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Exosome regulation of immune response mechanism: Pros and cons in immunotherapy

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ABSTRACT

Due to its multiple features, including the ability to orchestrate remote communication between different tissues, the exosomes are the extracellular vesicles arousing the highest interest in the scientific community. Their size, established as an average of 30–150 nm, allows them to be easily uptaken by most cells. According to the type of cells-derived exosomes, they may carry specific biomolecular cargoes used to reprogram the cells they are interacting with. In certain circumstances, exosomes stimulate the immune response by facilitating or amplifying the release of foreign antigens-killing cells, inflammatory factors, or antibodies (immune activation). Meanwhile, in other cases, they are efficiently used by malignant elements such as cancer cells to mislead the immune recognition mechanism, carrying and transferring their cancerous cargoes to distant healthy cells, thus contributing to antigenic invasion (immune suppression). Exosome dichotomic patterns upon immune system regulation present broad advantages in immunotherapy. Its perfect comprehension, from its early biogenesis to its specific interaction with recipient cells, will promote a significant enhancement of immunotherapy employing molecular biology, nanomedicine, and nanotechnology.

1. Introduction

Eukaryotic and prokaryotic cells can extend their molecular identity utilizing extracellular vesicle secretion [1]. Extracellular vesicles are double-lay phospholipidic membrane delimited nanoscale particles [2,3]. Among the existing diversity of extracellular vesicles, exosomes are the ones arousing the highest scientific interest. Exosomes were defined by Trams et al. as a type of cells-released vesicles that ‘‘may serve a physiological function’’ [4]. This conception proved to be highly accurate, as the enlargement of knowledge helped to confirm the nature of exosomes extracellular vesicles as an element serving the purpose of a specific biological function achieved by cells of different nature [5],

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rather than simple scavenging agent expulsing cellular waste in the outward membrane. Although incomplete, still the exosome content is nowadays widely known and may be classified into the categories of proteins, lipids, ribonucleic acid (RNA), or desoxyribonucleic acid (DNA). The nature of exosome cargoes is significantly influenced by the cells from which they emanate [6]. Exosomes are known to be able to deliver their content in the extracellular space to recipient cells, triggering multiple reactions. These exosome cargoes are the ones that characterize the nature of exosome interactions with a certain type of cells.

Most cells, including immune and tumor cells, can uptake exosomes while interacting with them. The interactions between exosome and recipient cells result from multiple reactions entangled with immune regulation mechanisms. According to their origin, exosomes will likely induce an efficient immune response leading to the clearance of the antigenic element or decrease the surveillance and spontaneity of the immune system, which will promote the spread of invaders such as cancer cells and metastasis [7]. This dichotomic nature of exosomes creates a broad and complex network of biological reactions, building an immune cycle that highlights exosome's potential in cancer diagnostic, immunotherapy, chemotherapy, and drug delivery.

Exosomes are extracellular vesicles occupying the latest place regarding their size. They are located in the range of 30–150 nm in diameter, in comparison with the two remaining known other types of extracellular vesicles, namely the apoptotic bodies (1000–5000 nm) and microvesicles (50–1000 nm) [8]. Eukaryotic cells are enriched with a filtering mechanism regulated by sorting organelles such as endosomes [9]. Exosomes are formed through the endocytosis pathway, which corresponds to the maturation process of the early endosome, to the late endosome (Fig. 1B). The fusion of primary endocytic vesicles is the first step in the formation of the early endosome (EE) [10]. Many incoming endocytic cargoes share their contents and membrane composition by combining the EEs in clathrin- or caveolin-dependent or independent pathways [10]. EEs can either return the cargo to the plasma membrane as "recycling endosomes" or change into "late endosomes." Reaching the late Endosome (LE) demands the early endosome to undergo different stages of inner modification associated with the gradual change of its content [11].

Early endosome emanates from the inward invagination of the plasma membrane and mediates the sorting of different biomolecules contained in the cell through its lumen. The achieved filtration goes along with an inward sprout of the limiting membrane of the early endosome, which brings the early endosome to morph into the late endosome, the final stage of maturation of the inward membrane endosomes. Late endosome displays numerous smaller membrane-bound vesicles in its inward membrane environment, to which it owes the alternative designation of the multivesicular body (MVB). The MVB processes to an invagination leading to the formation of a new type of inward cell vesicle: the intraluminal vesicle (ILV). This invagination coincides with the integration into the ILV of cytoplasm inclusion, transmembrane, and peripheral proteins, that follow a highly regulated filtering pathway known as the endosomal sorting complex required for transport (ESCTR) [11]. Although most of the ILV-integrated biomolecules result from an ESCRT-dependent pathway, some other proteins that were proved to be present in the ILV emanate from an ESCTR non-dependent Pathway as well.

ESCTR filtering machinery comprises four subunits involved in sorting ILV cargoes according to the type of pathway (dependent-independent) required by the biomolecules. They are ESCRT 0, ESCRT I, ESCRT II, ESCRT III, and ESCRT IV. The involvement of each of the subunits was shown to be conditioned by the ubiquitinated protein (Ub-Protein). Indeed, the integration of cargoes into inward-sprouting vesicles results from an upstream signal of the endocytosis phenomenon initiated by ubiquitination. Ub protein possesses many Lys residues that allow it to create covalent chains with the C-terminal carboxylate of the subsequent Ub moiety. In the Ub-Prot-dependent pathway, cargoes are meant to face Ub-Prot at a crossroads, representing a mandatory stage that most biomolecules should go through at the early beginning of the sorting ESCTR-dependent pathway. The Ub-Prot interacts with each cargo, establishing a biochemical checkpoint for each. Out of this interaction, cargoes display the ubiquitination marker, recognized by the filtering machinery subunits.

In the Ub-Prot-dependent pathway, all the subunits are involved. The subunits known as HRS and STAM in humans ensure the hierarchy of the ESCRT sorting machinery working process, wherein ESCTR 0 and ESCRT 1 as already mentioned above, cluster the microdomains of the future Micro vesicle Exosome and enroll the subunits ESCRT 2 and ESCTR 3 that will perform the scission and budding of the microdomain [12]. ESCRT 0 identifies the ubiquitinated proteins using HRS heterodimer and STAM 1/2 [13,14]. HRS is a protein located in the cytosol, shown to be coupled with other types of proteins such as Eps 15 and Clathrin [9,15]. The clathrin successfully enrolled by HRS helps to move the ESCRT sub-complex toward the ubiquitinated cargoes. This mechanism is followed up by the ESCRT I and ESCRT II joining ESCRT 0 to strengthen the recognition domain that will develop an increased affinity with the endosomal area leading to its definitive sprouting. Finally, the ESCRT III gathers with the complex to strangle off the sprouting part of the endosomal area, releasing the buds in the endosome [16].

The ILV accumulates into the MVB lumen, where it is going two undertake two different destinies. Although the criteria that determine the path of the MVB is still unknown, research has shown that MVB will nonetheless follow two main destinations, mainly related to the level of cholesterol stored in the vesicle [17]. The first group of ILV called the degradative MVB, corresponds to the vesicle presenting a lack of cholesterol. These vesicles will migrate to lysosomes, mediating the lysis of vesicle content. The other, also called the secretive MVBs, corresponding to high-level cholesterol vesicle, will fuse with the plasma membrane and be released in the extracellular space by exocytosis as exosomal microvesicles [18]. Degradative MVB destination to scavenger lysosomes is also considered to be regulated by the de-ubiquitination mechanism mediated by the de-ubiquitination enzymes (DUBs) [19]. In fact, due to the interaction with the DUBs enzymes, the cargoes that will display the ubiquitination markers will follow the degradative pathway. Meanwhile, those which will lose their ubiquitination mark will follow the sprout-out pathway leading to their outward release into the shape of the exosome.

ILV transformation into exosome goes through the outward budding of the endosome, a mechanism that highly involves ALIX protein's action. The Alix protein is one of the proteins markers of the exosome, mediating its biogenesis. Indeed, Alix protein like PAR 1 binds with the cargo directly or indirectly carries the syndecans and tetraspanin CD63, and allows the delivery of un-ubiquitinated cargos to ILVs, by coupling with ESCRT-III [12]. Alix and syntenin were shown to interact utilizing LYPX L motifs, which help the budding of the endosomal membrane [20].

Exosome formation may also be processed through an ESCRT-independent pathway (Fig. 1A). Exosome formation mechanism aims toward an invagination of the melanosome, the occurring area of the phenomenon. The melanosome is an organelle related to both endosome and lysosome in the melanocyte. It was shown to contain Pmel17 protein which engages its luminal domain with lipids, contributing to the formation of ILVs [21,22]. The Pmel17 protein is not dependent on ESCRT machinery and was shown to be found in the clathrin-coated early exosome. The melanosomal ILVs outward budding, leading to exosome release, was shown to be regulated by Tetraspanin CD63, another protein involved in the ESCRT and Ceramides independent pathway of exosome formation [23]. Protein PLP (proteolipid protein) is delivered to ILVs in an ESCRT-independent way from lipid-rich portions of an endosomal membrane such as cholesterol, ceramide, and sphingomyelin. The defection of sphingomyelinase has been linked to the high sensitivity of ceramide-rich sections of endosomes to inward budding [12].

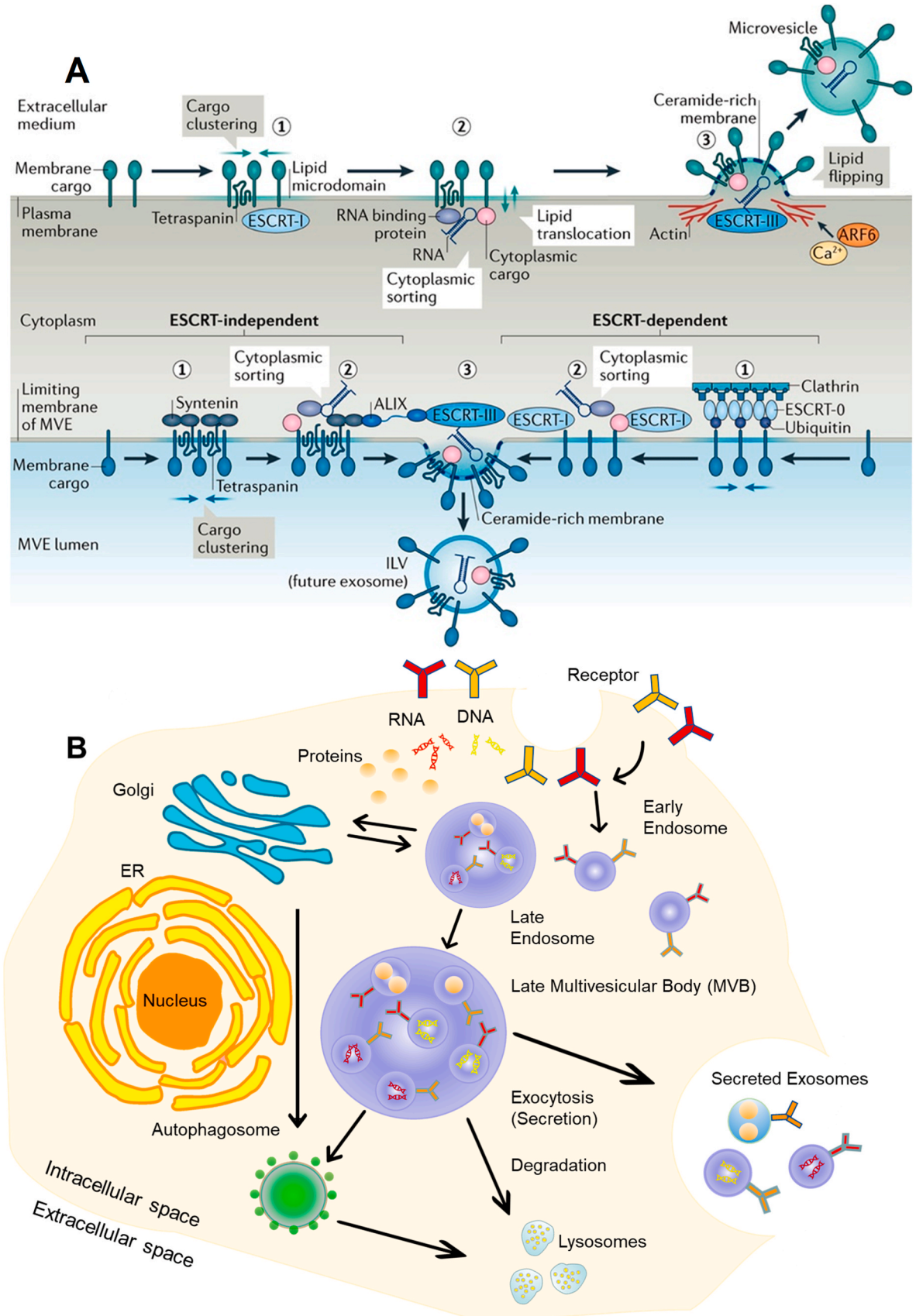

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Fig. 1. Exosome biogenesis: (A) Pathway of exosome biogenesis, namely the ESCRT-dependent and ESCRT non-dependent pathways [28]. The ESCRT-dependent path involves the four subunits of the ESCRT filtering machinery. The sorting process is conditioned by the ubiquitination of the cargoes, operated in ESCRT-0 associated with the clathrin proteins complex. This ubiquitination constitutes a biological checkpoint required to transfer cargoes to the next subunit (ESCRT 1, 2, 3). The cargo journey leads to ESCRT-3, helped by the membrane-rich-ceramides, which manages to incorporate the cargo into one of the multiple inward cell sprouts of the ILVs, which will further become the exosomes. The ESCRT-independent pathway involves the ALIX proteins, syntenin, and tetraspanin that carry different cargoes to the plasma membrane area, wherein they undergo a clustering for cellular exocytosis. (B) Description of the various stages, followed by exosomes from the early endosome to the ILVs and late endosome. All along the process, the future exosomes acquire multiple cargoes, some of which will be directed to the autophagosome for cellular lysis. Meanwhile, the others are well conserved in various clusters of the MVBs, further expelled out of the cells under the shape of exosomes [29].

Although controversial, studies have shown that exosome biogenesis is related to specific types of proteins involved in the maturation and exosome inner material loading process. Thus, researchers are currently more focused on exosomes produced through ESCRT-dependent and ESCRT non-dependent pathways [24,25]. However, recent studies demonstrated that a specific type of exosome formation must be mediated by components that do not belong to the ESCRT, such as four-membrane domain proteins and lipid-raft [26].

The acquisition of exosome content is a phenomenon that takes place all along the biogenesis of exosomes, simultaneously with each step of exosome evolution from EE to MVBs. The maturation of exosomes is mainly ensured by the ESCRT group of proteins, which, along with their associate proteins, including Alix, TSG101, HSC70, and HSP90β, are likely to be present in exosome intravesical environment regardless of their specific origin and function. However, as mentioned above, exosomes are also produced through an ESCRT-independent pathway, which instead involves the action of sphingomyelinase enzymes [27]. Also, a set of tetraspanin proteins, such as CD63, CD9, and CD81, involved in the mechanism of penetration, invasion, or fusion, are highly present in an extensive range of exosomes produced through an ESCRT-independent pathway (Fig. 1A).

Exosomes are enriched with heat shock proteins (HSPs), mostly chaperone proteins. They are either internal such as HSP70, or external such as HSP60, and participate in protein maturation mechanisms, including folding, translocation, cell proliferation, apoptosis signalization, and metastasis. During the sorting process, which leads to the formation of ILVs, the exosomes were shown to encapsulate different biomolecules mainly influenced by the parent cells. Among those molecules are nucleic acids such as messenger RNA (mRNA), micro RNA (miRNA), non-coding RNA(ncRNA), and DNA (Fig. 2) [30].

Based on the observation of exosome biogenesis, which unveils a correlation between exosome production and cell mechanism to eliminate unused material, exosomes were first perceived as a vesicle involved in cell purification by carrying cell waste to the external environment [27]. However, further studies showed that exosome has multiple functions beyond cell debris manager. Indeed, exosomes are proven to mediate the biochemical crosstalk between cells [32,33]. This crosstalk includes transferring genetic material (RNA, DNA, miRNA) from one type of cell to another, leading to cell genotype modification, representing the basis of target cell reprogramming [34]. Exosome's ability to carry markers from its mother cells and deliver them to other cells far away permits it to regulate multiple fundamental biological mechanisms. For instance, exosomes with a high presence in blood, breast milk, and semen possess putative functions, which are resourceful for embryonic development and sperm maturation, thus facilitating mammalian reproduction [35]. The process of exosome intercellular communication considerably influences the enhancement of tumor progression, metastasis, angiogenesis, and improved drug resistance in the tumors [36]. They are also involved in immune system stimulation and can behave in certain circumstances as antigen-presenting vesicles, thereby enhancing the adaptive immune response [37]. Also, exosomes prevent nerve cell degeneration by prohibiting particular unfolded

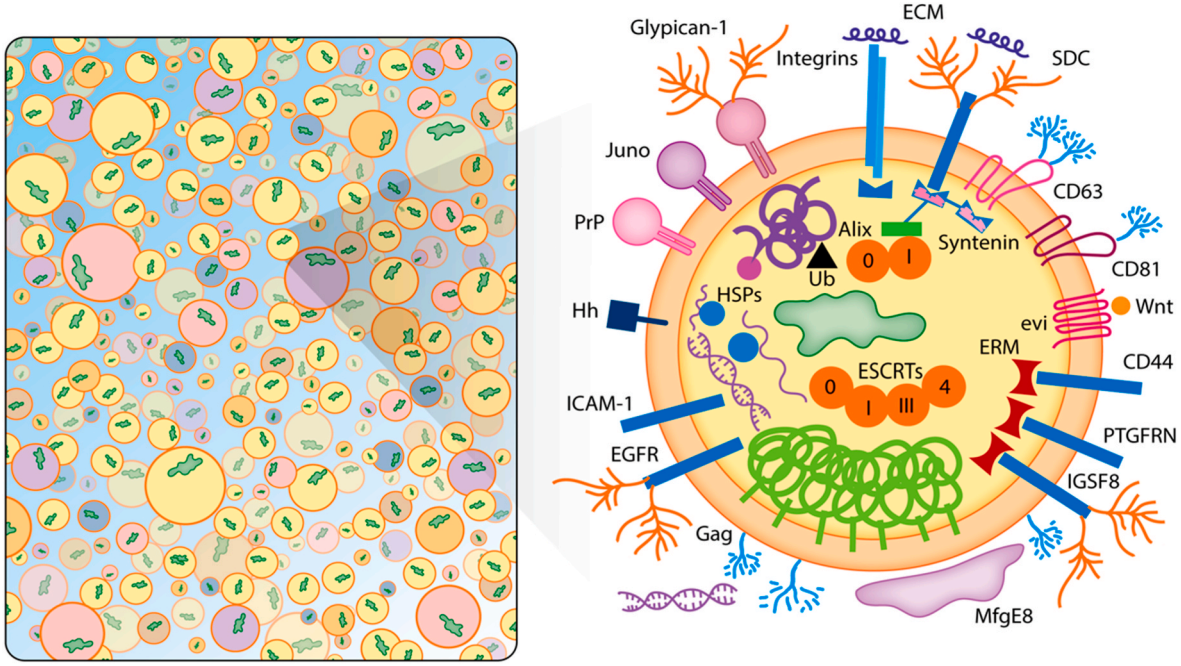

Fig. 2. Content of exosome [31]. The exosome comprises an extensive range of biomolecules, including nucleic acids (DNA, miRNAs, UC. RNAs, circ.RNAs), proteins, and enzymes, varying according to the releasing cells. Most frequently, exosome displays specific proteins that are used for their metabolism, namely the ESCRTs complex of proteins, ALIX, syntenin, tetraspanin, ubiquitination protein involved in exosomes biogenesis, HSPs proteins involved in the inflammatory signal triggering mechanism, while proteins including CD81, CD44, CD63 playing the role of biomarkers of exosomes presence and many other molecules.

proteins or abnormally folded proteins from aggregating in the brain [38]. It is to be noted that, the cargoes acquired by exosomes during it biogenesis are not identical among all type of exosomes. They are correlated to the type of tissues from which exosomes are released. The above-described biogenesis mechanism, gives an empirical perspective about the correlation between the content of exosome and its biogenesis. Thus, in Fig. 2 for instance, the graphical illustration of exosomes content portrays this idea by representing the basic biomolecules that are found in most of the exosomal vesicles, regardless of their origin. However, differences between exosomes are mainly seen by the type of nucleic acids and protein they inherit from the secreting cells. In certain case, this diversity can be observed through the difference of availability of cargoes from one type of exosome to another.

In this review, we analyzed various cases in which exosomes might be involved in immune response activation by enumerating in each condition whether exosomes act as an adjuvant for the immune system or as an opponent. Indeed, we have extensively discussed the role of exosomes in mediating either immune activation, immune suppression, or both simultaneously. This review enlists the different immune cells, such as T-cell, NK-cell, and other cells involved in exosome machinery to regulate the immune response. It can provide a group of organized data that may allow a better understanding of exosomes by the scientific community. We have also explained the tumor-derived exosomes as an immune system suppressor. Thus, appealing to multiple innovative approaches in designing exosome-based immunotherapeutic nanomedicines from a disease-curing perspective.

2. Exosome-mediating immune response

Cells' ability to secrete and uptake exosomes enables them to be genetically modified. As mentioned above, the communication between cells mediated by exosomes consists of the release and uptake of exosomes carrying a specific type of mother cells materials, such as protein, DNA, RNA, and lipid [39]. This mechanism is capital in immune system regulation by exosomes derived from immune cells. Indeed, immune cells derived exosomes can specifically organize communication between innate and adaptive immune cells, which leads to more efficient regulation of cancer progression [40]. However, in some instances, the exosome content may enhance tumor cells' resistance to drug therapy, making exosomes appear as double-facet entities towards cancer, leading to the suppression or the activation of the immune response (Fig. 3) [41]. Hence, exosomes derived from immune cells are a vital tool for cancer diagnosis and immunotherapy and serve as a vehicle in drug delivery therapy [42]. Adaptive and innate immune responses involve coordinated actions of multiple biomolecules, including proteins, antigens, antibodies, nucleic acid (DNA, RNA), and small proteins-peptide. The exosomes were shown to regulate the immune responses in different ways due to the presence of an extensive and varied range of biomolecules. Thus, exosome immune activation and regulation will take multiple forms according to the type of biomolecule responsible for the triggering. In this section, we describe the mechanism used by different exosome cargoes, more specifically, exosome nucleic acids (RNAs, DNAs), exosomal proteins (including enzymes), and tumor-derived exosomes (TEXs) to induce or suppress the immune response.

2.1. Exosome-mediating immune activation

2.1.1. Immune activation mediated by exosome's nucleic acids

Exosomes inner ward nucleic acids are a part of the chain reactions leading to a new immune status. Indeed, exosome mediates the transfer of genetic information as RNA, unveiling the possibility of using extracellular vesicles as a delivery platform for gene therapy. Exosomes of exogenous RNA are shown to behave as damage-associated molecular

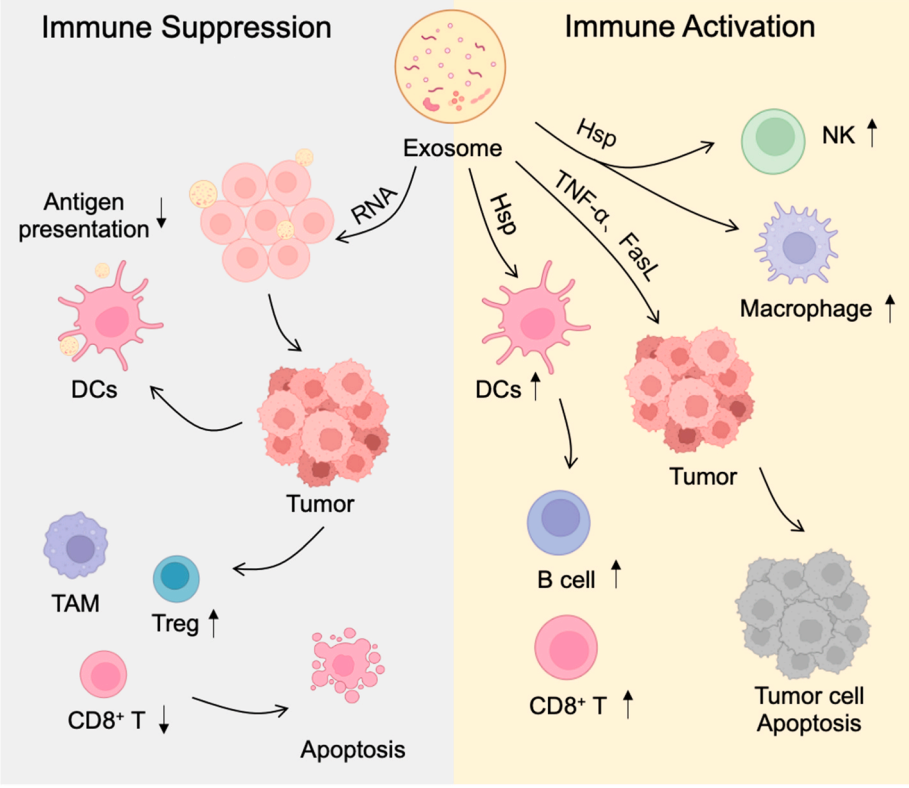

Fig. 3. Regulation of the immune response mechanism by the exosome. Exosome shares their cargo to reprogram the recipient's cells and trigger an immune response. Exosome proteins such as HSPs, FasL, and TNF can induce DCs secretion, increase DCs presenting features, and promote immune cells secretion: NK cells, Macrophages, T cells ($CD8^+$, B cells), and tumor cells necrosis (immune activation). Exosomal RNAs can promote the expression of cancerous proteins, thus leading to tumor growth, decreasing DCs presenting features, decreasing immune cell secretion, and compelling some of them to death under apoptosis (immune suppression).

patterns (DAMPs), triggering different associated innate immune response mechanisms, among them the activation of the pattern recognition receptor (PRR) regarding precise conditions of stress and pathological status [43]. DAMPS are represented by the cancer cells or pathogenically infected cells derived exosomes DNA. The DAMPS play a considerable role in innate immune cell activation, such as dendritic cells (DCs) or macrophages. Indeed, many tumors are granted with proteins-related Interferon Stimulated Gene (ISG) on their surface. Those are gene expressions resulting from the interaction between interferon proteins, danger signaling proteins released by infected cells to stimulate the expression of the damage signal gene. Exogenous RNAs (Exo-RNA) are observed to reach the stage of DAMPs, thus facilitating the innate immune response in the case of a subset of breast cancer cells put upstream in contact with stromal fibroblast [44].

In this condition, ISG induction is mediated by transferring stromal fibroblast cell-derived exosomes to breast cancer cells. Exo-RNA will activate the viral RNA PRR RIG-1, which leads to a signal transducer and activator for transcription 1 (STAT1) activation and ISG induction. In a study carried by Boelens and colleagues, neurogenic locus notch homologue protein 3 (NOTCH3) transcriptional response was used as a second-line chemotherapy. NOTCH3 is regulated by STAT1 which subsequently mediates the amplification of the NOTCH3 transcriptional mechanism, thus promoting the spread of tumor cells and enhancing tumor triptolide (TPT) [44]. The TPT showed a considerable ability to trigger the release of exosomes enriched with DNA possessing immune-stimulating properties by the cancer cells. Indeed, exosomes were mainly up-taken by DCs and displayed a high efficiency in secreting DNA to activate the stimulator interferon gene (STING) dependent pathway, leading to an anti-tumor immune response. The release of immune-stimulating DNA is observed through radiation therapy. Although this nucleic acid appears oxidized, it can nonetheless trigger DCs secretion by activating the STING-dependent pathway [45]. Recent studies have demonstrated that the exosome content is much more complex than already enlisted. In addition to proteins and nucleic acids, exosome cargo also encompasses diverse metabolites. Like nucleic acid, exosome-mediated remote communication between cells leads to the transfer of those metabolites to cancer cells through the exosomal pathway as a result of modifying the metabolism of recipient cells, which may contribute to the spread of cancer [3,46].

2.1.2. Immune activation mediated by exosome proteins

Exosomes exhibit a range of proteins that enable them to regulate the immune response. Those proteins are often associated with immune cells, increasing the spontaneity of the immune system's reaction. Interleukin-6 (IL-6), for instance, is entangled with the DCs maturation mechanism and the dragging of immune cells to the tumor sites, leading to higher antitumor immunity [45]. Exosomes' external proteins are highly involved in antigen-presenting mechanisms that turn naive cells into adaptive immune antigen-specific cells. Exosomes derived from adaptive immune cells, such as B-cells, displayed major histocompatibility complex-II (MHC-II) peptide complexes, enabling them to activate antigen-specific T-cell clones in humans and mice.

Moreover, the Antigen-presenting cell (APCs) derived exosomes also play a vital role in the antigen presentation mechanism. Exosomes released from tumor cells or pathogens-infected cells carry several tumoral or pathogens antigen proteins on their surface, which will be quickly taken up by DCs, leading to an enhanced ability to mediate a more specific immune response—assimilated tumoral antigens pulse DCs to achieve the activation of antigen-specific cytotoxic T cells (CD+8) secretion as demonstrated by the experiment on mice. This in vivo experiment consisted of the injection of exosomes carrying tumor antigen, which permitted to observe a high release of antigen-specific $CD8^+$ [47]. In a rat pancreatic adenocarcinoma study, tumor-derived exosomes interact with DCs, demonstrating an efficient anti-cancer effect by activating tumor-antigen-specific cytotoxic T cell (CTL) response [48].

Simultaneously, the exosome containing pathogenic antigens stimulates the activation of T cells in the presence of DCs, as illustrated in the mycobacterium bovis bacillus Calmette–Guerin experiment (BCG), where mice injected with macrophage-released BCG were able to stimulate T cell secretion [49]. However, exosome regulation of immune response by antigen-presenting mechanism was shown to be achieved through either direct or indirect pathways. The direct path implies direct engagement of exosome peptide-MHC with T-cells; meanwhile, the indirect approach consists of absorption of peptide-MHC antigen by DCs upstream (Fig. 4), which will later process the antigen and present it to the $CD8^+$ [50]. Exosomes possess intracellular proteins contributing to the immune activation mechanism as well. For instance, the well-known HSPs are essential in cell survival and adaptation while dealing with multiple origins stresses [51]. HSP70 provides exosomes the ability to promote DCs maturation in mice. In addition, HSP70 demonstrated its high cardio-protective effect [52], which emanates from its capacity to trigger HSP27 phosphorylation. This process results from the upstream activation of the toll-like receptor-4 pathway (TLR4), involving extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) and p38 mitogen-activated protein kinase (p38MAPK) [52]. Also, the protein (HPS60) belongs to intra-vesicular and extra-vesicular compartments [53]. Its immune regulation activity, either immune-stimulant or immunosuppressing, is mainly subordinated to the undertaking interaction between the chaperonin and immune system components. Indeed, HSP60 was shown to participate in macrophage and neutrophils secretion leading to the maintenance of an inflammation reaction in chronic obstructive pulmonary disease (COPD) and ulcerative colitis (UC) disease [54,55]. Although HPS60's role in hypertension (HT) pathogenesis is still not deciphered, its implication in autoimmune diseases is well established. HSP60 is eager to mediate the secretion of antibodies against itself, leading to multiple autoimmune reactions in all tissues containing HSP60 [56–58]. Certain types of exosomes were shown to encapsulate much more heat shock proteins, such as heat shock-induced released exosomes from B lymphoma cells. Those exosomes presented a high amount of HSP60 and HSP90 while displaying highly immunogenic molecules such as MHC-I, MHC II, CD40, CD86, RANTES, and IL-1β, thereby leading to stimulation of specific adaptive immune cells such as $CD8^+$ T cells to produce an antitumor effect [59].

2.1.3. Immune cells-derived exosomes-mediating immune activation

Numerous studies demonstrated the spontaneity of immune cells toward invading cancer cells, which are automatically erased in a significant number of cases, in a phenomenon called immune surveillance [60]. Indeed, the immune cells were proven to trigger the immune response using their released exosomes.

2.1.3.1. Natural killer cells (NK-cells). In many cases, the immune activity ensured by immune cells derived exosomes, such as NK-cells, aims to destroy cancer cells efficiently. NK-cells constitute the first barriers of defense against an enormous scope of pathogenic invaders, which often makes them labeled as ensuring the immune-surveillance of the host organism. This ability is strengthened by the fact that NK cells are granted the feature of recognizing antigenic elements that do not even display MHC I proteins markers, thus contributing to the efficient targeting and clearance of cancer-infected cells [61]. Besides their specific features, including the mediation of innate immune response, the recognition of infected cells depraved of class I MHC proteins, and the anti-cancer effect, the NK-cells could additionally influence the immune response mechanism by releasing exosomes extracellular vesicles [62]. In an investigation on cancer patients, the NK-cells derived exosomes displayed NK-cells characteristic markers, including CD56, NKG2D, CD94, CDL40, and killer proteins such as FasL Perforin or granzyme [63–65]. Cancer cells homing deficiency to tumor sites were destroyed by the direct diffusion of NK-cells derived exosomes, which primarily interact with the cancerous tissues, thus exerting NK-cell cytotoxic effect

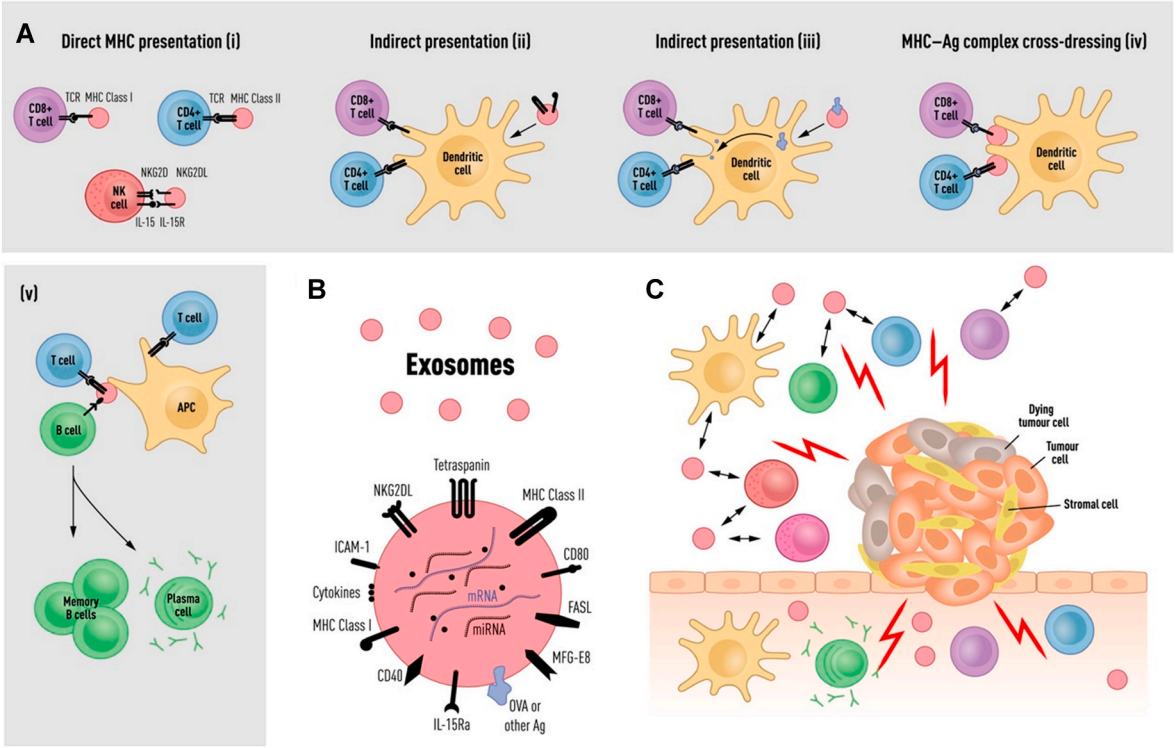

Fig. 4. Potential interactions of autologous (syngenic) and allogenic exosomes with immune cells [85]. Exosome's content includes MHC I and MHCII complex of proteins, which grants it the feature of triggering the activation of innate and adaptive immune response by stimulating the immune cells involved in each of these mechanisms by acting like an antigen-presenting entity (b). Thus, creating a complex and more robust response toward the antigenic element. This strategy of defense is usually utilized against located tumors (c). The direct stimulation occurs wherein exosomes successfully present their cargoes recognized as MHC elements to immune-killing cells, including $CD4^+$, $CD8^+$, and NK cells (a.i). The indirect stimulation is ensured by antigens-presenting cells such as dendritic cells, which, consequently, to exosome internalization, exhibit antigenic elements transferred by exosomes (a.ii, a.iii). In some instances, exosomes might remain on the surface of APCs, which then carry indirectly exosomes antigenic components to stimulate immune cells; this phenomenon is called MHC-Ag complex cross-dressing (a. iv). Exosome presentation of antigens involved B cells, which memorized the invaders' antigenic pattern to ensure a further, more spontaneous response (a.v).

toward cancer cells [66]. The efficiency of NK-cells derived exosomes upon eradicating cancer cells by using the different killing mechanisms was highlighted in the CHLA255 neuroblastoma cells and SupB15 leukemia cells. The results revealed several damages, leading to a decrease in their cellular viability after treatment involving NK-cells derived exosomes. These exosomes have been demonstrated to activate caspase-independent and caspase-dependent cell death pathways to eradicate cancer cells [67]. The immune escape mechanism and tumorigenic potential were also inhibited by NK-cell-derived exosomes carrying tumor suppressor elements [68].

An investigation of NK-derived exosomes revealed an abundant Fas Ligand (Fasl) population on their surface. FasL is a transmembrane protein often expressed by different categories of T cells, such as lymphocytes or NK cells. FasL is well known for its physiological function of destroying cells presenting a non-self-phenotype profile (tumor cells) by inducing the apoptosis and the perforin pathway of cells [62]. In addition to FasL, NK-92 cells-derived exosomes were shown to present the TNF-alpha factor. TNF-alpha is a component of the reaction channel leading to an inflammatory response. To initiate the pro-inflammatory and apoptosis pathway that will destroy foreign antigen cells, NK-92-derived exosomes presenting TNF-alpha bind mainly with the ligand TNF-α to the TNF receptor (TNFR1). This TNF-alpha-induced reaction cascade will interrupt the cells' proliferation signaling pathway [65]. NK-92 cells were shown to display proteins and nucleic acids that they used to influence the target cells genetically. Among these nucleic acids is mir-186, which was demonstrated to be a high oncogene element in various human tumors [69]. V-myc myelocytomatosis viral-related oncogene (MCYN)-amplified Neuroblastoma (NB) tumor cell viability was shown to be significantly low in front of the high cytotoxicity displayed by NK-92 cells-derived mir-185. This high annihilation effect on MCYN-amplified NB tumor cells was hypothesized to result from the direct targeting of TGFBR2, TGFBR1, AURKA, and MYCN [68].

The multiple features of NK-cells-derived exosomes against tumors attract the particular interest of researchers in designing the most efficient way of collecting NK-cells exosomes on a large scale both for in vivo and in vitro studies. This question has been addressed by Jong et al. in a study that aims to extract a significant amount of NK-cells exosomes using the polymer precipitation method [70]. This extraction technique might be taken further to clinical translation in the future.

2.1.3.2. Dendritic cells. Alongside the NK-cells, the particular antigen-presenting feature of the DCs also allows them to trigger an immune reaction. Indeed, by interacting with a specific type of cells, DCs-derived exosomes (DEXs) may compel them to release immune system stimulators such as cytokines, which leads to the release by the immune system of immune cells such as macrophages, natural killer cells, or even neutrophiles. In the case of the interaction between exosome and SK-BR-3 Adenocarcinoma cells, exosomes were proven to increase the amount of IFN-gamma cytokines through stimulation of $CD3^+$ T cells [71]. For B-cells activated pathway, DCs displaying tumor necrosis factor-alpha (TNF alpha) released exosomes that demonstrated a high affinity with the nuclear factor- k-light-chain enhancer located on B cells. This k-light-factor-exosomes interaction was proven to trigger an inflammation response in human umbilical vein endothelial cells (HUVEC) [72]. DCs were demonstrated to release several diverse exosomes according to their composition. Among the component of DCs-derived exosomes are the previously described chaperone proteins, including the HSP70 and

HSP90, which were shown to induce the activation of the $CD4^+$ and $CD8^+$ T cells but also MHC-I, MHC-II, and CD86 [73,74]. However, the inability of exosomes derived from DCs to interact directly with the CTL cells presents a new gateway for engineered immune activation. Studies on the use of DEXs in activating a targeted immune response revealed that DEXs could be used to reeducate a larger colony of DCs, which displayed antigenic peptides recognized by MHC-I or MHC-II. DCs subsequently interacts with $CD8^+$ T cells and increase their secretion in a more critical immune response in vivo. Although this model was efficiently used, the $CD8^+$ T cells activation was shown to be more efficient while reeducated DCs were associated with $CD4^+$ T cells, used as a helper for its ability to uptake APCs membrane molecules and display the antigen of interest as demonstrated by Kennedy and colleagues in the studies carried on $CD4^+$ in vivo [75].

Furthermore, the immuno-stimulant effect of Dendritic cells derived exosomes was investigated in a study carried out by Wang and colleagues, wherein they aimed to design a $CD4^+$ T cells- based vaccine [76], able to stimulate the activation of $CD8^+$ directly. The stimulation of $CD8^+$ through $CD4^+$ T cells- based vaccines resulted in an acquired immunological memory expressed by the vital secretion of the HER2 kinase-specific humanized monoclonal antibody known under the designation of the trastuzumab [77]. The study was based on the ability of the $CD4^+$ T to uptake the ovalbumin DCs-derived exosomes (OVA_{Exo}), which upstream contained a characteristic antigenic peptide of MHC-I (pMHC-I), a crucial element in long-term immunological memory as well as CD80 inward IL-2 signaling and the signaling of endogenous CD40L [75,78,79]. While administered in the C57BL/6 mice, the $CD4^+$ T-based vaccine (OVA_{TExo}) demonstrated an ability to cognate with $CD8^+$ T inducing a more significant CTL activation, by a process that until nowadays remains unclear but which was hypothesized to emanate from the DCs derived exosome ability to target the CD4+T with their expressed pMHCI, thus being captured by T cells receptors. The process, using $CD8^+$ and $CD4^+$ T cells to induce anti-tumor immune responses by mediating the DCs-derived exosomes containing CD80 and endogenous IL-2 in vivo, confirms the ability of DEXs to mediate the immune response efficiently and be used in vaccine design for cancer immunotherapy [76,80].

In addition, exosomes derived from DCs were shown to trigger a targeted immune response by inducing the secretion of inflammatory markers. A study carried out on the DCs presenting alpha-fetoprotein (AFP) revealed that AFP-based DCs released exosomes caused an activation of the $CD8^+$ T cells through a cascade of reactions that started from the induction of a high release of the Interferon-gamma (IFN-gamma) and IL-2, leading subsequently to the suppression of the T cells immunosuppressive elements such as CD25+Foxp3+Tregs, as well as IL-10 and TGF-beta [81]. However, although the possibility of an efficient activation of the immune response by the bias of DCs-derived exosomes presenting antigenic MHC peptides remains, pertinent observation still highlights the ambiguity of the immune activation phenomenon. Indeed, in particular studies, the immune activation appeared to occur independently from the DC-based exosome pMHC if the entire antigen was shown to be present [82]. The ability of DEXs to induce the stimulation of immune killing cells (e.g., $CD8^+$ T cells) results from a strategy used by DEXs to operate the presentation of MHC-I or MCH-II antigenic peptides through two main ways, which are deeply portrayed in Fig. 4. The direct presentation consists of DEXs presenting its antigen directly to the immune cells, thus educating them for a more aggressive response toward antigenic invaders. The indirect presentation consists of DEXs being internalized and expressed by DCs, which are further mediating the presentation of the antigen upon immune cells (Fig. 4). This phenomenon involves many cells simultaneously and enhance the immune response upon cancerous cells.

2.1.3.3. T lymphocytes ($CD8^+$ T cells, CD4 + helper T cells). T-cells may be organized into two categories regarding their phenotype, determining their surface receptors' specificity and antigenic proteins' specificity. The first is the $CD8^+$ CTLs, and the second is the $CD4^+$ helper T cells. However, due to the diversity of the $CD4^+$ helper T cells surface antigens, as well as the multiple biological functions they mediate, the helper cells may be further divided into plenty of sub-categories, including the follicular helper T-cells (Tfhs), regulatory T cells (Tregs), Th17 cells, etc. [83,84].

$CD8^+$ CTLs are capital in triggering the reaction cascade, leading to an immuno-stimulant effect toward an exogenous antigen. Indeed, $CD8^+$ CTLs may compel the launch of an immune response through the direct presentation of MHC-I protein displayed on its surface. This bunch of proteins is consequently meant to catch the antigenic element, thus improving the immune response toward every invading pathogen and the host organism's malignant cells. Though, as previously explained, the CD8+CTLs were demonstrated to release exosomes granted with the $CD8^+$ CTLs equivalent feature of eradicating cancer cells [86]. This feature of CD8+CTLs-derived exosomes was highlighted in a study carried out on a mouse infected with melanoma, wherein the fibroblast stroma responsible for the spread of the tumor, ending in metastasis, was shown to be highly interrupted by the intra-tumoral administration of the of activated $CD8^+$ T cell-derived exosomes [87]. Although $CD8^+$ CTLs were demonstrated to mainly possess a low affinity with the invading antigenic elements, releasing higher affinity CTLs remains crucial for immunotherapy. In this perspective, a study carried out by Wu and colleagues highlighted the side effect of the presence of IL-2 on high-affinity CTLs, which through a still undeciphered mechanism induced the secretion of low affinity CTLs, which released exosomes are highly important in cancer immunotherapy [88]. The process leading to an efficient immune response involving the $CD8^+$ T cells can be summarized into three capital levels that are: (1) antigen, (2) co-stimulation, (3) Inflammatory elements (IL-12). Thus, a study carried by Li and colleagues revealed that the activation of $CD8^+$ T cells bystander was possible through the induced release of exosomes by stimulation of the IL-12. After stimulation, IL-12 activated $CD8^+$ T cells, further demonstrated to secrete exosomes displaying different markers. This variety of exosomes results in the activation of the $CD8^+$ T cells bystander effect, responsible for the higher efficiency in immunotherapy through the production of immune elements such as granzyme B (GZB) or IFN-γ [89].

$CD8^+$ T cell activation is assisted by CD4+T cells, also labeled as helper cells, which displayed markers that are primarily CD4 proteins able to enhance immune response while coupled with MHC II proteins presented by APCs. Thus, CD4 helper T-cells were demonstrated to release exosomes that are mainly enriched with characteristic exosomes markers, including LAMP-1, TCR, and LFA-1, but also with CD4 typical markers such as CD4, TCR, LFA-1, CD25, and FasL. These exosomes were shown to promote the antitumor effect through CTL activation [75] and be used to diagnose inflammatory disease. In contrast, the alteration or absence of bioactive messenger of these exosomes coincides with an underlying inflammatory reaction [90]. As previously described, like Dendritic cells, $CD4^+$ T conjugated to MHC II complex cells derived exosomes can efficiently target and interact with the immuno-deficient cells, thus leading to their destruction [91]. The inflammatory response may also be mediated by exosomes released from the CD4 + helper T cells, which were highly potent in activating phagocyte B cells [92,93].

2.1.3.4. B lymphoma cells. B lymphoma cells were shown to induce the activation of CD8 +T cells. Indeed, an antitumor effect can be observed through B lymphoma cell activity, which can release exosomes. These B lymphoma-derived exosomes were demonstrated to be highly enriched with heat shock proteins, including HSP60 and HSP90, meanwhile possessing a higher amount of immunogenic molecules than the regular rate, such as MHC I, MHC II, CD40, CD86, RANTES, and IL-1β [59]. Also, in an assay involving a DC-derived exosome-based vaccine, B lymphoma cells demonstrated an ability to stimulate the substantial spread of an

extensive range of clonal T cells. However, inversely, exosomes derived from the lymphoma B cells were shown to promote the expansion of the clonal T cells through their interaction with DCs. This phenomenon contributes to the unleashing of immune cells by targeting elements with an immunosuppressive purpose, such as specific cytokines, including IL-14 and IL-10 [94]. Consequently, this DC-B lymphoma-derived exosome interaction pathway leads to a higher release of inflammatory factors such as IL-6 and TNF-α.

2.1.3.5. Immune cells-derived exosomes mediating innate and adaptive immune response communication. Immune cells-derived exosomes are entangled in a complex cycle of interaction that enables them to be released in both innate or adaptive immune responses. Innate immune cells are the first to retaliate upon the threat of an invading antigen and infected cells. However, if the pathogenic element demonstrates a higher ability to overcome the innate immunity clearance mechanism, the regulation of immune response is handed over to the adaptive immune cells. In some instances, such as cancer development, adaptive and immune cells are found to take action concomitantly in a dynamic qualified as innate and adaptive immune cells communication. This phenomenon is graphically illustrated in Fig. 5 and seems to occur when innate and adaptive immune cells are found in the infected area in the struggle against whatever pathogenic element. Although mutual interaction between innate and adaptive immune cells cannot be streamed and observed live, the results of their communication led to the hypothesis of their virtual interaction with adaptive immune cells, including DCs, T cells, and B cells. This communication is partly ensured by adaptive immune cells derived exosomes that were shown to re-educate innate immunity cells. Mast cells were shown to activate the phosphorylation of its extracellular signal-regulated kinase (ERK) after close contact with T cells-derived exosomes. Indeed, proteomic analysis revealed that these exosomes were enriched with proteins that can trigger EKR phosphorylation, including small GTPase/mitogen-activated protein kinase (RAS/MAPK) signaling proteins [95]. Additionally, mast cells re-education by T cells exosomes was observed by its increase of the cytokines (IL-24) secretion after efficient uptake of T-cells derived exosomes [96,97]. Altogether, innate and adaptive immune cells' mutual communication mediated by exosomes may contribute to the activation of immune response and, unfortunately, suppress immune mechanisms, thus spreading disease.

2.2. Exosomes as an immune response suppressor

2.2.1. Tumor-derived exosomes as an immune system suppressor

2.2.1.1. Tumor-derived exosomal miRNA and exosomal gDNA. The regulation of the immune system by exosomes goes mainly through its ability to ensure communication between cells of the same or even different lineages. Knowing that exosome genetic material such as miRNA is highly similar to the profiles of the tumor cells that produced them [98], their interaction with uncontaminated cells may result in a tremendous phenotypic change. Double-stranded genomic DNA (gDNA) is found in tumor-derived exosomes (TEX) generated from tumor cell lines and extracellular vesicles (EVs) obtained from cancer patients' plasma [99]. Different exosomes had diverse gDNA content that could include specific mutations, according to analyses of gDNA fragments of the MLH1, PTEN, or TP53 genes [99,100]. Oncogenic mutations can be carried by TEX and transferred to recipient cells [101]. The TEX included nearly 10,000 mRNA types, many of which are known to play essential roles in cell biology, such as immunological control and inflammation [102]. Indeed, recent data suggest that dysregulated miRNAs play a crucial role in tumor genesis, development, and metastasis by boosting oncogene [103] or tumor suppressor [104]. Valadi et al. discovered that exosomes contain a subset of cellular mRNA and miRNA that can be transmitted to target cells [105]. Valadi et al. studies unveiled that tumor exosome-derived miRNA can inhibit the mRNA for signal transduction components in T-cells [106]. This exosomal miRNA was hypothesized to mirror the phenotype profile of the secreting tumor cells from which the exosome originates, since released exosomes contain diverse RNAs, including miRNA. Guilherme Rabinowits' studies on exosomes as lung cancer biomarkers revealed that miRNAs' expression profile across the genome differs significantly between primary lung malignancies and noncancerous lung tissues [98]. 12 RNAs were shown to be involved in this process: hsa-miR-17-3p, hsa-miR-21, hsa-miR-106a, hsa-miR-145, hsa-miR-146, hsa-miR-155, hsa-miR-191, hsa-miR-192, hsa-miR-203, hsa-miR-205, hsa-miR-210, hsa-miR-126*,

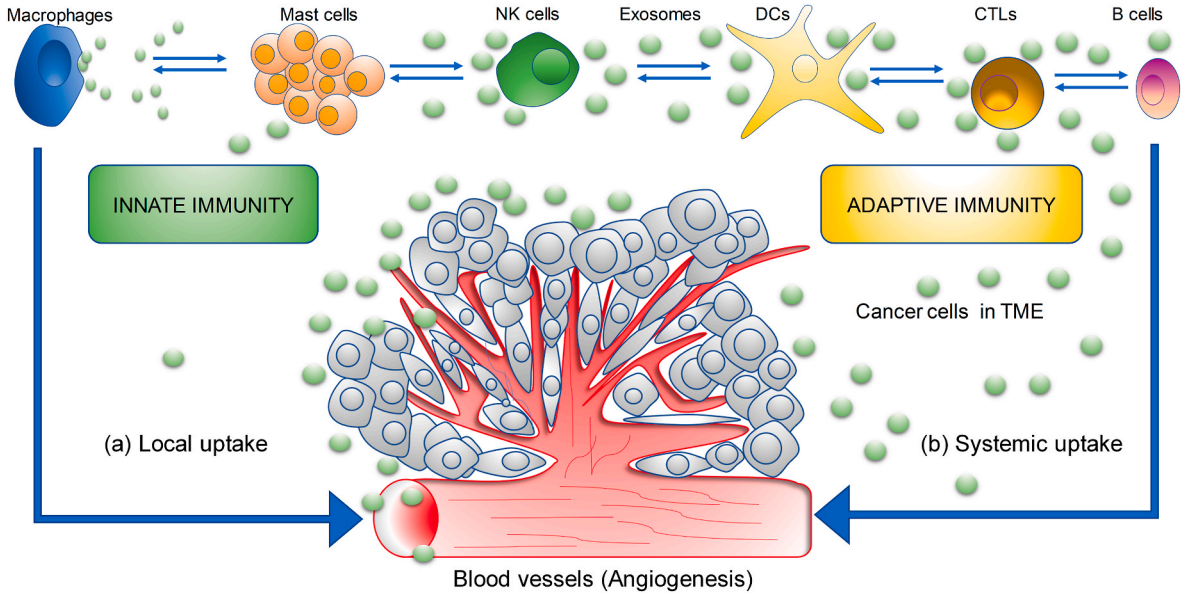

Fig. 5. Exosomes mediate the communication between different types of immune cells across the innate and adaptive immune systems. Exosome interaction with varying cell types induces a simultaneous activation of both primary and secondary immune cells. Similarly to the model exhibited in Fig. 4, the exosome creates a cloud of highly immune-responsive cells wherein the macrophages, NK cells, and mast cells directly interact with the tumor cells and each other (local uptake for innate immunity cells). Meanwhile, the DCs ensure the direct and indirect presentation of antigens upon Tumor, T, and B cells. Educated T and B cells interact with the tumor cells(Systemic uptake of adaptive immunity cells) [40].

[107]. Double-stranded genomic DNA (gDNA) is found in TEX generated from tumor cell lines and EVs obtained from cancer patients' plasma [108]. Different exosomes had diverse gDNA content that could include specific mutations, according to the analyses of gDNA fragments of the MLH1, PTEN, or TP53 genes [108,109]. Oncogenic mutations can be carried by TEX and transferred to recipient cells [110]. Immune cells are triggered by interacting with receptor ligands or extracellular vesicles such as exosomes. However, knowing that exosomes derived from tumor cells carry along metabolites markers, nucleic acid, and proteins emanating from the tumor environment, it can interfere with the maturation and secretion of cells that are in charge of ensuring the immune response, such as DC, T and NK activating cytotoxicity, which is going to lead to a general immune suppression, an enhancement of tumor cells to drug therapy, and apoptosis of T-cell because of their ability to achieve cells communication by carrying multiple and diverse biomolecules [111,112]. Exosome immune suppressive activity originates from cancer cells-derived exosomes capable of transferring tumor-specific biomolecules triggering tumor development and metastasis [113]. An extensive range of tumor cells with varied histological backgrounds was demonstrated while extracted from the plasma of cancer patients to release a significant number of micro vesicles either in vitro or in vivo [114–117]. These microvesicles and exosomes, more specifically, were indeed shown to exhibit a plethora of surface proteins, such as Fas-L or PD-L1, that enable them to suppress the immune response either by interacting with the receptor-ligand [118,119] of the target cells causing the gradual inhibition of $CD8^+$ and NK cells anti-tumor activity or by internalizing them [120]. For instance, a tumor-derived exosome proteinic profile differs from normal cells.

Observation of tumor-derived miRNA showed that their impact on receptor cells mainly led to inhibiting their biological function and a higher risk of metastasis associated with increased angiogenesis in a specific area. This phenomenon was pointed out to be more likely to happen in the case of the deletion of the Caveolin-1 protein in M2-macrophages [121]. Indeed, exosomal miR-1246, derived from ovarian tumor cells, was demonstrated to downregulate caveolin-1 while internalized by M2-macrophage, thus leading to increased angiogenesis and metastasis [122]. A study by Guo and colleagues on breast mice bearing 4T1 breast cancer allowed further hypothesized macrophages derived miR-183-5p from promoting proinflammatory secretion [123]. The secretion of inflammatory cytokines, including IL-1b, IL-6, and TNF-α, is associated with the activation of NF- κB signaling in macrophages, which was shown in Guo and al studies to be negatively regulated by miR-183 interaction with the 3′UTR of the protein phosphatase-2 catalytic subunit alpha gene (*PPP2CA)* [123].

$CD8^+$ T cells' immune features were shown to be drastically diminished toward the uptake of miR-498 and miR-3187-3p derived from melanoma cell exosomes. The importance of CD8+T cells and their decreased secretion resulted from the miR-498 binding with the tumor necrosis factor (TNFα) on the 3′UTR site in CD8 T-cells. Similarly, miR-3187 inhibited the activation of the signaling and T cells receptor (TCR) by targeting the CD45 gene PTPTC 3′UTR site [124].

Exosomal miR-24-3p derived nasopharyngeal carcinoma (NPC) indicates patients' survival odds since patients displaying an exceptionally high amount of this type of miRNA showed fewer survival odds. The miR-24-3P was revealed to be particularly aggressive regarding the side effect emanating from its interaction with T cells. Indeed, by targeting FGF11 mRNA, which is involved in the regulation of the STAT-1, STAT-3, and phosphorylation of extracellular signal-regulated kinase (ERK) in T cells, a weakening of the immune response through the decrease in the T cells proliferation was consequently observed. Also, the targeting of FG11 mRNA was shown to reduce inflammatory markers such as IFNγ and IL-17, thus a decrease in the production of th1 and th17, respectively. Meanwhile, the proliferation of immunosuppressive Foxp3+ Tregs was observed [125].

In the case of non-small cell lung cancer (NSCLC), the proportion of has-miR-125-5p was shown to indicate the state of a patient. An analysis of the plasma of patients diagnosed with NSCLC revealed a higher proportion of has-miR-125-5p than the healthy group. The features of miR-125-5p include the inhibition of the secretion of INFγ and TNFα in γδT cells but also promotes cells apoptosis [126]. Furthermore, based on the miR-125-5p biomarker feature, the plasma of patients recovering from NSCLC after anti-PD1 immunotherapy was analyzed and revealed a decrease of miR-125-5p, confirming its quality of accurate biomarker of the NSCLC [127].

2.2.1.2. Tumor-derived exosomal long non-coding RNAs. The communication of cells constituting the tumor micro environment (TME) is ensured by long non-coding RNAs (lncRNAs) related-mechanisms which mostly lead to an inhibition of the immune response and promote an aggressive immune escape mechanism. For instance, in the case of pancreatic cancer cells, lncRNA ENST00000560647 emanating from those cancer cells were demonstrated to promote the spread of cancer by tricking the surveillance of $CD8^+$ T cells by preventing DCs from presenting alarming antigen [128]. A qualitative analysis of the serum of a patient developing a Kras mutant lung cancer unveiled a higher concentration of exosomal lncRNA derived from prostate cancer-associated transcript 1 (PCAT-1) than a patient with a wild-type Kirsten rat sarcoma mutant gene cancer (KRAS WT). The chemoresistance of this type of cancer was hypothesized to be carried by the lncRNA since it was shown to be associated with disease progression [129,130]. Additionally, KRAS WT was demonstrated to be involved in a physiological mechanism that enhances the release of immunosuppressive miRNAs such as miR-182 and miR-217, which are meant to promote the accumulation of lymph metastatic foci by infiltrating the cancer-associated fibroblast (CAF), thus contributing to tumor growth [127].

Chemotherapeutic resistance of breast cancer was demonstrated to be associated with the tendency of cells to engage in aerobic glycolysis. Aerobic glycolysis comes from the degradation of HIF-1α, which is ensured by the transmission of HIF-1α- stabilizing -lncRNA (HISLA) by the extracellular vesicles derived from the tumor-associated macrophages (TAM) to a more significant number of breast cells. The upregulation of HISLA causes the progression of the disease or lymph node metastasis [131], helping to maintain TAMs feature of tumor-promoting M2-like profile in a TME deprived of oxygen [132,133] but also inhibiting CD4 + and CD8 + T cells infiltration in the tumors [134]. Aerobic glycolysis in TAMs was shown to occur in the TME through the lactate-HISLA interaction, wherein the lactate demonstrated the ability to upregulate HISLA, thus promoting chemotherapeutic resistance [131].

Moreover, the immunosuppressive features of exosomes derived from cancer cells were described as the consequence of the polarization of macrophages in the tumor environment. This chemical modification of macrophages gives them a higher efficiency to inhibit the biological pathway that would lead to a controlled polarization of cells, thus inducing tumor size increase in many cases, healthy cells invasion, or migration of tumor cells. Indeed, tumor growth spread and invasion in the TME were shown to be promoted by the uptake of the exosomal lncRNA urothelial caner-associated 1 (UCA1) released from the hypoxic bladder cancer cells [135]. The polarization of M2 macrophage was demonstrated to be induced by exosomal lncRNA SOX2 derived from the NSCLC. Through this process, SOX2 was shown to soak the miR-627 of Tamm Horsfall Protein-1 (THP-1) macrophages, thus promoting the expression of the gene of interest involved in the M2 polarization, including Smad2, Smad3, and Smad4 [136]. The polarization, migration, and invasion of M2 macrophage are also mediated by the exosomal lncRNA distal- less homeobox-6-antisense 1(DLX6-AS1) emanating from hepatocarcinoma cells (HCC). This lncRNA aims to interact with the miR-15a to upregulate its target gene C-X-C motif chemokine ligand 17 (CXCL17) [136].

Furthermore, due to its ability to decrease the proliferation rate of T cells and its power to prevent phagocytosis in DCs [137], the exosomal

metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was hypothesized to be correlated to tumor stage and metastasis [138]. This observation was sustained by a study on healthy subjects and a group suffering from NSCLC. LncRNA MALAT1 was highly expressed on exosomes collected in the NSCLC patients' group. MALAT-1 was involved in the positive regulation of proto-oncogene MAF, a transcription factor of IL-10 in th1 cells. This cytokine was recurrently pointed out to suggest meager patient survival odds [137,139,140]. Exosomes derived from cancer-associated fibroblast (CAFs) were shown to release lncRNA nuclear enriched abundant transcript 1 (NEAT). NEAT was demonstrated to target miR-26a/b in endometrial carcinoma (EC) cells through a sponging mechanism, leading to higher expression of the STAT-3 and STAT-3 regulated protein YKL-40. Certain studies highlighted STAT-3 and YKL-40 as a bunch of proteins involved in cancer development, thus suggesting that the upregulation of the miR-26a/b target proteins by NEAT lncRNA represents an underlying mechanism of the involvement of NEAT lncRNA in promoting tumor growth and proliferation of CAFs toward EC cells [141].

2.2.1.3. Tumor-derived exosomal ultra-conserved RNAs. An organism's genome possesses an ultra-conserved area, called ultra-conserved RNAs (Uc-RNAs), which can interact with miRNAs and affect their biological function. Ultra-conserved RNAs may indicate cancer activity since they display typical expression pathways compared to healthy cells. TUC339, derived from HCC, is known nowadays as the first exosomal Uc-RNAs to contribute to cancer cell migration and invasion of healthy cells [142–144]. Also, increased angiogenesis was observed in the lymph and hypothesized to emanate from esophageal squamous cell carcinoma (ESCC) cells exosomal Uc.889 effect on endothelial cells proliferation and tube formation. The mechanism of lymph-increased angiogenesis results from the upregulation of the p38MAPK gene by altering EC cells mRNA on their ephrin receptor A2 (EPHA2) out of its binding with Uc.889 [145]. Although studies on the Uc.RNAs influencing tumor cell proliferation and tumor growth in the TME are still poorly developed, but the previously described Uc.RNAs highly suggest its involvement in tumorigenic activity in the TME. Other cancers were proven to be enhanced by lncRNAs, including colon cancer which was shown to proliferate and migrate under the influence of the lncRNAs encoded from the human transformer 2β gene (TRA2B).

Further, Uc.138 showed the ability to induce chemotherapeutic resistance [146]. Also, NF-kB signaling was shown to be upregulated by Uc.63, thus leading to more manageable germinal center cells (GCs) growth and progression [147]. In urothelial carcinoma, Uc.63 was demonstrated to be associated with the reduction of the androgen receptor (AR) activity by downregulating the sensitivity of cisplatin [148]. Certain cancers appeared to result from mRNAs misled by decoy elements that aim to inhibit their biological function. In NSCLC, for instance, many mRNAs were demonstrated to be decoyed by Uc.339, including miR-339-3p, miR-663b-3p, and miR-95-5p, thus promoting proliferation and cancer cells growth by enhancing the expression of their target oncogene cyclinE2 [149].

2.2.1.4. Tumors-derived exosomal circular RNAs. The Circular RNAs (CirRNAs) present tumorigenic features established by their particular shape. Indeed, due to their circular form, circRNAs possess non-coding RNA strands linked on their 3′ and 5′ regions by covalent bounds [132], thus preventing them from being hooked and digested by ribonucleases, increasing their stability [150]. Certain cirRNAs were shown to be released by cancer cells to mediate cancer cells' remote communication with healthy cells in the TME. For instance, as previously described, tumor growth in the case of HCC is regulated by the polarization of macrophages. Circ-0074854, a circRNAs, was shown to induce M2 polarization, thus HCC cell growth and migration, as a result of their binding with RNA binding protein HuR in HCC cells [151]. Other circRNAs aim to inhibit NK cells' killing function toward invading pathogens and abnormal cells. NK cells are proven to be highly impotent, while circular ubiquitin-like with PHD and ring finger domain 1 RNA (circUHRF1) were found to be secreted by HCC cells. The underlying mechanism of NK cells' impotence resulted from the upregulation of miR-449c target mRNA, T cell immunoglobulin, and mucin domain-containing *protein3* (TIM3) by the binding between circUHRF1 and miR-449c [152]. In HCC, CircUHRF1, while highly expressed, can partially stop NK-cell infiltration in tumors, meanwhile increasing the chemo-resistance of the HCC upon anti-PD1 therapy [152]. Exosomal NSCLC circ-CPA4 can target the mRNA encoding for programmed death-1 ligand (PDL1) of NSCLC cells and compete with let7 miRNA in inhibiting the 3′UTR of PDL1 mRNA. This inhibition of PDL1 mRNA leads to a higher secretion of the NSCLC exosomes, reducing the CD8+T cells' function and consequently enhancing cancer development, epithelial-mesenchymal transition (EMT), and cisplatin insensitivity [153]. PDL1 is also targeted by exosomal circRNA-002178 of lung adenocarcinoma (LUAD) cells by soaking miR-34, thus reducing CD8+T cells unleashing. The reduction of $CD8^+$ T secretion for immune response, through circRNA-002178 -PDL1 targeting pathway is facilitated by CD8+T cells weakening process, resulting from the uptake of NCSCL exosomal miR-28, which aims to upregulate PDL1 target gene [154]. Various studies on the exosomal circRNAs derived from cancer cells showed their relative role in promoting tumor growth and cancer spread.

2.2.1.5. Tumor-derived exosomal proteins and cell reprogramming (precursors cells, blood cells, immune cells). Proteins such as HSP, mainly superficial HSP60, appeared to be in a higher number of tumor cells derived exosomes. HSP60 demonstrated a dichotomic nature in the regulation of immune response. In addition to stimulating immune cells, which will suppress tumor development, it was also shown to be involved in not only tumor cells' survival capacity toward immune clearance but also highly contribute to tumor-cell growth. Indeed, the higher presence of HSP60 in cancer cells-derived exosomes was correlated to an enhanced capacity of tumor cells to escape the apoptosis mechanism, loss of replicative senescence, uncontrolled proliferation, and neoplastic transformation [155–157]. Specific experiments were carried out to assess the level of implication of HSP60 in tumor cell growth, one of those investigations implying short hairpin RNA plasmids used as an inhibitor of HSP60 expression. It revealed a total arrest of tumor cell growth [158].

Similarly, an observation of the correlation between HSP60 activity and bone cancer cell growth was unveiled by an in vitro experiment aiming to knock down HSP60. The results showed that the knockdown of HSP60 had a suppressive impact on osteosarcoma cell growth [159]. HSPs involvement in the mediation of immune suppression is described in more detail in Fig. 6, wherein HSPs (HSP72), alongside other proteins including growth factors (FasL, TRAIL, NKGD2), are shown to mediate the disruption of immune cells secretion, and the weakening of the killing ability of T lymphocyte (e.g., CD8+Tcells), macrophages or NK cells (Fig. 6). Many Studies on micro particles derived from cancer cells were carried to assess the process by which they may prepare the way for cancer cells to migrate from one location to another, thus contaminating other cells. For instance, exosomes derived from lung cancer cells were shown to encompass multiple microparticle subunits, such as platelet microparticles (PMPs) and endothelial microparticles (EMPs) in smaller amounts. For faster growth, the cancer cells need to settle in a highly vascularized environment created by inducing the biogenesis of a higher amount of small blood vessels (angiogenesis) as illustrated in Fig. 5. Thus, an increased angiogenesis rate can be used to diagnose tumor cell development. Numerous studies were carried out on the involvement of exosome-derived PMPs in promoting endothelial angiogenesis in vitro and in vivo [160–163].

Consequently, a correlation between microvesicles derived from cancer cells and the increase of angiogenesis was established among

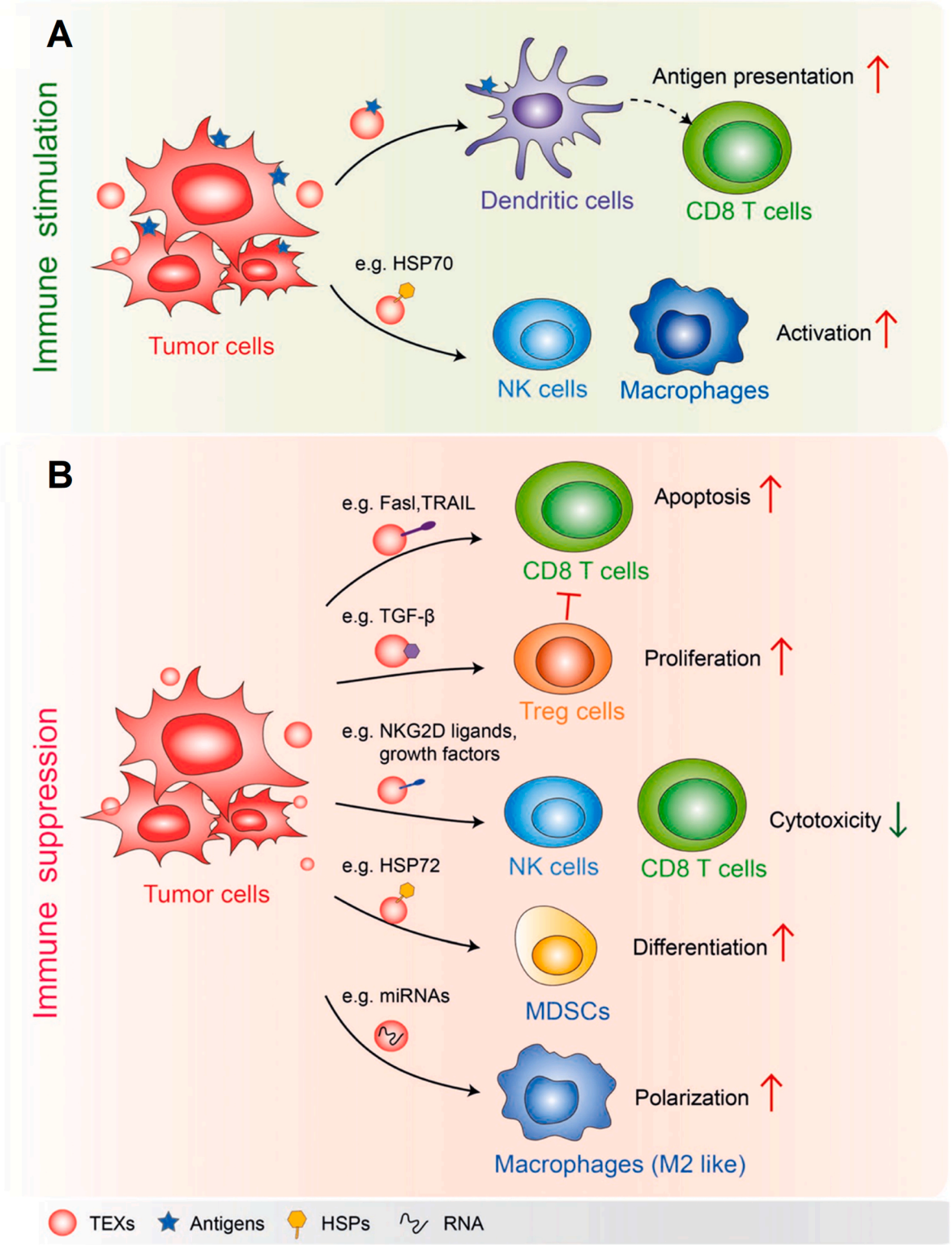

Fig. 6. Functions of tumor-derived exosomes in tumor immune environment [178]. (a) Exosomes derived from tumor cells encompass the double features of immune suppression and activation described in this work. Immune stimulation of TEXs occurs when certain cargoes of TEXs, such as HSP70 proteins, allow TEXs to induce a cascade of inflammatory reactions, leading to the signaling, activation, and increased secretion of the NK cells and macrophages. Also, TEXs can transfer their antigens to DCs, thus growing their presenting ability and increasing $CD8^+$ secretion. (b) Immune suppression of TEXs results from the action of many types of cargo toward an extensive range of immune cells. TEXs nucleic acids (e.g., miRNA) induce polarization of macrophages (M2-like), and TEXs proteins such as HSPs (HSP2) can regulate the differentiation of myeloid-derived suppressor cells (MDSCs). Meanwhile, growth factors such as NKG2D ligand, TGF-ß, and FasL/TRAIL generate simultaneous reactions wherein NK cells and $CD8^+$ T cells cytotoxicity is weakened, promoting Tregs cells proliferation and forcing $CD8^+$ T to death under apoptosis.

ovarian carcinoma, fibrosarcoma, and prostate carcinoma [164]. Also, lung cancer-derived exosomes display a vascular endothelial growth factor protein (VEGF) induced by PMPs mRNA, allowing cancer cells to adhere to endothelial cells [165]. Exosome immune suppressive activity was also analyzed by studying the effect of melanoma and colorectal carcinoma–derived exosomes on the differentiation of human monocyte precursors into dendritic cells [116]. This study confirmed the hypothesis of the tumor cells derived exosomes, mediating the cross-talk between tumor cells and normal cells by carrying tumor cells material and transferring it to the non-infected cells to redefine their phenotype. In this case, we witnessed the breaking down of the maturation and differentiation process of monocyte into dendritic cells. Monocytes are skewed by modifying transforming growth factor-beta (TGF-beta)–secreting myeloid suppressive cells. These profound changes occurred in monocyte as a decreased expression of human leucocyte antigen class II (HLA-DR negativity), a deficit of costimulatory molecule up-regulation, and a maintain of surface CD4 expression. Thereby, the modified cells acquire a new feature consisting of the secretion of TGFh that is involved in disrupting T lymphocytes effector function and proliferation. The exosomes derived from metastatic melanoma have also shown this phenotype change effect of cancer cells derived exosomes toward cells emanating from a non-metastasis environment. Studies have shown that bone marrow-derived cells are highly involved in the formation process of pre-metastatic niche [166], which is the early stage of the creation of primary tumors and the further development of metastasis [167,168]. Although its role is not unveiled, its mediating cross-talk feature between bone marrow-derived dendritic cells (BMDC) and primary tumor cells constitutes the gateway of exosomes involvement in homing both cell types to metastasis sites hypothesis [15,169,170]. Exosomes were first demonstrated to be present in melanoma through an analysis of ras-associated binding (rab)-related proteins and were shown to educate BMDC by upregulating MET onco-protein (tyrosine protein kinase). As a result, BMDC is programmed to present pro-vasculogenic and pro-metastatic phenotype. The induced metastatic niche formation by genetically educating BMDCs demonstrated an ability to early genetically program hematopoietic progenitors' cells to lead them further to express a vasculogenic and metastatic phenotype [171].

A study by Sonja Ludwig and colleagues demonstrated that exosomes emanating from the plasma of patients suffering from head and neck cancer (HNC) contained biomolecules ensuring an immunosuppressing activity. In this study, exosome concentrations were used as a scale to distinguish patients with Alzheimer's disease (AD) from those with no evidence of disease (NED) after oncological therapy. The study unveiled that in the case of early-stage patients (NED), exosomes were highly efficient in suppressing T-cell proliferation while triggering T cells specific suppressors such as Treg. Also, these exosomes were demonstrated to be highly involved in inducing $CD8^{+}$ apoptosis. In addition, AD patients' exosomes were shown to influence NK cells by down-regulating the expression of NKG2D [172].

Exosomes derived from tumor cells are also responsible for skewing bone marrow precursor cells' development. Rivoltini and colleagues were the first to discover that TEXs hindered the differentiation of human monocytes [173,174]. When peripheral blood monocytes (PBMCs) were co-cultured with TEXs, they differentiated into TGF-expressing DCs that released prostaglandin E2 (PGE2) and inhibited the production of cytotoxic T lymphocytes (CTLs). DCs produced in the presence of TEXs exhibited modest amounts of costimulatory molecules and inhibited T cell proliferation dose-dependently. In in-vivo trials in mice later validated these findings through in-vitro studies [174]. In addition to monocyte, TEXs target dendritic cells as well. DCs cells internalize pathogenic antigens (Ags) and self-non-tumor derived Ags. DCs process those materials and present them to the $CD4^{+}$ and CD8+T cells through MHC-2 and MH-1, respectively [71]. However, by interacting with DCs progenitors cells such as myeloid and lymphoid progenitors in the born marrow or even monocyte cells, tumor-derived exosomes induce an abnormal differentiation of DCs that has been proved to be the origin of the inactivity of the immune system toward the invasion of tumors [175,176]. In the cases of breast, lung, cervical, or colorectal cancer, a significant decrease in accumulated matured DCs was noticed; meanwhile, infiltrated myeloid-derived suppressor cells (MDSCs) were highly present [110].

In addition to their involvement in the abnormal differentiation of DCs, exosomes derived from tumor cells were shown to alter the function of other DCs [108]. An experiment ex vivo using tumor lysate unveiled that at the early-stage of tumors, the phenotypic characteristic exhibited by DCs which have not reach full maturation, can still trigger the excretion and proliferation of different types of T cells. Further, it was shown that at an advanced stage of tumor development, the DCs were still unable to reach full maturation. This phenomenon can be noticed by observing its half-mature phenotype that profoundly alters antigen-presenting activities [109,177]. At an advanced stage of tumor development, the amount of DCs is drastically reduced, and does not prevent DCs from displaying many MHC-II molecules coupled with costimulatory CD40. In addition to an increased arginase I, DCs were shown to express co-inhibitory molecules such as B7–H1 as well, while IDO activity was similar to one observed in MDSCs [108,110].

2.2.2. *Immune cells-derived exosomes mediating immune suppression*

Exosomes derived from immune cells and tumor-derived exosomes are engaged in immune combat, also known as a tug-of-war [10], wherein immune-cells derived exosomes are often puzzled and misled by tumor cells-derived exosomes decoy mechanisms. Because of this interaction, immune cell-derived exosomes promote cancer cell proliferation by playing an immune suppressor role [10].

2.2.2.1. Dendritic cells, natural killer cells, and mast cells. In the previous section, the role of exosome derived from DCs and NK cells was introduced as promoting the immune activation. However, the ambivalent nature of exosome previously described, allow them to reverse engineer the basic mechanism of certain cells (DCs or NK cells in this case) and turn them into a threat for the organism. This phenomenon is observed through immune cells mediating feature of presenting antigens to immune system cells so that they can efficiently adapt their response toward invaders. However, while interacting with tumor cells, they appeared to be easily misled by the phenotype profile of the cancer cells they were interacting with. Thus, DCs using their released exosomal vesicles were shown to increase the ability of the tumor to escape the host immune clearance and machinery. These tumor cells are likely to spread more extensively. This mechanism was observed through the proliferation of HCC cells, which were demonstrated to be highly helped by DCs derived exosome (DEX) [179]. Many studies underlined the transfer of genetic material from exosome to recipient cells as the primary way exosomes use to re-educate immune cells and dismiss their activity. However, some studies emphasized the interaction of exosomes and the surface proteins of immune cells, resulting in immune cells' decreased potency upon antigenic invaders. In the acute myeloid leukemia (AML) case, NK-92 cells were demonstrated to be dismissed by some inhibitory agents displayed by exosomes that exhibited an antigenic marker associated with leukemia in addition to the used inhibitory factors [180]. Pro-tumor effect coupled with immune suppression was demonstrated to be related to matrix metalloproteinase (MMP-9) [181]. MMP-9 is highly involved in the lysis of extracellular matrix to achieve standard physiological mechanisms, such as reproduction and development of embryos, but also immune suppressive activity leading to the spread of cancer cells [182]. MMP-9 expression was correlated to the activation of tumor cells' FasL-signaling pathway. Indeed, due to their essential colony of surface FasL, $CD8^{+}$ T cells derived exosomes were hypothesized to be the central element responsible for the MMP-9 breakdown of extracellular matrix proteins that bring an essential proliferation and metastasis of Fas+ tumor cells [183].

A network of small-sized cells called mast cells (MCs) also ensures

intercellular communication of tissues. Like other cell lines, these cells can secrete exosomes to mediate their biological function, including RNA and protein transfer and immuno-regulation [184,185]. MCs were shown to be highly involved in developing inflammatory bowel disease (IBD), disrupting intestinal barriers by downregulating the inflammatory mechanism. MCs-derived exosomes delivered miRNA, specifically miR-233, from MCs to intestinal endothelial cells. Exosomal miR-233 was demonstrated to inhibit tight-junction protein expression, including Protein 1 (TJP-1, ZO-1), Occludin (OCLN), and Claudin 8 (CLDN8) [186]. Also, MCs were shown to promote lung cancer proliferation by activating the c-KIT oncogene. The KIT protein belongs to the family of tyrosine kinase growth receptors [187]. Based on whether or not this protein is expressed in MCs, physicians can diagnose a higher or lower odds of survival for patients suffering from this pathology and are willing to undergo surgery. Indeed, regarding the recurrent pattern of KIT-protein expression in MCs, it was shown that a tumor KIT positive was correlated to a higher rate of death [188].

Meanwhile, the KIT negative was associated with increased odds of survival [189]. Similarly, MCs-derived exosomes were used for proteomic analysis to assess the presence of c-KIT protein from a diagnosis perspective in lung cancer therapy [190]. While interacting with A549 cell lines, exosomes derived from MCs were demonstrated to not modify the phenotype of epithelial cells to a mesenchymal likewise phenotype but only to upregulate the multiple phosphorylations associated with the EMT [191].

2.2.3. *Tumor-associated macrophage*

Exosomes emanating from tumor-associated macrophages (TAM) were shown to present bioactive lipids and biosynthetic enzymes that they were likely to use to inhibit inflammatory signals in tumor cells [192,193]. Also, TAM-derived exosomes were hypothesized to be involved in the mechanism influencing glucose metabolism shift from standard glycolysis to lactate and aerobic glycolysis. Indeed, under aerobic glycolysis, tumor cells produce an extensive range of biosynthetic elements, promoting tumor cells' survival under different types of stress and inhibiting apoptosis [194–196]. This phenomenon is also known as the Warburg effect. It describes the physiological action undertaken by TAM-derived exosomes hypoxia-inducible factor-1 (HIF-1),

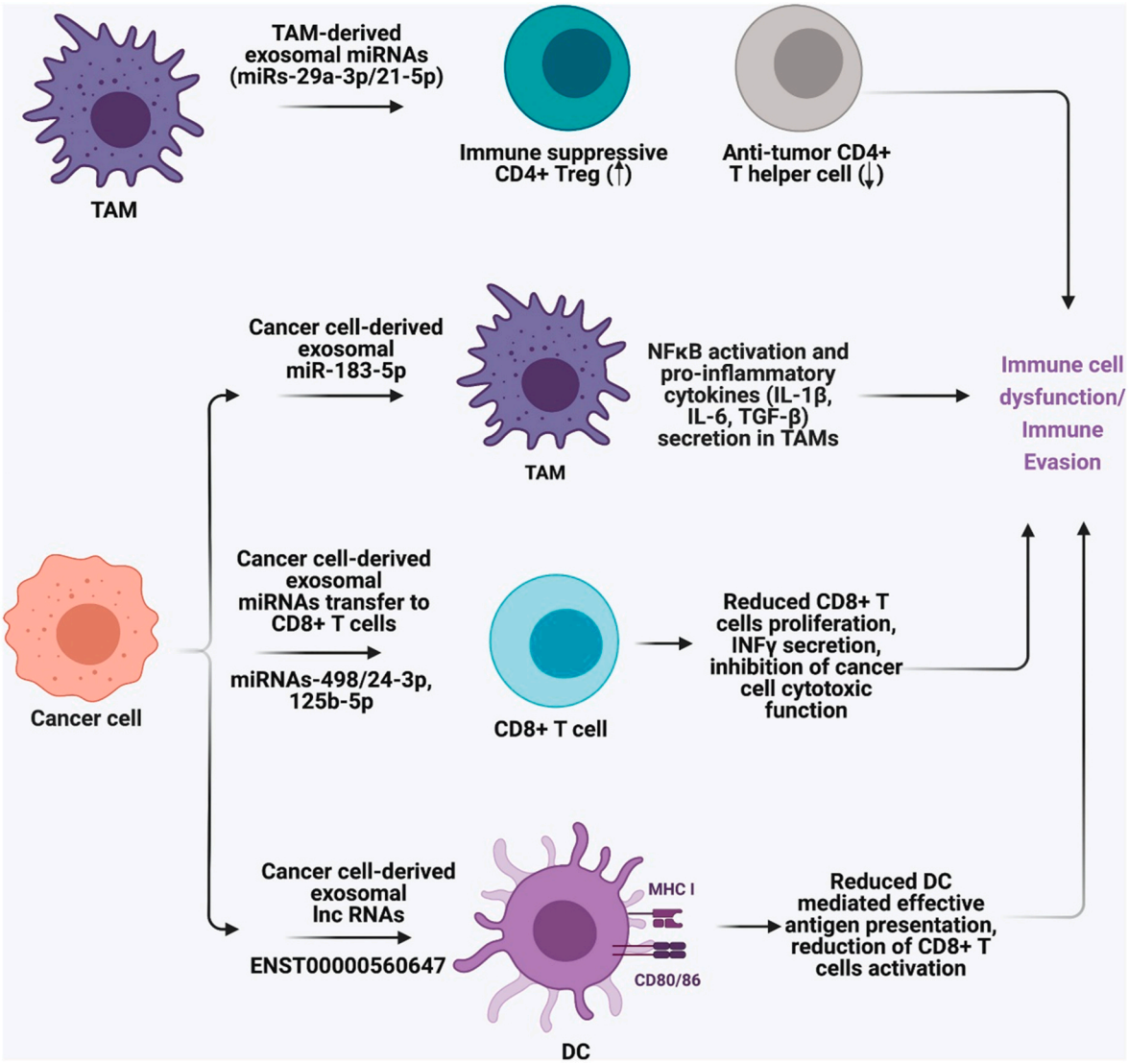

Fig. 7. Tumor cells and TAM exosomal nucleic acids mediating immune suppression [201]. TAM and Tumor cells release exosomal nucleic acids, more specifically miRNAs or lncRNAs, able to be integrated into the genetic program of immune cells. TAM-derived exosomal miRNAs reduce the anti-tumor ability of the host immune system by decreasing the production of CD4+T helper cells while promoting the release of CD4+Treg cells and the expression of growth factors proteins which lead to immune cells dysfunction (e.g., apoptosis of $CD8^{+}$). Similarly, to TAM, tumor cells derived exosomal miRNAs/lncRNAs can affect the immune response globally by diminishing CD8 + T cells secretion and DCs antigen presentation feature.

an oxygen-sensing transcription factor considered the origin of this shift of glucose normal metabolism to aerobic glycolysis.

Furthermore, TAM-derived exosomes were hypothesized to induce HIF1-alpha activity on glucose metabolism by reprogramming cells' phenotype, compelling HIF-1 alpha to interact with TAM-derived exosome long non-coding RNA between stromal and tumor cells [131]. Like lncRNAs, TAM-derived exosomes were demonstrated to release other nucleic acids to mediate an immune suppressive activity. miR-365 displayed high efficiency in upregulating the triphosphate-nucleotide and the induction of enzyme cytidine deaminase in pancreatic ductal adenocarcinoma (PDAC) cells. These coordinated actions result in an essential diminishment of the sensitivity of PDAC cells to gemcitabine [197].

In addition to miR-365, exosomes derived from M2 macrophages were demonstrated to secrete nucleic acids such as miR-21-5p and miR-155-5p. These miRNAs were proven responsible for enhancing the migration of colorectal cancer cells and their ability to move and invade non-contaminated areas [198]. Inflammatory responses are also easily blocked by the downregulation of cytokines mentioned as a capital element for inflammatory immune mechanisms. Cytokines signaling 3 (SOCS3) pathways were shown to endure a considerable suppression of their activity by alveolar macrophages (AM) in EVs [198]. Additionally, TAM-derived exosomes demonstrated metastasis-promoting features. In a study on epithelial ovarian cancer, Treg/T helper (Th) 17 was shown to undergo a reprogramming process by the TAM-derived exosomal miR-21-5p and miR-29-3p and consequently witness their equilibrium being disrupted by the suppression of signal transducer and activator transcription (STAT) 3 [199]. A similar phenomenon is described in Fig. 7 wherein tumor cells and TAM-derived exosomal miRNA are shown to be widely involved in the reprograming mechanism of immune cells, affecting capital features of an efficient immune response such as CD8 + T cells proliferation, cytotoxicity, as well as the presenting feature of DCs (Fig. 7) [200].

2.2.3.1. T-regulatory cells (Tregs). Investigation on T regulatory cells revealed that Tregs, more particularly $CD4^{+}CD25+$Tregs, are mainly involved in the negative regulation of the immune response of the host organism, thus contributing to immunological tolerance [202]. Current research on Tregs showed that other immune cells could release exosomes and extracellular vesicles, which they can use to regulate the immune response. Tregs-derived exosomes can migrate until the target cells and release their cargoes, mainly constituted of bioactive messengers such as miRNA and inducible nitric oxide synthetase (INOs), which demonstrated the ability to inhibit cells growth, induce cellular apoptosis [203,204] and suppress the anti-cancer effect of CTLs [205]. Tregs-derived exosomes inhibited immune cell activities by reducing lipopolysaccharide stimulation of IL-6. This phenomenon results from the increased secretion of IL-10 by DCs after Tregs' uptake of exosomal miRNAs, including miR-150-5p and miR-142-3p [206]. Tregs-derived exosomes features of immune response suppression were used in a medical surgery perspective to address the issue of immunological rejection while a donor's tissue is transplanted. Indeed, in a study by Chen et al., Tregs were demonstrated to have a high efficiency toward the downregulation of self-reactive $CD8^{+}$ T cells, thus creating an immune tolerance for freshly transplanted organs [207]. Further investigation on Tregs' immune response inhibition feature led to the conclusion that this immune suppressive function is provided principally by CD73 [208].

A complementary description of the different cell-secreting exosomes and their cargoes and biological function in the immune system regulation is provided in Table 1 below.

Table 1
Exosome content and cell-emanating exosomes regulate the immune response mechanism.

The origins of exosome	Cargos	Biological function
Dendritic cells	HSP70 and HSP90	Activate $CD4^{+}$ T helper cells and $CD8^{+}$ T cells [66,67].
	CD80 and CD40L	Promote endogenous induction of the IL-2 signaling pathway for immune response activation [68,71,73].
	pMHC-I	Target $CD4^{+}$ T helper cells for CTLs activation and anti-tumor effect [69].
	Alpha-Phetoprotein (AFP)	Activate $CD8^{+}$ T cells, induces inflammatory element release, and inhibit immunosuppressive elements [74].
$CD8^{+}$ T cells	MHC-I	Promote cancer cell recognition and destruction [78,79].
	IL-2	Enhance cancer cell destruction [81].
	IL-12	Stimulate a more extensive range of $CD8^{+}$ T cells [82].
$CD4^{+}$ helper T cells	CD4, MHC II, LAMP-1, TCR, LF-A, CD25, and FasL	Activating CTLs and phagocyte B cells promotes the antitumor effect [83,84, 86–88].
NK cells	FasL	Promote infected cell clearance by inducing apoptosis [61].
	TNF-gamma	Promote activation of the inflammatory response [62].
	miR-185-5p	Directly targeting oncogene MCYN, TGFBR1, TGFBR2, and AURKA [63,64].
Tregs cells	/	Bioactive messengers, including miRNA and INO, inhibit cell growth, induce cell apoptosis, and suppress the anti-cancer effect of CTLs [194–196].
	miR-150-5p, miR-142-3p	Increase secretion of IL-6, inhibit immune response mechanism [131].
	/	Downregulate $CD8^{+}$ T cells and enhance immune tolerance for transplanted organs [59,197].
B lymphoma cells	CD73	The core element responsible for immune suppressive features [208].
	HSP60, HSP90, MHCI, II, CD40, CD86, RANTES, and IL-1Beta,	Promote CTL activation, target immune suppressive elements, and induce the release of inflammatory factors [59,89].
Tumor-Associated Macrophage (TAM)	miR-29-3p/21-5p/183-5p	Immune suppression of $CD4^{+}$ T cells [199].
	miR-498	Reduction of CD8 +T cell proliferation and immune impotency [124].
	miR-24-3p	Inhibit T cell proliferation, induce IFN-γ decrease, expansion of Foxp3+Tregs [125].
	miR-365	Enhance the resistance of tumor cells [204].
	miR-21-5p/29-3p	Promote tumor metastasis by unbalancing Treg/Th17 [199].
	miRs-155-5p/21-5p	Enhance colorectal cancer spread [198].
	Lnc.RNAs	Promote immune suppression.

(*continued on next page*)

Table 1 (*continued*)

The origins of exosome	Cargos	Biological function
	CANX, COX2 TBXAS1, CYP	Inhibit inflammatory signal of tumor cells [192].
Tumor cells	Lnc.RNAs (lncRENST00000560647)	Inhibit DCs presenting antigen feature and stop $CD8^+$ T cells immune response. Promote disease spread and tumor growth [127–130].
	Lnc.RNAs (SOX2, DLX6-ASI)	Promote M2 macrophage polarization [136].
	Lnc.RNAs (MALAT-1)	Upregulate proto-oncogene Maf associated with higher patient mortality [137–140].
	Lnc.RNAs (UCA1, NEAT)	Promote cancer development [135,141].
	Lnc.RNAs (HISLA)	Promote disease and tumors progression and brings chemoresistance through lactate-HISLA interaction [131–133].
	TUc.339	Promote cancer cell migration and invasion [142–144].
	Uc.889	Promote angiogenesis in lymph [145].
	Uc.138	Promote chemotherapy resistance [146].
	Uc.63	Promote germinal center cell progression and growth by upregulating NK-B signaling [146].
	Uc.339	Promote cancer cell growth [149].
	miR-146	Promote angiogenesis and metastasis [121].
	miR-183-5p	Promote pro-inflammatory secretion in breast cancer [123].
	miR-498 and miR-3187	Decrease $CD8^+$ T cells secretion by binding to its 3′ UTR TNF-α site, inhibit TCR signaling by binding to CD45 PTPTC 3′UTR site [124].
	miR-24-3p	Weaken the immune response of T cells, and promote the secretion of immune suppressive Foxp3+ Tregs [125].
	mir-125-5p	Promote apoptosis [126,127].
	Circ-0074854	Promote M2 polarization and tumor cell growth [151].
	Circ-UHRFI	Inhibit the function of NK cells [152].
	Circ-CPA4, Circ-002178	Reduce $CD8^+$ T cell function and promote cancer spread [153].

3. Exosome tumor-targeting features: challenges and strategies of enhancement

3.1. Challenges of exosome tumor targeting

The profile of natural transporter renders exosomes significant advantages when it comes to immunotherapy. In cancer treatment, more particularly, exosomes offer the possibility of being coupled with various molecules known to be efficient toward tumor eradication, as supported by certain in vitro studies which showed that exosomes emanating from cells could be targeted homogeneously [209]. However, regarding the in vivo studies, it was demonstrated that the targeting ability of exosomes could not be fully foreseen since the result can vary from one experiment to another. For instance, in the studies led by Smyth and colleagues, the intravenous injection of exosomes released by 4T1, MCF-7, and PC3 cells, showed minimal tumor accumulation [210]. Another in vivo study was carried out to inhibit the scavenger receptor-A (SR-A). SR-A was inhibited through dextran sulfate, and its inhibition led to the impairing of the monocyte/macrophages, which mediate the clearance of hepatic in mice, thus resulting in a fivefold increase of exosome accumulation [211]. Therefore, exosome, although a suitable carrier for cancer therapy [212], requires certain molecular modifications to upgrade its tumor targeting ability [213,214].

3.2. Strategies for the enhancement of exosome tumor targeting feature

The enhancement of nanovesicle targeting features toward tumors is a new era of scientific research, which has led to the design of multiple strategies to overcome exosome off-target issues toward tumors. Two main approaches were developed: the molecular method and the mechanical process, which were demonstrated to be much more precise and efficient than the more common methods.

3.2.1. Molecular methods for the enhancement of exosome tumor-targeting features

The strengthening of tumor targeting ability of exosomes through molecular methods is mainly based on controlled biogenesis of exosomes. The displayed proteins by exosomes must be accurately predicted and known to be able to add valuable features in tumor targeting [215]. In 2020, a study by Kamerkar and colleagues highlighted the exciting capacity of exosomes secreted by normal foreskin fibroblasts to efficiently deliver KrasG12D siRNA to pancreatic tumor cells in vivo [216]. The effects of the successfully delivered siRNA were multiple in a pancreatic cancer mouse-based animal model, including the significant suppression of tumor growth, the effective downregulation of targeted KrasG12D, and the increase of survival rate of inoculated subjects [216]. This ability of exosomes secreted by fibroblasts to achieve the previously cited effects was mainly related to the proteins they expressed on their membrane, as stipulated by the molecular methods to improve the feature related to the tumor targeting. A recent study suggested another approach to show the importance of the exosome proteins expression profile. For this purpose, Zhou and colleagues altered cells secreting exosomes to obtain exosomes with a surface enriched with much more ligands than naturally occurring. This model targeted chronic myeloid leukemia (CML) by the controlled expression of Lamp2b-IL-3 on the exosomes surface. The strategy is based on the fact that the overexpression of IL-3 receptors by CML constitutes a highly adherent field for exosomes expressing Lamp2b-IL-3 ligand, which can promote the inhibition of CML cells from growing in vivo and in vitro [217].

The molecular enhancement of tumor targeting by exosomes can be achieved by combining exosomes with other molecular compounds, such as targeting peptides. These strategies are labeled a spatial-temporal pattern of exosome engineering and were demonstrated to transport therapeutic cargo with greater precision. Exosomes with miR-HER2 (human epidermal growth factor receptor 2) loaded on them are ligand-coated, allowing them to bind to HER2 on the surface of human laryngeal carcinoma cells and enter HER2-positive cells preferentially (Engineered exosomes from different sources for cancer-targeted therapy) [218]. The additional peptide coupled to the loaded miR-HER2 exosome was particularly promising as a molecular strategy for exosome tumor targeting strengthening since it displayed a higher tumoricidal effect than the exosome deprived of coated peptides [219]. Hepatocellular carcinoma (HCC) proliferation was discovered to be inhibited by exosomes-like nanovesicles (ELNVs) derived from the plant Asparagus cochinchinensis (ACNVs) via the activation of the apoptotic pathway [220]. Despite the substantial anticancer effects of natural ACNVs, the liver and spleen's macropinocytosis of the mononuclear phagocyte system (MPS) ensure that exosomes are quickly cleared from the bloodstream and accumulate very little in the tumor location. To alter the pharmacokinetic profile of ACNVs, researchers coated ACNVs with di-stearoyl phosphoethanolamine-polyethylene glycol 2000

(DSPE-PEG). As a result, the PEG-ACNVs effectively inhibited tumor growth in vivo while having less negative effects, and they also accumulated in large quantities in the liver [220].

The frequent glycolysis occurring in the TME, leading to the high production of lactate, is one of the hypotheses explaining the acidic nature of the TME but represents an important parameter to consider for the tumor-targeting modification of engineered exosome [221]. As an illustration, exosomes coated with i-motifs, a DNA strand rich in cytosine and pH-responsive [222–224], might deliver DOX to breast cancer and release DOX in an acidic manner [225]. Additionally, after being endocytosed by cancer cells, sodium bicarbonate ($NaHCO_3$) contained in exosomes could quickly produce CO_2 bubbles, successfully releasing paclitaxel (PTX) [226]. A pH and temperature-sensitive polymeric adhesive that can be tailored synthetically to bind to tumor cells at pH 6.8 but not at pH 7.4 at 37 °C was created, except i-motifs and SBC. This glue can be crucial in modified exosomes because of its pH sensitivity [227]. Consequently, using acidic TME to release therapeutic cargoes in a controlled manner is a viable strategy for creating a clinically phased drug delivery system.

3.2.2. Mechanical methods for enhancement of exosome tumor-targeting features

Mechanical methods consist of designing superparamagnetic nanoparticles, in which exosomes must be trapped along with the magnetic field carried by the superparamagnetic particles. This technique has displayed high efficacy in taking exosomes and delivering specific cargoes to the tumor site. The superparamagnetic exosomes nanoparticles approach was used by Qi and colleagues, who achieved to deliver doxorubicin and suppress the tumor growth while applying it to a liver cancer-based animal model bearing subcutaneous tumors [228]. This technique has been persuasive among the scholar community and resulted in an increased request for innovation in this area.

Superparamagnetic iron oxide nanoparticles (SPIONs) were designed by conjugation with exosomes secreted by neutrophils. The result showed a satisfying accumulation of the formulation at the tumor site while putting it under an external magnetic field [229]. Similarly, SPION-decorated exosomes and (TNF-alpha)-loaded displayed high efficacy in enhancing cancer targeting under an external magnetic field while coupled with mitigating toxicity in vitro and in vivo [230]. External laser irradiation and magnetic targeting also produce substantial tumor-targeted therapeutic benefits, particularly in photothermal therapy (PTT). For instance, drug-loaded thermosensitive liposomes and exosomes may be combined. The hybrid nanovesicles impressively accumulate at tumor locations and significantly target the mouse homologue tumor. The hybrid nanovesicles impressively gather at tumor locations and efficiently target the mouse homologue tumor. Notably, the photothermal agents included in the modified vesicles during laser irradiation could produce outstanding photothermal therapeutic effects [231]. Similarly, external near-infrared irradiation (NIR) could cause the controlled release of chemotherapy medicines in glioma [232,233]. However, although displaying a satisfying drug delivery feature and a controllable drug release, laser irradiation remains relatively inconvenient for clinical studies due to the difficulty of repeatability of the technique, including the high cost or the damaging side effects related to the radiation [163,234].

Additionally, exosome engineering focuses on using US waves, which recently kept arousing researchers' interest. One of the examples of this strategy is the Ce6 which was fused with exosomes with the integration of exosomes' surface of CP05-TK-mPEG for the delivery of Bm7 mRNA. The nucleic acid delivery was successful with a controlled release of Bm7 mRNA. The nanostructure was submitted to US irradiation, which impelled reactive oxygen species (ROS) produced by Ce6 to break the thioketal (TK) [235].

Combining internal forces with outside physical interferences, such as SPION with a magnetic field, thermosensor with laser irradiation, and US with Ce6, allows better tumor-targeting drug delivery geographically and temporally.

4. Concluding remarks and future perspectives

This review highlights the gradual importance acquired by exosomes extracellular vesicles. Over the past twenty years, exosomes relentlessly demonstrated significant features critical to the drastic increment of nanotechnology and nanomedicine fields. Although attracting a growing interest in pharmaceutical sciences, biochemistry, and molecular biology, certain aspects of this review aim to arouse the scientific community's attention to the unexploited mechanisms regulating exosome biological activity that are highly influenced by its biogenesis. Exosome biogenesis appears to be the origin of its phenotypic nature and immune regulation ability. Thus, the deep comprehension of exosomes' underlying mechanism, allowing them to ensure the crosstalk between cells of different characters, is becoming highly necessary. For instance, the ESCRT-dependent pathway has been highly developed and was described as the main road followed by endosomal material to maturate into an extracellular vesicle. However, ESCRT-dependent and independent pathways remain enigmatic in specific areas, such as the interaction patterns followed by ESCRT subunits proteins to bind a type of cargo more than others. These sorting preferences lead to exosomes displaying rich content; meanwhile, other exosomes seem deprived of essential features. More importantly, exosomes enriched with a high diversity of RNAs proved more likely to reeducate cells and trigger multiple reactions often related to immune activation or suppression. Although particularly promising, exosomes present certain flaws related to their capacity to target tumors while efficiently being used as a delivery vehicle. Techniques of enhancing exosome targeting ability include the biochemical strategies that consist of coupling it with certain molecules such as lipids and building a cell's culture in which exosome biogenesis can be meticulously controlled to shape them with an ideal protein profile for the desired purpose. Strategies involving irradiation or magnetic field can also be used to reduce the issue of exosomes off-targeting since studies have displayed that despite the high cost of these mechanical methods, and their difficulty of repeatability, they guarantee satisfying results for the delivery and the controlled release of nano-drug at the tumor site by exosomes. Exosome biogenesis in different cells should be addressed deeply since proteins involved in the production of exosomes and cell specificities are aspects to consider with higher interest for a better perspective in designing more accurate drug delivery carriers in immunotherapy. Thus, elucidating the bio-molecular mechanisms involved in the exosomal packaging of RNA may present an impactive outcome, especially in designing a culture of cells programmed to produce specific kinds of exosomes regarding the need. The use of a magnetic field or irradiation must be developed to reduce the side effect related to the radiation or the high cost of the material, which are the main challenges encountered in the engineering exosome for tumor targeting. These engineered exosomes would be used according to their content to simulate cancer or immune-sensitive environments that an exosome mediator would fully regulate.

Ethical statement

As this article is a review paper, we did not need "ethics approval," and there was no need for "consent to participate."

CRediT authorship contribution statement

Julien Milon Essola: did the research work, the writing and editing of the manuscript. **Mengjie Zhang:** did the research work, the writing and editing of the manuscript. **Haiyin Yang:** did the research work, the writing and editing of the manuscript. **Fangzhou Li:** did the research work, the writing and editing of the manuscript. **Bozhang Xia:** did the research work, the writing and editing of the manuscript.. **Jacques François Mavoungou:** did the research work, supervised the research,

and revised the manuscript. **Abid Hussain:** did the research work, supervised the research, and revised the manuscript. **Yuanyu Huang:** did the research work, supervised the research, and revised the manuscript.

Declaration of competing interest

The other authors declare no competing interests.

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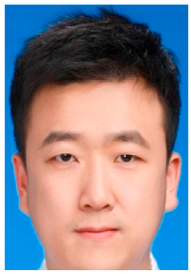

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