occupational Health Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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ABSTRACT

Environmental and lifestyle exposures have a huge impact on cancer risk; nevertheless, the biological mechanisms underlying this association remain poorly understood. Extracellular vesicles (EVs) are membrane-enclosed particles actively released by all living cells, which play a key role in intercellular communication. EVs transport a variegate cargo of biomolecules, including non-coding RNA (ncRNA), which are well-known regulators of gene expression. Once delivered to recipient cells, EV-borne ncRNAs modulate a plethora of cancer-related biological processes, including cell proliferation, differentiation, and motility. In addition, the ncRNA content of EVs can be altered in response to outer stimuli. Such changes can occur either as an active attempt to adapt to the changing environment or as an uncontrolled consequence of cell homeostasis loss. In either case, such environmentally-driven alterations in EV ncRNA might affect the complex crosstalk between malignant cells and the tumor microenvironment, thus modulating the risk of cancer initiation and progression.

In this review, we summarize the current knowledge about EV ncRNAs at the interface between environmental and lifestyle determinants and cancer. In particular, we focus on the effect of smoking, air and water pollution, diet, exercise, and electromagnetic radiation. In addition, we have conducted a bioinformatic analysis to investigate the biological functions of the genes targeted by environmentally-regulated EV microRNAs.

Overall, we draw a comprehensive picture of the role of EV ncRNA at the interface between external factors and cancer, which could be of great interest to the development of novel strategies for cancer prevention, diagnosis, and therapy.

1. Introduction

Cancer is a leading cause of premature death all around the world, accounting for nearly 10 million deceases in 2020. More worryingly, the global cancer burden is predicted to rise by 47% in the next 20 years, with the most prominent increase in countries with transition economies (Sung et al., 2021). However, these figures are likely to be greatly underestimated since they are based exclusively on demographic projections (population growth and aging), without considering the impact of concomitant lifestyle changes on cancer risk (Sung et al., 2021). In

Abbreviations: UV, ultraviolet; EV, extracellular vesicle; ncRNA, non-coding RNA; EXOs, exosomes; MVs, microvesicles; rRNA, ribosomal RNA; tRNA, transfer RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; lncRNA, long non-coding RNA; miRNA, microRNAs; circRNA, circular RNA; piRNA, piwi-interacting RNA; mRNA, messenger RNA; nt, nucleotides; CAF, cancer-associated fibroblast; CS, cigarette smoke; BAL, bronchoalveolar lavage; HBE cells, human bronchial epithelial cell; VEGF, vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition; TGFβ, transforming growth factor β; PTEN, phosphatase and tensin homolog; NRF2, nuclear factor erythroid 2-related factor 2; KRAS, Kirsten rat sarcoma virus; EZH2, enhancer of zeste homolog 2; CML, chronic myelogenous leukemia; IL-8, interleukin 8; VCAM1, vascular cell adhesion protein 1; PDEV, plant-derived EV-like nanoparticle; LPS, lipopolysaccharide; TCF7, transcription factor 7; MEV, milk EV; siRNA, small interfering RNA; OGT, O-GlcNAc transferase; Hotair, HOX transcript antisense RNA; PM, particulate matter; BCL2L1, Bcl-2-like protein 1; FMT, fibroblast to myofibroblast *trans*-differentiation; SPRY1, sprouty RTK signaling antagonist 1; DEHP, Di (2-ethylhexyl) phthalate; HHE cell, human hepatic epithelial cell; LATS1, large tumor suppressor kinase 1; PFEMF, power frequency electromagnetic field; IR, ionizing radiation; SOD1, superoxide dismutase 1; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; IGF1, insulin-like growth factor-1; MGMT, O-6-Methylguanine-DNA Methyltransferase; IGF1R, insulin like growth factor 1 receptor.

* Corresponding author at: EPIGET Lab, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.
E-mail address: valentina.bollati@unimi.it (V. Bollati).

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this regard, unhealthy behaviors linked to lifestyle "westernization" (e.g. smoking, physical inactivity, and consumption of highly processed food and sugary beverages) have been postulated to underlie the growing incidence of many early-onset cancer types (Ugai et al., 2022). Moreover, many environmental factors such as air pollution and ultraviolet light have been recognized as carcinogens, further stressing the contribution of the exposome (i.e. the sum of all lifelong exposures) on cancer incidence and mortality (Gatto, 2021). Accordingly, a recent study has shown that only a minority of cancer cases (10–30%) could be attributed to "bad luck", i.e. intrinsic causes such as random mistakes occurring during DNA replication (Wu et al., 2015). Despite the enormous relevance to public health, much remains to be clarified about the biological mechanisms linking environmental exposures to cancer risk. What has become clear is that malignant cells do need the support of neighboring non-tumor cells for their survival and growth, and this requires intricate crosstalk between cancer and the tumor microenvironment (Hanahan and Weinberg, 2011). In this framework, extracellular vesicles (EVs) have recently emerged as pivotal players in exchanging information between cells, by transporting a wide variety of proteins, lipids and nucleic acids. Delivery of such a molecular payload elicits biological effects in recipient cells; in particular, many studies have pointed out that EV-borne non-coding RNAs (EV ncRNAs) could exert an important modulatory function on cellular proliferation, differentiation, and motility (Sun et al., 2018; Zhang et al., 2020). Besides, exposure to many environmental and lifestyle determinants has been demonstrated to alter the profile of EV ncRNAs, with potential pathological implications (Monti et al., 2021).

In this review article, we summarize the most recent evidence concerning the effect of smoking, diet, physical exercise, ambient pollution and electromagnetic radiation on EV ncRNAs, focusing on the impact of such ambient-induced changes on tumor-related processes. Hopefully, this knowledge will contribute to better elucidate the role of EV ncRNAs at the interface between the exposome and cancer, which could be of great interest for the development of novel strategies for cancer prevention, diagnosis and treatment.

1.1. Extracellular vesicles as carriers of non-coding RNA

Extracellular vesicles (EVs) are membranous nanoparticles (approximatively 50–1000 nm) produced by virtually all living cells, which can be found in the majority of biological fluids. According to their biogenesis, EVs are classified into exosomes (EXOs), which originate from the endosomal compartment, and microvesicles (MVs), which derive from outward budding of the plasma membrane. Over the last decades, EVs have aroused interest due to their emerging role in intercellular communication; indeed, there is now strong evidence supporting that EVs pose as "delivery boxes" containing a wide range of bioactive molecules, which are transferred from donor cells to recipient ones. The EV molecular payload encompasses thousands of proteins, lipids, metabolites and nucleic acids, which can be found in association with the EV membrane or within their lumen (Van Niel et al., 2018). Of this heterogeneous molecular cargo, much attention has been paid to EV non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs), ribosomal RNAs (rRNAs) and transfer RNAs (tRNA) (Fig. 1, Table 1). For a more detailed description of their structure and biological functions, refer to (Van Niel et al., 2018; P. Zhang et al., 2019).

Of note, the ncRNA content of EVs differs substantially from the transcriptome of the cell of origin, suggesting a selective packaging of certain ncRNA species (O'Brien et al., 2020). Within EVs, ncRNAs are protected from degradation by nucleases and pH fluctuations, and can be safely shuttled not only to nearby cells but also to distant organs. Besides enhancing its stability, EVs could facilitate ncRNA delivery to specific cells, thus eliciting a targeted regulatory function (Kim et al., 2017; Lara et al., 2020). Indeed, numerous studies have reported that uptake of these EV-borne molecules can modulate gene expression, mRNA translation, chromatin remodeling, and ribonucleoprotein complex assembly, which in turn regulate a plethora of physiological process (Kim et al., 2017; Van Niel et al., 2018). Given their importance in maintaining cell homeostasis, it is therefore not surprising that alterations in the profile of EV ncRNA have been associated to many pathological conditions, including cancer (Hu et al., 2020).

1.2. EV NCRNA in cancer biology

Cancer is a heterogeneous process characterized by 8 "hallmarks", i.e. a series of functional adaptations that allow malignant cells to survive and thrive, by sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing

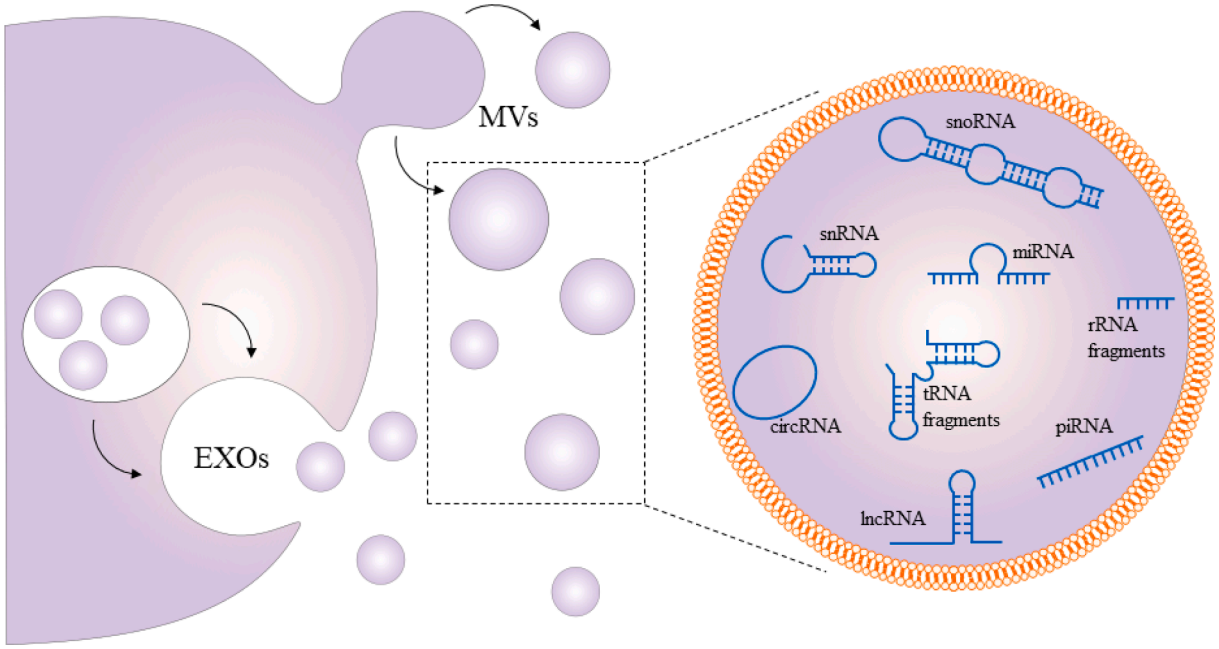

Fig. 1. Cells release EXOs and MVs carrying a variegate ncRNA cargo.

Table 1
Principal EV ncRNA species and their biological functions.

Full name	Abbreviation	Length	Main functions	Reference
microRNA	miRNA	~22 nt	Transcriptional, post-transcriptional and translational regulation of gene expression	(O'Brien et al., 2018)
long non-coding RNA	lncRNA	>200 nt	Regulation of gene expression and of chromatin structure	(Mattick et al., 2023)
circular RNA	circRNA	100–5000 nt	Regulation of gene expression, splicing, and protein functionality	(Santer et al., 2019)
small nuclear RNA	snRNA	100–300 nt	pre-mRNA splicing and maturation	(Bohnsack and Sloan, 2018)
small nucleolar RNA	snoRNA	60–300 nt	Modification of other RNA species (rRNA, snRNA)	(Kufel and Grzechnik, 2019)
piwi-interacting RNA	piRNA	24–31 nt	Regulation of chromatin state, transposon silencing	(Iwasaki et al., 2015)
ribosomal RNA	rRNA	120–4500 nt	ribosome assembly and functionality	(P. Zhang et al., 2019)
transfer RNA	tRNA	76–90 nt	transport of amino acids to the ribosomes	(P. Zhang et al., 2019)

angiogenesis, activating invasion and metastasis, reprogramming energy metabolism and evading immune destruction (Hanahan and Weinberg, 2011). Interestingly, most of these acquired capacities are associated with an altered bi-directional communication between malignant cells and neighboring non-cancer cells, which is necessary for the creation of a hospitable microenvironment that dynamically adapts to the tumor needs (Dominiak et al., 2020). For instance, immune cells must be trained not to attack the growing tumor, and surrounding fibroblasts must be converted into cancer-associated fibroblasts (CAFs) to promote angiogenesis and provide trophic support. To do so, transformed cells adopt different signaling strategies, which include the release of "oncosomes", i.e. EVs harboring an oncogenic molecular cargo (Meehan et al., 2016). In general, tumor cells have been found to secrete an increased number of EVs if compared to their non-malignant counterparts, which retain an altered ncRNA profile capable of triggering molecular alterations in recipient cells (Bebelman et al., 2021, 2018). Indeed, many studies have shown that ncRNA carried by tumor EVs can stimulate proliferation, migration, and therapy resistance of fellow cancer cells, besides contributing to the reprogramming of stromal and immune cells. However, non-cancerous cells from the tumor microenvironment do not play a passive role, but try to counterbalance the tumor influx by releasing EVs bearing ncRNA with tumor suppressive properties. Overall, the sum of all these pro- and anti-tumorigenic signals exerts a strong influence on the fate of the tumor (as reviewed in (Hu et al., 2020)).

In this framework, EV ncRNAs have attracted interest as non-invasive biomarkers for cancer diagnosis and prognosis, as well as for treatment monitoring (R. Xu et al., 2018). Moreover, EV-mediated delivery of ncRNAs could hold promise as a novel therapeutic strategy thanks to the low immunogenicity and toxicity of EVs, as well as to their capacity to cross barriers that would otherwise compromise the reaching of hardly accessible target sites (O'Brien et al., 2020).

1.3. EV NCRNA at the interface between environmental exposures and cancer

Cells are constantly subjected to a multitude of stimuli, either coming from the outside (e.g. viral infections, nutrient intake) or from the inside (e.g. hypoxia, oxidative stress). As key players in intercellular crosstalk, EVs are most likely to take part in the adaptive response set up by the organism following to such exposures. Indeed, directly exposed cells release EVs with an altered molecular cargo, whose delivery to recipient non-exposed cells could elicit functional effects by promoting their survival, adaptation and growth. Nevertheless, exposure to stressful agents and other detrimental cues can perturb cell homeostasis and result in changes in EV content which have been associated with multiple pathological processes, ranging from cardiovascular and respiratory diseases, to neurological disorders and cancer (Monti et al., 2021; Qin et al., 2020).

Here, we discuss the importance of EV ncRNA at the interface between the exposome and cancer initiation and progression. In particular, we decided to address the effect of the so-called "external exposome", i.e. environmental exposures that come from the outside, without delving into the potential impact of the "internal exposome", which include the resident microbiota and a series of biological outcomes deriving from cumulative exposure experiences (such as cytostatic and oxidative stress, or hypoxia- and heat-induced responses). Specifically, we focus on smoking, diet, physical exercise, air and water pollution, and irradiation due to their established role in cancer biology. For a complete description of the studies cited in the following paragraphs, reporting an effect of environmental exposures on EV ncRNA, see Supplementary Table 1. As several studies report about microvesicles or exosomes without providing evidence of their biogenesis route, we will comprehensively refer to EVs as encouraged by International Society of Extracellular Vesicles (ISEV) guidelines (Théry et al., 2018).

1.4. SMOKING

1.4.1. Cigarette smoke

Consumption of tobacco products is the principal lifestyle risk factor contributing to the global burden of cancer-related deaths, and has been estimated to cause about 85% of lung cancer cases (Alkoussa et al., 2020; Sasco et al., 2004). Indeed, cigarette smoke (CS) contains more than 4500 different chemicals, of which approximatively 60 have been classified as carcinogens (Aguayo et al., 2020). The tumorigenic potential of several compounds might resides in their pro-oxidative activity and in their capacity to form DNA adducts, whose accumulation increases the risk of developing somatic mutations within genes controlling cell proliferation and transformation (Ma et al., 2019). In addition, smoke carcinogens exert a modulatory action on cell-to-cell communication, with a significant impact on EV-mediated signaling. Besides stimulating EV shedding (Mobarrez et al., 2014; Saxena et al., 2021), CS could alter their molecular cargo, including ncRNAs. Here, an *in vitro* study reported that human airway epithelial cells exposed to CS condensate release EVs that differ for their miRNA and piRNA cargo with respect to untreated controls; in particular, miR-3913-5p, miR-574-5p, and miR-500a-5p were found to be upregulated, whereas miR-618 levels were reduced (Corsello et al., 2019). Also, another study found that three miRNAs (let-7e, let-7 g, and miR-26b) were downregulated in EVs isolated from bronchoalveolar lavage (BAL) of smokers (n = 10) if compared to controls (n = 10) (Héliot et al., 2017). In this context, it is plausible that such CS-induced changes in EV ncRNAs might affect multiple cancer-related biological processes in recipient cells. Liu and colleagues showed that transformed human bronchial epithelial (HBE) cells treated with CS extract release EVs enriched with miR-21, an oncomiR that promotes angiogenesis by increasing VEGF levels in normal HBE recipient cells via the STAT3 pathway (Liu et al., 2016). The same research group also reported that the upregulation of EV miR-21 could compromise airway remodeling by altering the crosstalk between the bronchial epithelium and neighboring fibroblasts, with the latter acquiring a myofibroblast phenotype following to the uptake of EVs from CS-treated HBE cells (H. Xu et al., 2018). The effect of CS on EV miR-21 levels was also supported by *in vivo* evidence, showing that smokers retain higher serum levels if compared to non-smokers (Liu et al., 2016; H. Xu et al., 2018). Another study reported that human lung epithelial cells treated with CS extract release EVs with an altered miRNA cargo that affect macrophage polarization, thus modulating inflammation and tumor growth (Chen et al., 2021). CS-induced EV

miRNA changes have been also proposed to play a role in metastasis formation. A retrospective study conducted on lung cancer patients (n = 810) revealed that current smokers have a higher incidence and a worse prognosis of brain metastasis if compared to non-smokers, and suggested that this effect might be partially mediated by EV miR-4466. Indeed, chronic nicotine exposure was found to foster brain recruitment and polarization of neutrophils; once activated, they release EVs enriched with miR-4466, which in turn supports metastatic colonization of the brain by increasing the stemness of colonizing lung cancer cells and by promoting metabolic adaptations necessary for tumor growth (Tyagi et al., 2022).

The importance of EV ncRNAs in CS-related tumorigenesis was also supported by a study showing that cancer-free, current smokers (n = 26) and patients with non-small cell lung cancer (NSCLC) (n = 26) share alterations in 31 EV miRNAs derived from BAL samples, which were predicted to target genes implied in cancer-related pathways; in addition, 7 EV mRNA and 7 EV lncRNA were found to be overexpressed in both smokers and NSCLC patients if compared to non-smoker controls (n = 48) (Wu et al., 2019). Indeed, miRNAs are not the only class of EV ncRNA that is modulated by CS exposure. Chen and colleagues showed that prostatic stromal myofibroblasts treated with CS release EVs with an altered circRNA cargo; in particular, CS-induced upregulation of EV circ-0001359 was found to promote epithelial-mesenchymal transition (EMT) in recipient epithelial cells, possibly promoting the invasion and migration of prostate cancer cells via the TGFβ signaling pathway (Chen et al., 2022). Besides, tobacco smoke fosters the progression of gastric cancer by inducing the release of EV circ-000670 by gastric cancer stem cells, resulting in increased stemness and EMT (Liang et al., 2022).

In contrast with the above-mentioned studies, concluding that EV ncRNA altered by CS might support tumorigenesis, Héliot and colleagues suggested that some changes might be beneficial. In their study, the authors showed that HBE cells treated with EVs from smokers and non-smokers differ for the expression miR-21, miR-27a, let-7e, and let-7g. Analysis of target mRNAs revealed that these miRNAs modulate the expression of many genes involved in lung carcinogenesis, including the tumor suppressors *PTEN* and *NRF2*, and the oncogenes *KRAS*, *EZH2* and *VEGFa*; surprisingly, cells treated with smoker EVs exhibited a general downregulation of all these genes, which was speculated to protect against oncogenic transformation (Héliot et al., 2017).

1.4.2. Other smoking products

There is growing evidence supporting that also alternative smoking products such as electronic cigarettes (E-cigs) might affect EV ncRNAs, possibly modulating cancer risk. Nevertheless, it is difficult to draw firm conclusions since few studies have been published so far, and due to the lack of E-cig product standardization. Analysis of circulating EVs from cigarette smokers, waterpipe tobacco smokers, E-cig users, dual smokers and non-smokers revealed that the five groups differ for the composition of EV-borne small ncRNAs; among them, 7 miRNAs were found to be commonly dysregulated in smoking/vaping subjects if compared to non-smokers; besides, overexpression of EV let-7a-5p, which is implied in lung carcinogenesis, was proposed as a suitable biomarker to distinguish non-smokers from all the other groups (Singh et al., 2020). Similarly, smoking/vaping was reported to alter the profile of circulating EV lncRNAs, whose altered expression was predicted to affect cancer-related biological pathways such as cell proliferation and differentiation (Kaur et al., 2020).

1.5. Diet and physical exercise

1.5.1. Diet

Nutrition is an important risk factor for cancer, with approximatively 5% of incident cases being attributable to unhealthy dietary habits (e.g. hypercaloric diet) in the United States (F. F. Zhang et al., 2019); conversely, the Mediterranean diet and other dietary regimens rich in antioxidants and anti-inflammatory nutrients have been proposed as a strategy for cancer prevention (Mentella et al., 2019). Interestingly, diet can modulate the ncRNA payload of EVs (Ji et al., 2021; López de las Hazas et al., 2021; Mantilla-Escalante et al., 2021), with a possible effect on tumorigenesis. A study conducted on overweight breast cancer survivors (n = 16) reported that 42 plasma EV miRNAs are differentially regulated after a 8-week Mediterranean diet intervention, and that these miRNAs target genes related to cancer progression and metabolic dysregulation (Kwon et al., 2020). The functional effect of EV ncRNAs induced by diet or specific nutrients is also supported by *in vitro* evidence. In this regard, Gasperi and co-workers showed that platelets treated with arachidonic acid (a polyunsaturated fatty acid derived from animal-based dietary sources) release EVs carrying increased levels of miR-223 and miR-126, whose internalization by breast cancer cells leads to reduced proliferation and migration, as well as to enhanced chemosensitivity to cisplatin (Gasperi et al., 2019). Another study reported that chronic myelogenous leukemia (CML) cells treated with curcumin, an antioxidant polyphenol mainly employed as a spice and as a food colorant, exhibit reduced proliferation and increased expression of tumor suppressor gene *PTEN*, and that such beneficial effect is mediated by the selective packaging and ejection of EV miR-21 from curcumin-treated cells. In line with this, CML xenograft mice inoculated with curcumin had reduced tumor size and higher plasma levels of EV miR-21 than controls (Taverna et al., 2015). Moreover, EV-mediated downregulation of cellular miR-21 was associated to reduced VEGF expression, suggesting that curcumin could also counteract angiogenesis (Taverna et al., 2015). Indeed, miR-21 enriched EVs released by curcumin-treated CML cells was also observed to reduce the motility of recipient endothelial cells and to downregulate the expression of the pro-angiogenetic factors IL-8 and VCAM1 (Taverna et al., 2016).

1.5.2. Dietary EVs

Many studies reported that edible plant-derived EV-like nanoparticles (PDEVs) might modulate inflammation and cancer-related pathways in mammalian recipient cells through delivery of their miRNA cargo (Xiao et al., 2018; Yin et al., 2022; Zhao et al., 2018). Indeed, PDEVs have been shown to be stable over a wide range of pH values and to be efficiently internalized by mammalian cells, potentially playing an important role in cross-kingdom communication (Ly et al., 2022; Urzì et al., 2022). As an example, PDEVs extracted from ginger bear anti-inflammatory miRNAs, whose internalization by colorectal adenocarcinoma cells can attenuate LPS-induced inflammation (Yin et al., 2022). Also, medicinal plants contain PDEVs carrying miRNAs with anti-cancer effects. PDEVs isolated from the seeds of *Moringa oleifera* (horseradish tree), commonly employed in African traditional medicine, contain miRNAs that were predicted to target apoptosis-related genes; indeed, different tumor cell lines treated with such EVs exhibit reduced viability and proliferation rates (Potestà et al., 2020). In addition, plant-derived miRNAs introduced by dietary consumption can resist to degradation and can be transported in the bloodstream (Chin et al., 2016). Chin and colleagues identified miR-159 as the most abundant circulating plant-miRNA in Western subjects, showing that it mainly localizes within EVs. Interestingly, they observed that miR-159 serum levels were inversely correlated with breast cancer incidence and progression. The protective role of this miRNA was demonstrated by treating breast cancer cells with serum EVs or with a miR-159 mimic, in both cases resulting in reduced proliferation due to targeting of TCF7, a component of the Wnt signaling pathway. Also, oral administration of the miR-159 mimic to a xenograft mouse model for breast cancer significantly inhibited tumor growth (Chin et al., 2016).

Owing to their stability and biocompatibility with mammalian cells, PDEVs have attracted considerable attention as potential drug delivery vehicles for anti-cancer therapy (Ly et al., 2022); in particular, many studies have demonstrated that PDEVs engineered to carry a regulatory ncRNA payload might be a promising strategy to counter cancer survival, growth and metastatization. In this regard, Del Pozo-Acebo and colleagues showed that PDEVs from broccoli loaded with exogenous

miRNAs can be efficiently taken up by colorectal adenocarcinoma cells and reduce their viability (del Pozo-Acebo et al., 2022). Another study reported that miR-18a encapsulated in PDEVs from grapefruit induces M1 macrophage polarization, which in turn inhibits the growth of colon tumor metastases in the liver (Teng et al., 2016).

In a similar way to PDEVs, also milk EVs (MEVs) resist to harsh degrading conditions and harbor a variety of bioactive ncRNAs, which can be taken up and regulate gene expression in the consumer's cells (Kandimalla et al., 2021). Interestingly, MEV miRNA have been found to exert a different regulatory function on normal and tumor cells. Human MEVs induced proliferation and EMT in normal colonic cells, but not in tumor ones, through the delivery of miR-148a-3p, which targets PTEN (Reif et al., 2019). MEVs are also rich in miRNAs predicted to target genes implied in immune responses and cancer-related processes (Chen et al., 2020). The miRNA content of MEVs was found to regulate cytokine release and migration of cultured macrophages (Sun et al., 2013). Also, MEVs have been proposed as nano-carriers for cancer therapy. Bovine MEV-mediated delivery of a mutant-allele specific siRNA targeting KRAS reduced proliferation of lung cancer cells and inhibited tumor growth in lung tumor xenograft mice (Aqil et al., 2019).

1.5.3. Physical exercise

Not only diet, but also physical activity is well-known to modulate cancer risk and progression. The anti-tumoral effect of exercise is partially mediated by a specific set of signaling molecules, called "exerkines", whose secretion was recently shown to be paralleled by increased EV release (Nederveen et al., 2021). Besides affecting EV number, exercise was also associated to changes in their ncRNA cargo (Doncheva et al., 2022; Oliveira et al., 2018; Sadovska et al., 2022; Vann et al., 2022), which might counter tumor progression. Oliveira et al. found that treadmill running could affect the ncRNA content of serum EVs obtained from rats, with 12 miRNAs and one tRNA being differentially expressed after training (Oliveira et al., 2018). Interestingly, most of these miRNAs were predicted to regulate the MAPK signaling pathway (Oliveira et al., 2018), which controls many cancer-related processes (Dhillon et al., 2007). Sadovska and colleagues showed that EV ncRNA from rat subjected to forced wheel running exercise were significantly different from that of sedentary ones, with potential impact on various cancer-related pathways. Indeed, injection of exercise-induced EVs into rat models of prostate cancer led to a decrease in primary tumor mass and in lung metastases (Sadovska et al., 2022). Besides, exercise might also alleviate tumor-related conditions fostered by EV ncRNA, such as cachexia. In this regard, breast cancer cells were found to promote skeletal muscle loss through the release of EV miR-122, which targets OGT, a post-translational modification enzyme with a key role in regulating Ca^{2+} flux in muscle cells. Interestingly, this pro-cachectic effect is countered by hypoxia and lactate treatment, suggesting a protective role of physical activity. In line with *in vitro* findings, mice subjected to high-intensity treadmill running showed increased OGT levels if compared to sedentary ones (Yan et al., 2022). If on one hand exercise has been suggested to play a protective role against cancer, physical inactivity might have the opposite effect. Lu and colleagues reported that gluteal-femoral fat squeezing, mimicking sedentary lifestyle, stimulates the release of EV-borne HOX transcript antisense RNA (Hotair), a pro-oncogenic lncRNA, from adipose tissue in mice. In turn, EV Hotair promotes aberrant proliferation of intestinal cells, thus increasing the risk of colorectal carcinogenesis. Consistently, analysis of circulating EV Hotair in 89 women showed that the highest levels were found in those with obesity and sedentary habits (Lu et al., 2017).

1.6. Air and water pollution

1.6.1. Particulate matter (PM) and other airborne pollutants

Airborne pollutants comprise a very heterogeneous set of gaseous molecules and solid components, many of which have been recognized as carcinogens by the International Agency for Research on Cancer (IARC) (Hamra et al., 2014). Among them, particulate matter (PM) stands out as 95% of the world population is exposed to outdoor concentrations exceeding the World Health Organization (WHO) safety threshold (Ritchie and Roser, 2019). Inhalation of PM triggers inflammation and oxidative stress in the airways, eventually causing tissue damage that might herald or foster tumorigenesis. In addition, PM exposure stimulates the release of EVs, which in turn modulate intercellular communication, tissue regeneration and immune responses in the respiratory system (Alkoussa et al., 2020). Of note, there is a growing body of evidence suggesting that some of these effects might be mediated by the ncRNA payload of PM-induced EVs, which is enriched with miRNAs with pro-inflammatory, pro-thrombotic and pro-oxidative properties (Pavanello et al., 2016; Pergoli et al., 2017; Rodosthenous et al., 2018). For instance, nasal epithelial cells promote macrophage polarization towards the pro-inflammatory M1 phenotype by transferring EV miRNA-19a and miRNA-614 upon atmospheric PM exposure (Shin et al., 2020). Besides, Wang and colleagues reported that 36 miRNAs are differentially expressed within EVs released by lung adenocarcinoma cells treated with $PM_{2.5}$ if compared to untreated controls, and provided *in vivo* and *in vitro* evidence of their involvement in lung tumorigenesis (Y. Wang et al., 2021). Similarly, long-term $PM_{2.5}$ exposure was shown to promote proliferation, EMT and migration of pulmonary epithelial cells. Transcriptomic analysis revealed that 45 EV miRNAs and 843 protein coding genes were differentially expressed between treated and non-treated cells, and the partial overlap between EV miRNA target genes (predicted *in silico*) and altered cellular gene expression supported the hypothesis of a functional role of $PM_{2.5}$ -regulated EV miRNAs (Xu et al., 2019).

Given its heterogeneity, PM might contain traces of substances with known tumorigenic properties, such as asbestos, airborne metals, and silica dust; however, long-term and high-level exposure to these volatile PM components mainly concerns a limited portion of the general population, and in particular workers employed in specific industrial sectors (Marant Micallef et al., 2018). In this context, EVs might participate in modulating the effect of such occupational exposures on cancer risk, by shuttling an altered ncRNA cargo. A study conducted in our lab showed that healthy steel plant workers (n = 55) chronically exposed to PM-associated airborne metals retain increased levels of 17 EV miRNA, 3 of which (miR-302b, miR-200c, miR-30d) are implied in inflammation and oxidative stress pathways (Pavanello et al., 2016). Also, dust particles-exposed workers with pneumoconiosis (n = 54) had lower serum EV let-7a-5p levels than healthy controls (n = 100). Target gene prediction analysis revealed that downregulation of EV let-7a-5p is associated with increased expression of the anti-apoptotic *BCL2L1* gene, which might contribute to poor survival in lung adenocarcinoma patients (Zhang et al., 2018). Similarly, Niu and co-workers showed that miR-7219-3p is upregulated in macrophages and derived EVs following to silica treatment, and that this miRNA promotes proliferation, migration and fibroblast to myofibroblast *trans*-differentiation (FMT) by targeting *SPRY1*, a negative regulator of the Ras/ERK/MAPK signaling pathway. These findings were confirmed in mice after 4 weeks of silica exposure, whose lung tissue displayed increased miR-7219-3p levels and number of myofibroblasts (Niu et al., 2022). Human bronchial epithelial (HBE) cells transformed by treatment with hydroquinone, an active metabolite of benzene, stimulate proliferation of co-cultured normal HBE cells by transferring EV miR-221 (Jiang et al., 2020). Di (2-ethylhexyl) phthalate (DEHP), a plasticizer widely employed in industry, has been found in association with PM and has been linked to lung toxicity. Lung epithelial cells exposed to DEHP release an increased number of EVs and EV miR-26a-5p uptake stimulates EMT, migration and invasion capacity in non-exposed recipient cells (Qin et al., 2021). EV miRNAs could also be exploited as early diagnostic markers for occupational diseases, as well as promising therapeutic options. Patients with malignant pleural mesothelioma (n = 23) can be distinguished from asbestos-exposed, cancer-free subjects (n = 19) by a two- EV miRNA

signature (miR-103a-3p + miR-30e-3p) (Cavalleri et al., 2017). Another study showed that mesothelioma cancer cells dispose of miRNAs with tumor suppressor properties, such as miR-16-5p, through EVs; indeed, inhibition of EV secretion or force-feeding of cancer EVs back to producing cells results in increased cellular levels of miR-16-5p and reduced viability, proliferation and invasiveness (Munson et al., 2019).

1.6.2. Waterborne arsenic

In addition, certain water contaminants have been recognized as carcinogenic agents. In many developing countries, groundwater is rich in inorganic arsenic, whose chronic exposure has been linked to an increased risk of many malignancies, mainly at the lung, liver, and skin levels (Martinez et al., 2011). Interestingly, recent *in vitro* studies have shown that cultured cells treated with arsenite, the most toxic form of arsenic, release EVs with an altered ncRNA cargo, which may participate in carcinogenesis. Here, Xu and colleagues demonstrated that arsenite-transformed HBE cells can stimulate proliferation of neighboring non-neoplastic HBE cells, through the transfer of EV miR-21 (Y. Xu et al., 2015). Arsenite-induced upregulation of this EV miRNA was also observed in both exposed mice and humans, and was found to promote myofibroblast differentiation of recipient lung fibroblasts (P. Wang et al., 2021). Similarly, another study showed that arsenite treatment of human hepatic epithelial (HHE) cells induces the shedding of EVs enriched with miR-155, which is taken up by normal HHE cells and promote the acquisition of a pro-inflammatory phenotype (enhanced expression of cellular miR-155 and *STAT3*, and increased secretion of IL-6 and IL-8). In line with these findings, subjects with symptoms of arsenicosis (n = 16) had higher serum inflammatory markers and EV miR-155 levels than non-exposed controls (n = 16) (Chen et al., 2017). Also, exposure to arsenite was found to induce M2 polarization in macrophages, which in turn enhance proliferation, migration, and invasion of co-cultured hepatocellular carcinoma cells by transferring EV miR-15b. This miRNA targets *LATS1*, a tumor suppressor gene whose downregulation promotes cancer progression; accordingly, blocking EV shedding or transfecting polarized macrophages with a miR-15b inhibitor antagonizes EV miR-15b-mediated tumorigenic effect (J. Li et al., 2021).

1.7. Electromagnetic radiations

1.7.1. Ultraviolet light and other non-ionizing radiations

Ultraviolet (UV) light is a type of non-ionizing radiation that has been linked to an increased risk of skin cancer. Although low doses of UV light (especially UV-B) are deemed necessary for vitamin D production, long-term or high-intensity UV irradiation can cause oxidative and genotoxic damage, whose accrual can promote premature skin aging and photocarcinogenesis (Mullenders, 2018). Indeed, 65% of melanoma cases and 90% of non-melanoma skin cancers have been attributed to UV exposure (Pleasance et al., 2010). Of note, irradiated cells respond to UV insults by releasing a wide array of signaling molecules and effectors, including EVs, that trigger metabolic adaptations in neighboring non-irradiated cells (Szatmári et al., 2019a). Recent evidence suggests that this mechanism, called “bystander effect”, might be partially mediated by EV ncRNAs (reviewed in (Du et al., 2020)); consistent with this hypothesis, UV-mediated bystander effect was found to be abrogated by RNase treatment (Le et al., 2017). Also, recent studies reported that UV exposure of cultured melanocytes increases EV shedding and alters EV miRNA content, many of which are implied in cancer-related pathways such as DNA damage response, senescence and apoptosis (Sha et al., 2020; Shen et al., 2020). Wang and colleagues have recently demonstrated that EVs released by human skin fibroblasts treated with UV-A or UV-B radiation retain increased levels of miR-4655-3p, which was found to reduce proliferation and induce oxidative damage and apoptosis in recipient cells; in contrast, transfection with a miR-4655-3p inhibitor suppressed these outcomes (Wang et al., 2022). Also power frequency electromagnetic fields (PFEMFs), which are non-ionizing, low-frequency radiations generated by electric power systems such as household appliances, can affect the miRNA content of circulating EVs, as demonstrated by Li and colleagues. In this study, serum EVs isolated from mice exposed to PFEMFs had altered levels of miRNAs targeting genes implied in many disease states, including cancer (Li et al., 2018).

1.7.2. Ionizing radiations

Unlike UV rays, which can only penetrate the outermost layers of our body, high-energy ionizing radiations (IRs) can reach internal organs and cause DNA damage all along their trajectory. Thanks to their genotoxic properties, IRs are widely employed for cancer treatment (Baskar et al., 2012). The most common therapeutic strategy consists in externally irradiating the cancer site through a beam of high-energy particles or waves (mainly X-rays, but also gamma rays and charged particles), promoting cell cycle arrest and apoptosis of malignant cells (Baskar et al., 2012). Similarly to UV light, multiple studies have shown both *in vitro* and *in vivo* that also IRs might prompt changes in EV ncRNAs targeting genes implied in cancer-related cellular processes (Moertl et al., 2020; O'Leary et al., 2017; Szatmári et al., 2019b), possibly influencing the communication between irradiated and bystander cells in the tumor microenvironment. Such IR-induced alterations in EV ncRNA regulatory network might act synergistically with radiotherapy, thus facilitating the killing of recipient non-irradiated cells. EVs derived from pancreatic cancer cells exposed to X-rays are more efficiently internalized than EVs from non-irradiated ones, and induce oxidative stress and DNA damage in recipient tumor cells. This effect is possibly mediated by IR-associated upregulation of EV miR-6823-5p, which suppresses *SOD1* expression in recipient cells thus increasing ROS levels and genotoxic stress (Nakaoka et al., 2021). Another study showed that irradiated fibroblasts release EVs enriched in oncogenic miR-21, whose internalization by non-irradiated cells was associated to chromosome aberration and DNA damage, as well as to increased cellular miR-21 levels (S. Xu et al., 2015). Similarly, irradiated fibroblasts secrete EVs that promote oxidative stress and inhibit proliferation of recipient cells by delivering EV miR-34c (Rastogi et al., 2018). Besides, Tan *et al.* showed that EV miR-27a transfer from keratinocytes irradiated with either α-particles or X-rays to co-cultured fibroblasts induces oxidative stress and reduce migration in the latter (Tan et al., 2019).

However, there is also evidence supporting a detrimental role of IR-induced EV ncRNAs, which might foster tumor progression. Here, a study reported that EVs released by glioma cells contain increased oncogenic miR-889 and decreased tumor suppressive miR-516 and miR-365 under radiation stress (Mrowczynski et al., 2018). Another study showed that EVs obtained from the culture medium of breast cancer cells after treatment with a therapeutic dose of X-rays are more numerous and larger than EVs released by untreated cells, and enhance invasiveness of recipient non-irradiated cancer cells possibly through delivery of miRNAs (Al-Abedi et al., 2021). Similarly, Li *et al.* reported that exposure of bronchial epithelial cells to energetic heavy ions (^{48}Ti, ^{28}Si, and ^{16}O) stimulate EV release by about 4-fold if compared to non-treated controls. miRNA profiling revealed that EVs from irradiated cells harbored a lower number of miRNA species, but were enriched with miRNAs implied in cancer initiation and progression such as miR-1246, miR-1290, miR-23a, and miR-205 (Z. Li et al., 2021). Also, glioma stem cell-derived EVs induce survival, proliferation and invasiveness of recipient non-stem glioma cells irradiated with a ^{60}Co source, possibly by transferring EV miRNAs targeting *PTEN* (Ma et al., 2022). EV miRNAs from irradiated cells have been also found to promote autophagy. In this regard, Song and co-workers found that bronchial epithelial cells exposed to ^{60}Co gamma rays induce autophagy in bystander cells through EV miR-7-5p, which downregulates the EGFR/Akt/mTOR signaling pathway (Song et al., 2016). The same group also demonstrated that X-ray treatment increased miR-7-5p expression in EVs released by astrocytes and oligodendrocytes from mice brains, and that tail vein injection of such EVs was accompanied by downregulation of *Bcl-2* in mice lungs, thus supporting a long distance bystander effect on autophagy

regulation (Cai et al., 2017). Interestingly, EV ncRNAs are also implied in spreading resistance to radiotherapy and other cancer treatments, with huge implications in the clinical setting. X-ray irradiation of glioblastoma cells causes a decrease of cellular miR-603 levels through its ejection via EVs. This leads to de-repression of *IGF1* and *IGF1R*, which in turn promote the acquisition of stem-cell phenotype and resistance to radiotherapy. Export of miR-603 additionally de-repressed *MGMT*, which encodes a DNA repair protein responsible for detoxifying DNA alkylating agents commonly employed for glioblastoma treatment. In contrast, administration of exogenous miR-603 had tumoricidal effect, suggesting a new strategy for tumor treatment (Ramakrishnan et al., 2020).

2. Discussion and conclusions

2.1. Bioinformatic analysis of EV miRNA gene targets

We further validated the role of environmentally-regulated EV-borne ncRNA in cancer-related processes through bioinformatic analysis (Fig. 2). In particular, we chose to focus on EV miRNA, due to their well-established role in downregulating gene expression in recipient cells, and due to the small number of studies concerning the effect of exposures on other EV ncRNA species, which might generate misleading results at this stage. First, we extrapolated a list of EV miRNAs (Supplementary Table 2) that are reported to be environmentally regulated by the studies listed in Supplementary Table 1. The list includes both miRNA selected *a priori* (based on literature or database search) and those derived from untargeted experimental approaches (next generation sequencing, expression panels). For studies that performed a preliminary screening of differentially expressed EV miRNAs, followed by a validation step, only validated EV miRNAs were included. For studies testing different exposure conditions/doses, only commonly dysregulated EV miRNAs were considered; otherwise, we included all EV miRNAs that are dysregulated under at least one experimental conditions. For simplicity, exposures were classified into 4 groups (i.e. “smoking”, “diet and physical exercise”, “air and water pollution”, and “electromagnetic radiation”). For each group, we removed repeated miRNAs and miRNAs that were not found in the miRbase database (Griffiths-Jones, 2006). As a result, we included in our analysis 53 miRNAs in the smoking group, 89 miRNAs in the diet and physical exercise group, 72 in the air and water pollution group, and 88 in the electromagnetic radiation group (Supplementary Table 3). We found that 38 miRNAs were shared by at least two exposure groups; among them, miR-21 stands out for being the only miRNA that has been reported to be modulated by all exposures. miR-21 is an oncomiR which has recently aroused interest for its diagnostic, prognostic and therapeutic potential in cancer (Bautista-Sánchez et al., 2020); indeed, this miRNA exerts a pro-tumoral action by promoting metastasis formation and immunosuppression (Chi et al., 2022). There are multiple studies reporting that miR-21 can be transported by EVs; therefore, it is possible that its environmentally-induced release via EVs might foster tumorigenesis.

The shared miRNAs were further investigated to establish whether different exposures regulate them in the same direction; as a result, we obtained a very heterogeneous picture, possibly due to the lack of standardization in the methodologies adopted by independent studies (for a complete report on the directionality of EV miRNA regulation, according to the cited studies, see Supplementary Table 4).

Finally, the shared miRNAs were investigated by gene-target analysis using the R package miRNAtap (version 1.32). Specifically, the gene targets found in at least 3 out of the 5 miRNAtap databases were selected to perform a Gene Ontology (GO) enrichment analysis. For each miRNA, a complete report showing the number of target genes and the top biological process they participate in is reported in Supplementary Table 5. Using the R package multiMiR, we found that 88% of the gene targets predicted by miRNAtap have been experimentally validated. The GO IDs with a significant p-value (K-S test, p-value < 0.05) were classified into 7 groups of cancer-related biological processes, as shown in Fig. 3. More than half (154/263) of GO processes were found to be implied in cell division and proliferation, in the response to external stimuli and oxidative stress, and in apoptosis. Given the biological significance of this discovery, it is crucial to acknowledge that the results may be influenced by the prevalence of cancer-related studies in miRNA research.

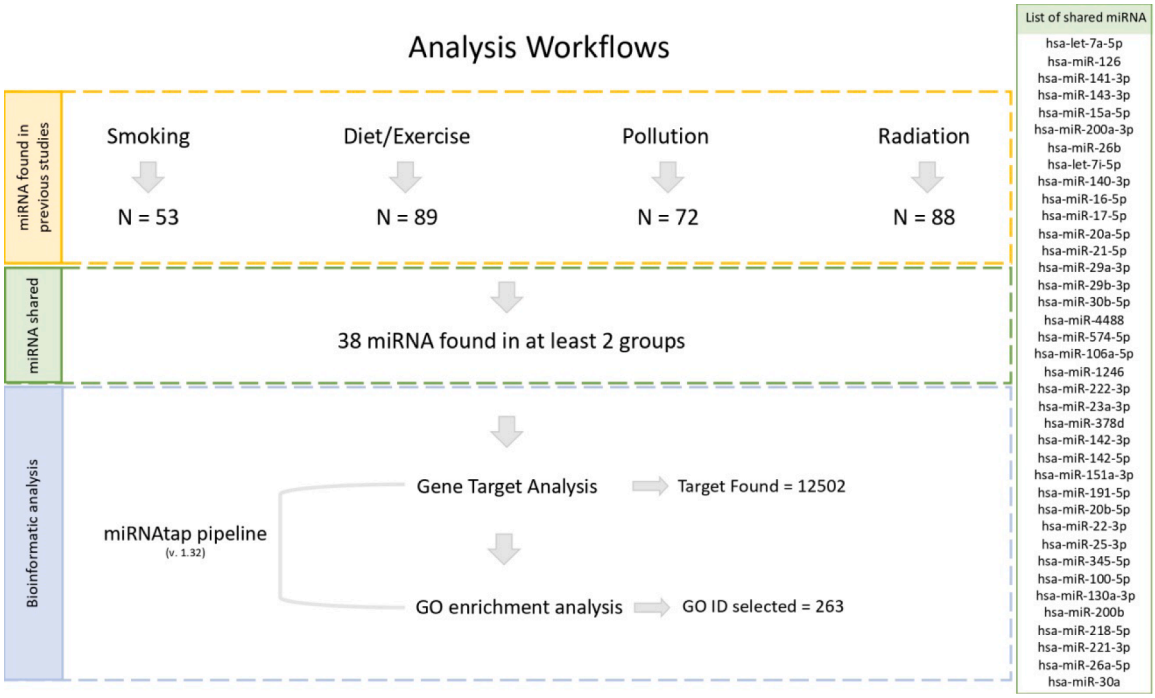

Fig. 2. Analysis workflow of EV miRNA selection and bioinformatic analysis.

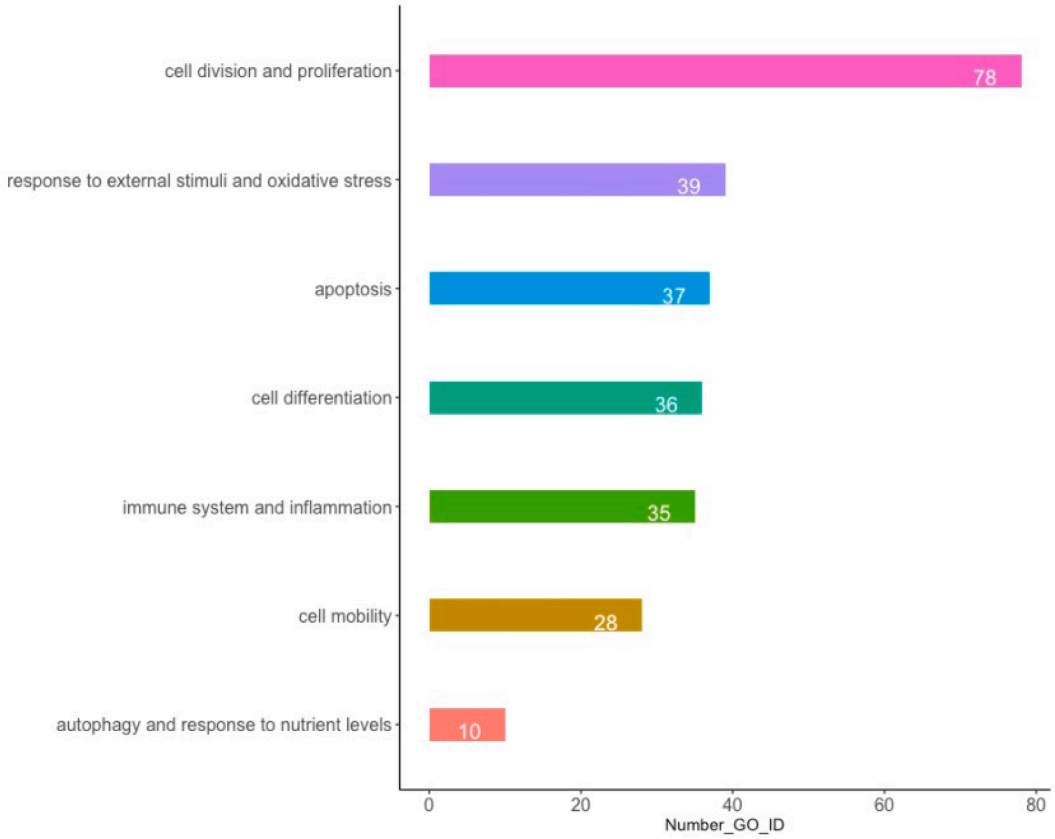

Fig. 3. Number of GO IDs implied in cancer-related processes. For each process, the number of GO_IDs is indicated in the bar.

2.2. *Summary and future directions*

Environmental exposures can modulate intercellular communication by affecting EV size, number and content, with possible implications in many downstream biological processes (Monti et al., 2021). In particular, ambient-induced alterations in EV ncRNA could affect the expression of genes involved in tumor-related pathways controlling cell proliferation and differentiation, metastasis formation, and the response to anticancer drugs (Fig. 4). Such changes have been speculated to occur as part of an adaptive response to external cues, e.g. posing as an active attempt to survive a toxic agent or to warn neighboring non-exposed cells of the threat; nevertheless, there is also evidence suggesting that they could be an unwanted consequence of cell homeostasis loss and therefore occur due to the incapacity of the cell to cope with the external stimulus.

On one hand, smoking, environmental pollutants and unhealthy dietary regiments have been generally associated to EV ncRNA alterations potentially contributing to cancer; on the other hand, physical exercise and healthy diet could exert anti-tumoral properties mediated by EV ncRNA. Nevertheless, as in the case of ionizing radiations, it is more likely that the net effect might be dose, time- or context-dependent, making it difficult to translate such experimental findings into firm conclusions. Indeed, one of the most important limitations of our analysis is that there is high inter-study variability regarding exposure doses, which could explain some discrepancies in the conclusions drawn by independent research works. The importance of exposure dose is also underlined by some of the cited works, showing that quantitatively different treatments might elicit different tumor-related effects (Moertl et al., 2020; Szatmári et al., 2019b). This could be of particular relevance when evaluating the effect of emerging environmental contaminants, such as nanoplastics and other nanomaterials, whose impact on human health have not been fully elucidated yet; nevertheless, their effect on EVs remains largely unknown (as reviewed by (Lima et al., 2022)), since the majority of studies have focused on more commonly investigated exposures.

Overall, there is still a lack of studies simulating real-life scenarios, i.e. focusing on the effect of multiple exposures (the exposome) on EV ncRNA. In addition, much of our knowledge regarding the regulatory roles of EV ncRNA derives from *in vitro* studies, while the few research works conducted in humans or on animal models generally involve a limited number of individuals. Larger population-based studies and clinical trials are needed to translate the potentiality of environmentally regulated EV ncRNA into applications for cancer diagnostics, prognostics, and therapy. A more deep comprehension of the role of EV ncRNA at the interface between environmental exposures and cancer might also highlight novel risk factors contributing to tumor onset and progression, thus prompting new preventive strategies aimed at reducing the impact of external factors on cancer burden. Nevertheless, translation of EV ncRNAs to the clinic is still hampered by many technical difficulties, mainly regarding the lack of rigorous standardization in each phase of EV characterization (from pre-analytical steps, to data interpretation) (Gandham et al., 2020). Besides, the identification of tissue-specific determinants associated to EVs (which are nowadays available only for few EV subpopulations, such as L1CAM for neuron-derived EVs (Gomes and Witwer, 2022)) might provide additional information on the cell origin and impact of EV ncRNAs, making them far more promising than circulating cell-free biomarkers.

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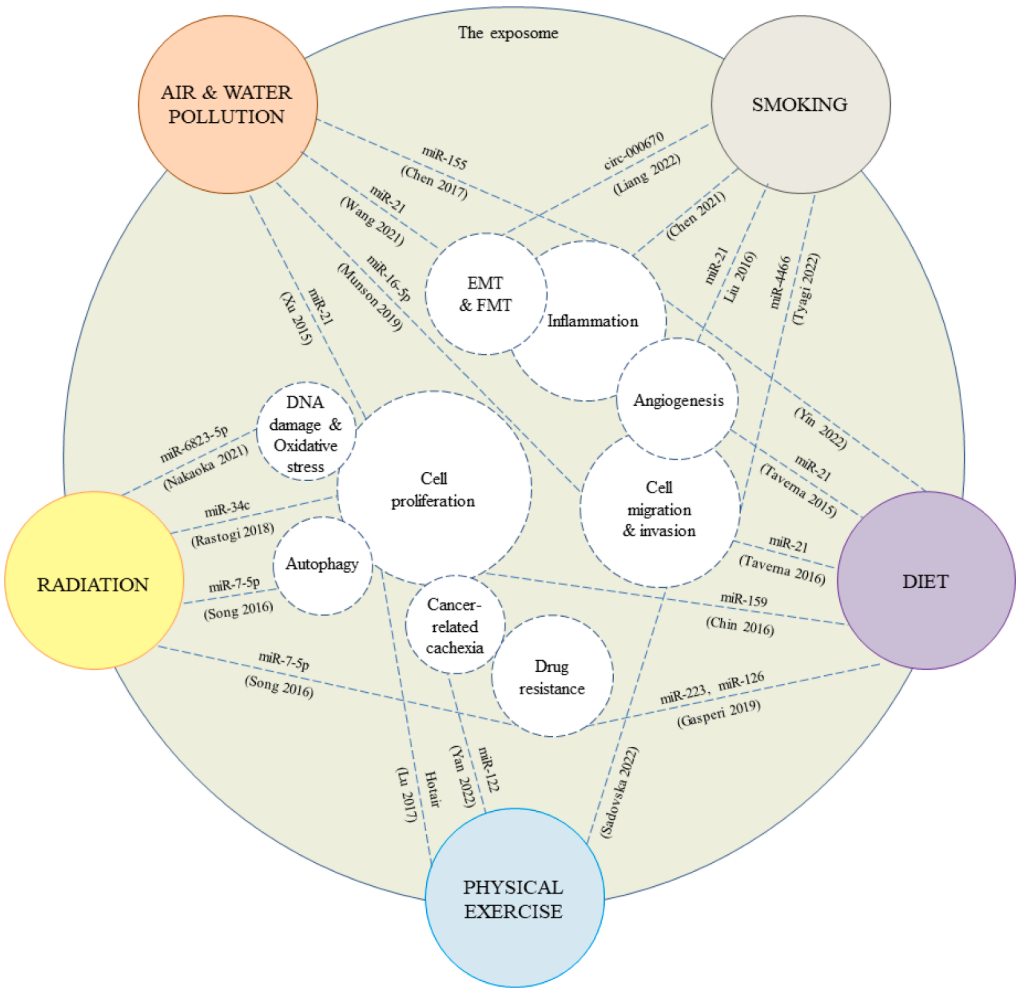

Fig. 4. Effect of environmental and lifestyle exposures on EV ncRNAs, and their implications in cancer-related processes. For each association, one EV ncRNA (with the corresponding citation) is indicated as an example. For studies reporting numerous EV ncRNAs, only the citation is indicated. Cancer-related processes affected by multiple exposures via EV ncRNAs are embedded in larger circles.

CRediT authorship contribution statement

Paola Monti: Writing – original draft, Writing – review & editing. **Giulia Solazzo:** Writing – review & editing. **Valentina Bollati:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108255.

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