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Exosomes: intriguing mediators of intercellular communication in the organism's response to noxious agents

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Exosomes are small extracellular vesicles that range from 30 to 150 nm in size and are formed through cellular endocytosis. They consist of proteins, lipids, and nucleic acids at varying ratios and quantities. The composition and spatiotemporal dynamics of exosomes suggest that they play a crucial role in intercellular communication. The information conveyed by exosomes significantly impacts the regulation of health and disease states in the organism. The term "noxious" refers to all harmful environmental agents and conditions that can disrupt the physiological equilibrium and induce pathological states, regardless whether of radiological, biological, or chemical origin. This review comprehensively examines the presence of such noxious agents within the organism in relation to exosome formation and function. Furthermore, it explores the cause-effect relationship between noxious agents and exosomes, aiming to restore physiological homeostasis and prepare the organism for defence against harmful agents. Regardless of the specific bioinformatic content associated with each noxious agent, synthesis of data on the interactions between various types of noxious agents and exosomes reveals that an organized defence against these agents is unachievable without the support of exosomes. Consequently, exosomes are identified as the primary communication and information system within an organism, with their content being pivotal in maintaining the health-disease balance.

KEY WORDS: biological mediators; extracellular vesicles; harmful agents; intercellular crosstalk; signalling

Exosomes are bi-layered extracellular vesicles measuring 30–150 nm that originate from cellular endocytosis. They consist of various biomolecules, including proteins, lipids, deoxyribonucleic acids (DNA) and ribonucleic acids (RNA), which includes microRNAs (miRNA), and non-coding RNAs (ncRNA). The term "exosomes" for these vesicles of endosomal origin was first proposed in 1987 (1–3).

Initially, exosomes were regarded as extracellular carriers of unwanted cellular waste. However, in-depth research revealed their complex composition, which resulted in the growing interest from the scientific community in exploring these structures that continues on. The molecular composition of these vesicles and their spatiotemporal dynamics indicated a potential for significant roles in intercellular communication and signalling, which has been substantiated by several studies (4, 5). Exosome formation via cellular endocytosis occurs when multivesicular bodies fuse with the plasma membrane and release their contents into the extracellular microenvironment (3, 6, 7). Recent literature (8) has provided compelling evidence that all cells within an organism are capable, in some capacity, of either producing exosomes or receiving biosignals from them. Due to their capacity for intercellular information transfer, exosomes play a pivotal role in physiological regulation, disease progression, immune response, and disease development (9).

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Exosomes are secreted by a variety of cell types, primarily immune cells (e.g. B cells and T cells), as well as stem cells, mast cells, platelets, and even cancer cells (3, 4). Exosomes can also be found in various biological fluids, including serum, urine, breast milk, cerebrospinal fluid, and saliva (3, 10). They act as modulators of the body's homeostasis by participating in various physiological processes at the molecular, tissue, and organ levels. This modulatory role of exosomes is particularly pronounced within the immune system, where they serve as messengers between different immune cells (11–14). On the other hand, research has shown that the content of exosomes is highly specific to certain diseases, including neurodegenerative conditions such as Alzheimer's and prion diseases, as well as viral infections and cancer (3, 15, 16). Evidence suggests that exosomes also regulate sensory processing mechanisms, including nociception (15). Exosomes are, in fact, a normal and natural product of cells within the organism and are not prone to immunogenicity, which would otherwise trigger a host immune response. Ultimately, the biomolecular content carried by exosomes plays a crucial role in the regulation of health and disease in the organism (4, 16).

Due to these unique properties, exosomes have become of great interest as biomarkers for predicting various diseases. The molecular content of each exosome is crucial for the induction of specific diseases, as well as for the recovery of the organism. For example, exosomes play a role in several cardiovascular diseases, such as atherosclerosis, myocardial infarction, ischemia-reperfusion injury,

and heart failure. As a result, recent therapeutic and preventive strategies for these conditions have increasingly focused on the use of exosomes (3, 11, 16). Research on the mouse nervous system has shown that serum exosomes treated with Gamma-Aminobutyric Acid (GABA) activate neuronal cells to induce neurite outgrowth. These findings suggest that these exosomes act as mediators, transmitting signals to activate neurons, and that specific foods, including GABA, can produce exosomes that stimulate neuronal activity. This raises the concept of developing targeted foods that regulate brain function through the secretion of functional exosomes from the gut (17). Furthermore, studies on the skeletal system have shown that exosomes possess the ability to transmit multidimensional, abundant, and complex information, acting as powerful "dogrobbers". They mediate intercellular communication crucial for the delicate dynamic balance between the destruction and reconstruction of cells and tissues within the skeletal system (18).

Exosomes are also formed and appear as signalling and transport vesicles in various inflammatory conditions, organism intoxication, and irradiated tissues, among others. Taking into account the aforementioned, the aim of this paper was to provide a comprehensive overview that would shed new light on the association between the formation and response of exosomes as a general response of an organism to the presence of noxious agents in the organism. Furthermore, by summing up the data, the similarities and differences in the exosomal response and their formation following exposure to specific types of noxious agents would be identified, which in turn could be valuable for further research in the development of various biomarkers, including those valuable for early detection of diseases (3, 8). The literature search strategy started with use of the term "exosome" that appeared in articles covered by academic journals included in the PubMed database, starting from 1987 until the most recent papers on the subject, published in 2024. An in-depth analysis of the papers resulted in nearly eighty papers, on the basis of which this review was compiled.

For a clearer understanding of the comprehensive approach model presented in this paper, all harmful substances and environmental phenomena are collectively referred to as "noxious agents", and they have been categorized into biological, radiological, and chemical. The common characteristics of all noxious agents are their ability to disrupt the physiological balance of the organism and induce pathological conditions (19). The biological noxious agents considered herein include bacteria, viruses, parasites, and biotoxins. The chemical ones included the most common environmental chemical pollutants, whereas radiological noxious agents are represented by ionising radiation.

NOXIOUS BIOLOGICAL AGENTS AND EXOSOMES

Bacterial infections and exosomes

Exosomes are highly active during the pathological processes in an organism. They are predominantly released by immune cells, which thereby regulate the course of various pathogen infections. Research has revealed and confirmed an extremely important regulatory mechanism of exosome action, which is based on a bidirectional process: promoting infection and promoting anti-infection. In both cases, exosomes serve as a bridge for intercellular communication or the connection between pathogens and host cells by transferring various signalling molecules, thus facilitating the transmission of information (1).

Exosomes can promote infection through three mechanisms: (1) by mediating further infection through the transfer of pathogen-associated molecules, (2) by participating in immune evasion by the pathogen, and (3) by inhibiting immune responses through the apoptosis of immune cells. On the other hand, exosomes can stimulate anti-infection through two mechanisms: (1) by inhibiting pathogen proliferation and (2) through direct infection, inducing an immune response related to the function of monocyte-macrophages, natural killer (NK) cells, T cells, and B cells (1, 5).

There is concrete evidence, based on studies involving bacteria, that exosomes mediate further infection in the organism by transferring pathogen-derived molecules (1, 20–22).

The potent pathogen *Staphylococcus aureus* causes pneumonia and, in some cases, sepsis, as well as infections of the bones and joints. It has been demonstrated that exosomes derived from neutrophils treated with *S. aureus* can induce an anti-inflammatory response in macrophages, leading to the production of interleukins such as IL-6 and IL-1β (21). Exosomes derived from *Staphylococcus aureus*-infected cells contain bacterial virulence factors, specifically the α-toxin molecule, and deliver it to distant cells within the organism (1, 23). Similarly, exosomes from *Bacillus anthracis*-infected cells transfer the virulence factor of lethal toxin to remote sites from the infection (24). A particularly intriguing mechanism is observed in the digestive system regarding the role of exosomes in *Helicobacter pylori* infection. Exosomes secreted from gastric epithelial cells expressing the Cytotoxin-associated gene A (CagA) contain the CagA virulence factor. These exosomes enter the circulation and "deliver" the CagA virulence factor to other organs and tissues (Table 1) (1, 25).

Furthermore, research focused on the lipid content of exosomes derived from macrophages before and after infection with *Salmonella typhimurium* revealed significant differences. The variations primarily involved glycerophospholipids, sphingolipids, and prenol lipids. These findings further support the signalling role of exosomes in pathogenic infections, contributing to the understanding of host-pathogen interactions (20).

Exosomes have been extensively studied in bacterial pneumonia. It has been established that in tuberculosis, exosomes isolated from cells infected with *Mycobacterium tuberculosis* promote the recruitment and activation of immune T cells. In this way, they contribute to the innate immune response (21, 26).

In pneumonia caused by *Streptococcus pneumoniae*, or pneumococcal pneumonia, the bacterium produces the pneumolysin toxin, which is the primary causative agent of the inflammatory processes. In this case, it was found that exosomes derived from neutrophils

exposed to pneumolysin can cause direct activation of platelets. This subsequently results in a significant increase in the number of platelets expressing CD62P (P-selectin present in megakaryocytes) and a higher surface expression of CD62P compared to platelets incubated with exosomes derived from untreated neutrophils (21, 27).

Pseudomonas aeruginosa is a pathogen known to form antibiotic-resistant biofilms. Studies have shown that the microRNA (miRNA) type let-7b-5b, carried by exosomes derived from respiratory epithelial cells, can act as RNA interference to reduce the ability of *P. aeruginosa* to form biofilms, thereby increasing the susceptibility of this pathogen to the beta-lactam antibiotic aztreonam (21, 28).

Another causative agent of pneumonia, *Legionella pneumophila*, has been studied in the context of exosome function. Exosomes collected from the supernatant of Tamm-Horsfall Protein-1 (THP-1) cells infected with *L. pneumophila* were used to infect healthy cells. The results showed an enhanced response in cells with increased expression of interleukin IL-8, tumour necrosis factor-alpha (TNF-α), interleukin IL-1β, and monocyte chemoattractant protein-1 (MCP-1), compared to uninfected cells (29).

Viral infections and exosomes

The connection between viral infections and the formation of exosomes in the body was proposed as a theory around 20 years ago. Given that early definitions of exosomes referred to them as "cellular waste", some studies even suggested that viruses and exosomes were essentially the same, with viruses being fully exosomes in every sense of the word (30). During the period of heightened scientific interest in the HIV virus, some studies suggested that retroviruses had "hijacked" and utilized the intercellular communication system for their spread, and even for biogenesis and replication (21). It is undeniable that this communication system referred to exosomes, and in this regard, research began to take the correct direction (30).

Subsequent findings (1, 31) revealed that exosomes isolated from cells infected with human immunodeficiency virus-1 (HIV-1) and human T-cell leukaemia virus-1 (HTLV-1) contain proteins of both viral and cellular origin, which inhibit the function of target cells, as well as dsRNA/ssRNA, and can increase the expression of certain genes, thereby promoting the spread of infection.

Target cells can be altered by exosomes at the protein or nucleic acid level, and the result is pathological consequences within cells and tissues (Table 1) (5, 32).

Recent studies have shown that exosomes serve as carriers of various viral components, including proteins, mRNA, microRNA (miRNA), and lipids. Exosomes transport these components to distant locations, delivering them to specific target cells, which then take up this bioinformation. For example, exosomes originating from the immune system, specifically T-cell lines infected with HTLV-1, carry and "deliver" the viral transactivator Tax, which can activate transcription in target cells (1, 33). Exosomes derived from cells infected with human herpesvirus 6 (HHV-6) contain fully mature virions and, through their transport role, facilitate more efficient viral spread (Table 1) (34, 35).

Exosomes can also transport prions. It is well known that prions are infectious particles or macromolecules that can cause transmissible spongiform encephalopathies (TSEs) in mammals. The yeast *Saccharomyces cerevisiae*, which can contain several types of prions, represents an ideal research model in that regard. The yeast prion prototype contains the translation termination factor Sup35. Findings of a study (36) demonstrated that cytosolic Sup35 NM prions were "packaged" into exosomes. Exosomes with such content can transfer the prion phenotype to neighbouring cells.

When we talk about the nucleic acid content carried by exosomes, it may originate from viral particles or be circular RNA (cRNA), which – based on research – has been strongly associated with tumour progression. In this context, exosomes are considered potential biomarkers for early diagnosis and disease monitoring, particularly in cancer (37–40). Epstein-Barr virus has been studied in the context of its transfer and correlation with exosomes. It was discovered that the latent membrane protein derived from cancer cells contaminated with Epstein-Barr virus can be exported in exosomes. Exosomes with such content inhibit the activity of natural killer cells and T-cell proliferation. Exosomes play a crucial role in the pathogenesis of human papillomavirus (HPV) tumours. In patients with this disease, different levels of miRNA content have been observed compared to the healthy population. It has been established that exosomes containing this miRNA content can regulate cell proliferation and apoptosis (35, 41).

Recently, research related to the correlation between exosomes and COVID-19 was conducted in several patient groups (fully recovered, asymptomatically recovered, moderately recovered, and severely/critically recovered) (42). It was primarily focused on lipid profiles in exosomes. Significant correlations were found regarding lipid content differences across the patient groups. Lipid abnormalities were also linked to glycerophospholipid metabolism and the biosynthesis of glycosylphosphatidylinositol. Furthermore, lipid analysis revealed that recovered patients from all groups were at a higher risk for developing diabetes and liver damage. Abnormalities in immune modulation were also observed in recovered patients, suggesting that such issues may persist after the illness. Research in this direction could further explain mechanisms that contribute to organ dysfunction during the disease and potentially aid in the development of new therapeutic approaches (42).

As evident from the literature review, viruses exploit exosome biogenesis systems to package their capsids, use exosomes for transport to target non-infected cells, and regulate virion production and viral particle formation (32). It could be argued that viruses also use exosomes for camouflage (mimicry) to evade or escape the host immune system's attack. In this sense, exosomes play a critical role in cellular communication during viral infections, and thus in immune modulation.

Table 1 Exosomes specifically formed in the human organism in response to various biological, chemical, and radiological noxious agents

Type of noxious agent	Pathogen / causative agent / disease	Exosomal content	Secreting cells	The role of the exosome	Ref.
B / bacterial agent	*Helicobacter pylori* virulence infection	cytotoxin-associated gene A (CagA)	CagA-expressing gastric epithelial cells	Developing extra-gastric disorders associated with CagApositive *H. pylori* infection	1, 25
B / bacterial agent	*Trypanosoma brucei*	Serum resistance associated protein	*T. brucei*	Allowing evasion from human innate immunity	48
B / bacterial agent	*T. brucei*	Immunogenic variant surface glycoprotein	*T. brucei*	Altering the physical properties of the erythrocyte membrane and causing clearance of infected erythrocytes by macrophages in the liver and spleen	48
B / bacterial agent	Gram-negative bacteria	Lipopolysaccharide	Gram-negative bacteria	Promoting caspase-11 activation and host defence against bacterial infection and pathogenesis of sepsis	1
B / viruses	Human Immunodeficiency Virus (HIV)	Cytoskeletal proteins (Actin, Tubulin, Lamin, Myosin), microRNA (miRNA)	Cellular target: Lymphocytes	Induce proinflammatory cytokines, inhibition of apoptosis, increased susceptibility of naïve T cells, downregulation of CD4 and MHC I, support viral reproduction and pathogenesis	32
B / viruses	Human Papillomavirus (HPV)	Immunoregulator molecules, miRNA	Cellular target: Epithelial cells	Apoptosis, viral proliferation	32
B / viruses	Human T-lymphotropic-1 virus (HTLV-1)-infected T-cell lines	Viral transactivator (Tax)	T lymphocytes	HTLV-1 infection, activating transcription of target cells	1, 33
B / parasites	*Plasmodium falciparum* / Malaria	Nucleic acid, lipides	*P. falciparum*-infected red blood cells	Promote malaria transmission and parasite survival, intercellular communication via gene delivery	45, 46
B / parasites	*Leishmania donovani* / Leishmaniasis	Nucleic acid, lipides	From *L. donovani*	Inhibit the macrophage immune response, induce macrophages to secrete IL-8 rather than TNF-α	46, 53
B / parasites	*Trichomonas vaginalis* / Trichomoniasis	Nucleic acid, lipides	From *T. vaginalis*	Facilitate *T. vaginalis* invasion and modulate host inflammatory activation, promote pathogen adherence to epithelial cells; inhibit IL-8 secretion by ectocervical cells and neutrophil migration to the infection site	45, 46
B / parasites	*Schistosoma japonicum* / Schistosomiasis	Nucleic acid, lipids	From *S. japonicum*	Mediate parasite-host communications and activate the host immune response, promote M1 macrophage polarization with increased production of pro-inflammatory factors	41, 46
B / biotoxins / animal toxins	*Bufo maxima* / Toxin β γ-CAT / Cytotoxicity, neurotoxicity, immunosuppression	Virulence factor	Toxin β γ-CAT Isolated from *Bufo maxima* skin secretions	Regulation of immune response, stimulate produce functional exosomes and activate immune T cell response	8
B / biotoxins / plant toxins	Plant toxins / *Trichosanthes kirilowii, Trichosanthin* toxin / toxic shock syndrome	Virulence factor	*T. kirilowi*	Vehicle of delivery, *Trichosanthin* toxin uses the delivery of exosomes to form unique toxin-loaded vesicles	1, 8
B / biotoxins / mycotoxin	*Fusarium sp.* / *T-2* mycotoxin / cytotoxic effects, immunotoxicity	Virulence factor	*Fusarium sp.* infected cells	Receptor-mediated, the exosome was used as a safe transport carrier for receptor cells to transmit HIF-1 α through the exosome. The release of exosomes is related to HIF-1 α in hypoxic tumours, which is beneficial to immune escape	8, 54

Table 1 continued

Type of noxious agent	Pathogen / causative agent / disease	Exosomal content	Secreting cells	The role of the exosome	Ref.
B / biotoxins / bacterial toxin	*Bacillus anthracis* / *Lethal toxin*/ anthrax	Virulence factor	*B. anthracis* infected cells	Vehicle of delivery, the lethal factor of anthrax *lethal toxin*, can be transmitted from cell to cell through exosomes, which may play a toxic role over a long distance	1, 8
B / biotoxins / bacterial toxin	*Corynebacterium diphtheriae, Diphtheria Toxin* / Diphtheria	Virulence factor	*C. diphtheriae* infected cells	Receptor-mediated, exosome directly induces toxin oligomerization on the membrane to protect cells	1, 8
B / biotoxins / bacterial toxin	*Vibrio cholerae* / *Cholera toxin*/ Cholera	Virulence factor	*V. cholerae,* infected cells	Receptor-mediated, *Cholera* toxin can be propagated and transmitted through exosomes in the form of bioactivity	1, 55
B / biotoxins / bacterial toxin	*Shigella sp.* / *Shiga toxin* / Shigellosis	Virulence factor	*Shigella sp.* infected cells	Vehicle of delivery, *Shiga* toxin exists on the surface of exosome	8
B / biotoxins / bacterial toxin	*Staphylococcus aureus*/ Alpha toxin / Toxic shock syndrome, sepsis, pneumonia	Virulence factor	*S. aureus* infected cells	Regulation of immune response, exosome acts as bait to capture membrane virulence factors (such as porotoxins) to prevent target tissue damage	8
C	Arsenite / Lung carcinogenesis, liver carcinogenesis	miR-21, miR-155	Lung and liver cells	Gene modulation, gene expression	8, 61
C	Cigarette smoke / Lung carcinoma, Alzheimer's disease	miR-21, IL-13, mediators of Wnt/ β-catenin pathway	Lung cells	Gene modulation, gene expression	41, 61
C	Pyridostigmine bromide, Permethrin / Gulf War Illness, neurological diseases	Spectrin breakdown products (SPBs)	Nerve cells	Neuromodulation	61
C	Manganese / Synucleopathies, other neurodegenerative diseases, Parkinson's disease	α-synuclein	Nerve cells	Neuromodulation	61
R	Ionising radiation / Tracheal carcinoma	miRNAs, integrins and chemokines	Immune and lung cells	Gene modulation, gene expression	61

B – biological, C – chemical, R – radiological, IL – interleukin, TNF-α – tumour necrosis factor

Parasites and exosomes

Parasites have been present in the human population since its origin. Their existence has been documented in texts dating back 3,000 to 4,000 years. Approximately 400 species of parasites use humans as their hosts, with about 90 species being highly dangerous and associated with a significant mortality rate (43, 44).

A fundamental scientific question is how parasites evade the host's defence mechanisms and successfully maintain their life cycle. One of the primary and potent tools they use is exosomes, which are released into the microenvironment they inhabit, thereby modulating it to their advantage (43, 45).

The interaction between the host and the parasite is bidirectional and is based on three types of communication: (1) exosomes originating from the parasite, (2) exosomes originating from host cells, and (3) exosomes originating from host cells stimulated by antigens derived from the parasite. The communication with the greatest impact on the parasite-host relationship, and consequently on the development of pathological conditions, is that mediated by exosomes originating from the parasite (43, 46).

Accumulating data from scientific research highlights the signalling and bioinformational roles of exosomes derived from parasites, which are aimed at maintaining parasitic physiology within a suitable microenvironment (46, 47).

Through their exosomes, parasites transmit bioinformational content to the host, thereby often modulating the immune response, which is their key target. It has been conclusively shown that the action of exosomes plays a critical, even decisive role in the development of diseases such as Chagas disease (caused by

Trypanosoma cruzi), leishmaniasis, giardiasis, trichomoniasis, amebiasis, malaria, and neosporosis (48–50) (Table 1).

Given the extent of this topic, this literature review is limited to the most recent scientific studies. The ways in which parasites modulate the host's immune response have been best demonstrated in a research study on the gastrointestinal nematode *Heligmosomoides polygyrus* (51). This parasite releases exosomes that are "eaten" by host macrophages. Upon uptake, these macrophages are modulated, resulting in the reduction of molecules associated with both type 1 and type 2 immune responses (IL-6 and TNF, as well as Ym1 and RELMa) and inhibition of ST2 receptor subunit expression for IL-33 (51).

On the other hand, the malaria parasite *Plasmodium berghei* releases exosomes that block the T-cell immune response. Exosomes derived from *Leishmania* can direct monocytes and dendritic cells toward anti-inflammatory phenotypes, thereby increasing Th2 cell polarization (52, 53).

The effects of exosomes from *Leishmania* on innate and adaptive immune responses have also been studied. Exosomes derived from *Leishmania donovani* modulated cytokine responses in human monocytes to IFN-γ, promoting IL-10 production while inhibiting TNF-α production. Additionally, these exosomes inhibited cytokine responses (IL-12p70, TNF-α, and IL-10) in dendritic cells originating from monocytes. A shift in Th cell polarization toward Th2 differentiation was also observed, which inevitably worsened the disease. Exosomes from *Trichomonas vaginalis* modulate the expression of cytokines IL-6 and IL-8 in ectocervical cells (50).

African sleeping sickness, caused by *Trypanosoma brucei rhodesiense*, has an aetiology based on immune evasion facilitated by exosomes. Specifically, trypanosomes in the bloodstream produce membrane nanotubes originating from the flagellar membrane. These nanotubes are incorporated into exosomes. In addition to their function in evading the innate immune response, these exosomes can fuse with host erythrocytes, leading to their rapid loss and anaemia. In other words, the exosomes cause modulation of erythrocyte function, rendering them dysfunctional (48).

Trematodes of the genus *Schistosoma*, the causative agents of schistosomiasis, also modulate the host immune response. This involves shifting the balance of Th cells toward Th2 production and macrophage polarization. The disruption of these strategic immune system targets has far-reaching consequences for health (47).

Such parasitic infections are chronic and often asymptomatic, with the communication between the parasite and host via exosomes, as well as the modulation of the host's immune response, playing a crucial role in the infection's course and the parasite's life cycle. All of this points to the immunosuppressive action of parasitic exosomes.

Biotoxins and exosomes

Biotoxins, or biological toxins, are metabolites produced by various organisms that have toxic effects on the human body. Since these are macromolecules, predominantly of protein nature, they cannot replicate within the organism. Biotoxins can be classified based on their origin into animal toxins, marine toxins, phytotoxins, and microbial toxins (Table 1) (8). In general, biotoxins interfere with normal intercellular signalling, induce oxidative stress and apoptosis, and most commonly affect the kidneys, liver, nervous system, and reproductive system. In the process of intoxication by biotoxins, exosomes play an active role as signal carriers. On a molecular level, the expression of exosomes in intoxicated receptor cells varies depending on the type of cell and the type of biotoxin. There are three main roles of exosomes in biotoxin intoxication within the organism: receptor-mediated, vehicle of delivery, and regulation of immune response (Table 1). The receptor-mediated role of exosomes primarily involves the activation of receptors on the surface of target cells, thereby initiating intracellular signalling pathways. This effect may lead to the target cells producing more or fewer exosomes, depending on the nature of the biotoxin and the type of recipient cell. This role of exosomes is most commonly observed in intoxication by bacterial toxins, such as cholera toxin, diphtheria toxin, or mycotoxins such as T2 (8, 54, 55).

Exosomes can also serve as delivery vehicles, where they fuse with the plasma membrane of cells or are directly endocytosed, introducing proteins, lipids, and other active molecules into the cells. In this manner, they regulate cellular function and biological behaviour. This role of exosomes is observed in plant toxins, anthrax, and shiga toxin (8, 56).

The role of exosomes in the regulation of the immune response begins with antigen presentation, followed by immune regulation through the expression of activation molecules or complement factors. Toxin-induced interactions *in vivo* involve complex biological processes. The presence of toxins can stimulate cells to produce exosomes, which are enriched with signalling molecules related to inflammation, or to recruit surrounding signalling molecules such as cytokines and chemokines (e.g., MHC-I and MHC II). When neighbouring or distant cells uptake these exosomes, they can activate or enhance inflammatory responses, thereby promoting the body's immune response to the toxin (8, 57). Generally, various immune cells (e.g., dendritic cells, lymphocytes) are exposed to the release of immunomodulatory exosomes. This role of exotoxins is also observed in animal toxins and *Staphylococcus aureus* alpha toxin (8, 58).

From the review of this literature, it can be concluded that exosomes play a dual role in immune system regulation; (1) as bioinformatic programs to induce innate or adaptive immunity and (2) for tactical evasion and resolution of inflammation (8, 46).

NOXIOUS CHEMICAL AGENTS AND EXOSOMES

Chemical noxious agents, which are essentially environmental pollutants, trigger various chronic diseases such as cardiovascular, respiratory, and neurodegenerative conditions when in contact with the organism. The most severe outcome can include the development

of various cancers. Recent studies show that during chemical agents' intoxication, exosomes are formed within the organism (59, 60). As signalling vesicles, exosomes can be involved in the processes that occur following direct exposure to environmental noxious agents, which consequently lead to chronic disease and eventually cancer. Cancer cells produce and release numerous signalling molecules, including exosomes, which attenuate the immune response and "recruit" neighbouring cells potentiating the malignant transformation (61).

Recent research has mainly focused on noxious chemicals that enter the body via inhalation. As airborne contaminants, the most common chemical toxins in the environment are pollutants released by industry, exhaust particles, and tobacco smoke. Most of the research has thus been focused on exosomes from the respiratory system and systemic circulation. It has been found that noxious chemical agents selectively affect the formation, release dynamics, and composition of exosomes. The release of such modulated exosomes results in pro-inflammatory and pro-thrombotic reactions within the organism (Table 1) (59–61).

In vitro and *in vivo studies* have shown that exosomes, through their specific content, primarily miRNA (micro RNA) and lipids, create a favourable microenvironment within the organism for the development of neoplasia. Neoplastic cells can produce growth factors, such as transforming growth factor beta (TGF-β), which promotes the growth of newly transformed tumour cells (62, 63). The miRNA content is particularly significant, as it can modulate the expression of genes for various biomolecules. For example, breast cancer cells that secrete exosomes containing miR-200 can transform normal cells into neoplastic cells (64). Exposure to tobacco smoke and air pollutants, such as asbestos, arsenic (As), radon, and soot, increases the risk of lung or bronchial carcinogenesis by causing intoxicated bronchial epithelial cells (HBE) to release exosomes containing miRNA (specifically miR-21), which stimulate and modulate normal bronchial epithelial cells (Table 1). Furthermore, exosomes of this origin and miRNA content increase the expression of homologous phosphatases and tensins. A crucial event is the uptake of miRNA from circulating exosomes by neighbouring healthy cells via endocytosis, in which this miRNA is endogenously activated (61).

Therefore, it is evident that in biochemical and bioinformatic processes following intoxication with noxious chemical agents, the organism reacts according to the same pattern, creating and releasing exosomes from affected cells that then modulate the environment and neighbouring cells. The most important content of exosomes for these modulations are the various miRNAs.

NOXIOUS RADIOLOGICAL AGENTS AND EXOSOMES

Noxious radiological agents originate from various radiation sources that can disrupt the physiological balance of the organism. Ionising radiation is considered the most harmful type of radiation for the human body. Its detrimental effects are utilised in the radiotherapy, which represents one of the main treatments for eradicate cancer cells. To counteract harmful effects of radiation on healthy cells, various radioprotective agents are currently available, but most of them have limited use and efficacy due to side effects, such as nausea, vomiting, diarrhoea, and hypotension.

Recent research focused on radiosensitivity and treatment of radiation induced injuries (65, 66) has shown that exosomes play an important role in these processes as well.

Exosomes are associated with so called non-targeted effects of radiation. Although this area is not fully understood to date, the evidences suggest that exosomes produced in irradiated cells play a signalling role in intercellular communication, primarily in inflammatory-anti-inflammatory activations, induction of cellular stress, and changes in gene expression (67–71). Exosomal epigenetic capabilities are mainly driven by modulated miRNA, which influences the gene expression of healthy target cells, thus modulating them. Epigenetic effects are manifested, amongst others, by altering the methylation pattern in target cells through the regulation of methyltransferases. Exosomal content can possess such "sophisticated" capabilities that it can even alter parts of histone structures (67–71).

There are various consequences of such events at the molecular level, which elicit responses at higher levels of the organization. For example, exosomes isolated from melanoma cells can potentially reprogram bone marrow progenitors through signalling via tyrosine kinases. These reprogrammed cells develop a neoplastic condition, thereby promoting cancer. In addition to creating a favourable environment for cellular metastases, exosomes can also promote the formation of tumours resistant to chemotherapy and radiotherapy (61, 69).

It is still unclear exactly what and how the content of exosomes is most affected; whether it is the type of cells, the type of radiation, or the dose. Clarifying these mechanisms in intercellular communication will certainly foster the discovery of new therapies, as well as prognostic and diagnostic biomarkers (67).

Ionising radiation induces the following molecular-level changes in mesenchymal stem cells: (1) reduces levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and promotes the production of the anti-inflammatory IL-10; (2) enhances IL-10 and TGF-β1 in human peripheral blood mononuclear cells; (3) facilitates the proliferation and immunosuppression of T lymphocytes; (4) reduces the presence of pro-inflammatory macrophages and neutrophils; (5) protects type II alveolar epithelial cells against apoptosis by downregulating serum amyloid A3 (SAA3); (6) inhibits the epithelial-mesenchymal transition (EMT). These changes have been shown to be induced by modulated mRNA (miR-181c, miR-let-7b, miR-21) derived from exosomes (Table 1) (11, 66, 72, 73).

Limitations

Despite the efforts to present as much recent knowledge on the topic as possible, this paper cannot address all relevant questions.

Therefore, the author focused here on providing an overview and giving a general insight into the role of exosomes in biological systems. This review is limited by lack of a presentation and discussion regarding specific examples of association between occupational exposure and exosomes. However, as such an approach would require too many additional details, they will be covered by a new forthcoming paper.

CONCLUDING REMARKS

There is no doubt that exosomes are the most important mechanism of intercellular communication. This mechanism is evolutionarily conserved and is undoubtedly as old as multicellular organisms themselves (5, 74, 75). Their absence would undermine the very concept of cellular cooperation in multicellular organisms. Exosomes transmit bio information both in the normal physiological state of the organism and in different diseases, including various infections and cancer (3, 16, 32, 76). They are always active and ubiquitous. This review focuses on the formation of exosomes in the organism under disrupted physiological conditions caused by noxious biological, chemical, and radiological agents. The most important knowledge of everything previously said is summarized in Table 1.

In the context of ever growing threats from different hazards, it is necessary to emphasize that exposure to noxious chemical and radiological agents is not limited to the industries but also extends to military operations. In modern warfare, the greatest threats no longer stem from conventional weapons but rather from the exposure of soldiers to chemical, biological, and radiological noxious agents. The spectrum of chemical agents encountered in military operations is exceptionally broad, with atmospheric chemical contamination frequently arising from toxic gases released during the bombing of oil and industrial facilities. Exposure to depleted uranium, commonly used in ammunition alloys and armour, represents a prevalent radiological threat in military operation zones. Biological threats primarily originate from parasites and pathogens causing tropical diseases (19).

Through this comprehensive approach in reviewing diverse literature and synthesizing data, a causal relationship between noxious agents and exosomes is considered. The bioinformation transmitted via exosomes to distant, unaffected cells plays an informational and regulatory role. In this way, the organism adapts to the new condition and attempts to restore physiological balance in the most efficient and rapid manner (1, 16, 77).

In bacterial infections, exosomes serve as regulators, promoting either an inflammatory or anti-inflammatory response in the body. Virulence factors are key components of exosomes, typically consisting of various macromolecules of lipid and protein composition (20–22, 26). Virulence factors are critical for bacteria due to toxin synthesis, such as in *B. anthracis*. In essence, in bacterial infections, the critical effect is the toxin and virulence factors, which exosomes recognize as important bioinformation to be relayed to distant cells (1, 8, 22). A similar process occurs in poisoning caused by animal and plant biotoxins (8, 78).

In contrast to bacterial infections, in viral infections, the most interesting content of exosomes is miRNA and its various components. Exosomes containing such material have epigenetic capabilities, meaning they can directly modulate gene expression in target cells. Furthermore, it has been observed that miRNA is present in the organism's exposure to chemical and radiological noxious agents. Therefore, it can be concluded that the content of exosomes and the transmission of bioinformation in viral infections, radiation, and intoxication by toxic substances is quite similar (32, 35, 61).

Since the content of exosomes shapes bioinformation, it is clear that the organism sometimes exhibits a uniform response to different types of noxious agents. Generally, when exosomes contain molecules such as miRNA, epigenetic changes in target cells can be expected, along with essential changes in gene expression. The majority of such events are related to the immune system's function, but also to detoxifying organs such as the lungs and liver (8, 61, 78).

This literature review also addresses parasites, but from the perspective of the action of their own exosomes. Exosomes originating from parasites play an essential role in creating a microenvironment favourable to their growth, development, and reproduction (43, 49, 50, 53).

The question is whether parasites would even survive in the absence of exosomes, and this area of research opens up various evolutionary questions in the context of the parasite-host relationship.

Exosomes play a crucial role in intercellular communication, a function that is especially important when the organism is exposed to various noxious agents of biological, chemical, and radiological origin. Given recent data and the latest research, it can be concluded that it is nearly impossible to imagine any organized defence mechanism of the organism against noxious agents without the support of exosomes. They are definitively the primary communication and information system of the organism, and their content is pivotal in regulating the balance between disease and health.

FUTURE DIRECTIONS

Considering that the environment is increasingly burdened by various noxious chemical, radiological, and biological agents , there is a growing interest in utilizing the specific properties of exosomes, especially in prevention, early diagnosis, and treatment of various diseases (5, 74, 75).

The application of exosomes in drug delivery is particularly promising as they can encapsulate sufficient quantities of therapeutic agents to exert a therapeutic effect, maintain the bioactivity of the therapeutic substance during circulation in the bloodstream until

reaching the target organ, and evade macrophage activity. A significant number of exosomes meet these criteria (3).

However, the primary challenges in the therapeutic application of exosomes lie in their isolation, characterization, and purification (76). On the other hand, relevant research highlights the immense potential of exosomes in radiotherapy. Exosomes could serve as prognostic indicators for patients undergoing radiotherapy, as their presence can influence the effectiveness of radiotherapy and mitigate its side effects (3, 71).

Exosomes also demonstrate significant potential in controlling inflammatory conditions, promoting wound healing, managing sepsis, altering immune responses, and modulating signal transduction pathways. In this capacity, they can be utilized as biomarkers and physiological modulators (74). Furthermore, exosomes derived from stem cells hold therapeutic potential due to distinct advantages over stem cells themselves. Compared to stem cells, stem cell-derived exosomes exhibit non-immunogenicity and a lack of tumorigenic potential. Exosomes can inherit therapeutic properties from their parental stem cells via the vertical transfer of pluripotency or multipotency (75). A critical question that remains is their role in the transmission of bioinformation at the moment of an organism's death and how all cells in the organism are informed of the cessation of life. This aspect remains to be further explored.

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Egzosomi kao medijatori međustanične interakcije u odgovoru organizma na nokse

Egzosomi su male izvanstanične vezikule veličine od 30 do 150 nm, a formiraju se putem stanične endocitoze. Oni se sastoje od proteina, lipida i nukleinskih kiselina (RNA) u različitim omjerima i količinama. Sastav egzosoma i njihova prostorno-vremenska dinamika upućuju na to da egzosomi imaju važnu ulogu u komunikaciji među svim stanicama. Informacije koje egzosomi prenose imaju važan učinak u kontroli zdravlja i bolesti organizma. Nokse su sve štetne tvari i pojave iz okoliša koje mogu narušiti fiziološku ravnotežu organizma i prouzročiti bolesno stanje, a mogu biti radiološkoga, biološkoga i kemijskoga podrijetla. Ovaj pregledni rad sveobuhvatnim pristupom povezuje prisutnost navedenih noksi u organizmu s ulogom i formiranjem egzosoma. Također, analizira se uzročno-posljedična veza noksa – egzosom radi uspostavljanja fiziološke ravnoteže i pripreme organizma za obranu od noksi. Bez obzira na specifičnosti svake bioinformacije o konkretnoj noksi, sintezom podataka o vezi između raznih vrsta noksi i egzosoma zaključeno je da je bilo kakva organizirana obrana organizma od noksi neostvariva bez pomoći egzosoma. Stoga su egzosomi definitivno glavni komunikacijsko-informacijski sustav organizma i njihov je sadržaj ključan u kontroli ravnoteže bolest – zdravlje.

KLJUČNE RIJEČI: biološki medijatori; izvanstanične vezikule; međustanična komunikacija; signali; štetni agensi