

The interaction between tumor derived exosomes and various cells in the progress of tumor

Xiaoqing Han ¹, Yun Long ², Jianv Yu ^{3,*}

¹ Shanghai Institute of Technology, Shanghai, China

² Guangzhou Medical University, Guangzhou, China

³ Wenzhou Medical University, Wenzhou, China

* Corresponding Author Email: 13211020479@stu.cpu.edu.cn

Abstract. Exosomes, actively secreted from cells to the outside, are a series of small vesicles which is full of biological functions, which bring a variety of active elements (lipids, proteins, nucleic acids and other biological information molecules). They are instrumental in impacting immune response, tumorigenesis, tumor invasion and metastasis. Exosomes that come from tumor can influence the growth of tumor and metastasis by regulating different types of cells, like endothelial cells, epithelial cells and immune cells. Exosomes can open the close connection of endothelial cells, enhance the infiltration of tumor cells, and promote tumor angiogenesis. In the meantime, exosomes can also target epithelial cells to promote the process of tumor metastasis. This impact is mainly reflected in the key event——EMT caused by exosomes, including the direct effect of exosomes and the indirect effect of exosomes on ECM regulation. The former is divided into three parts: inducing factor, signaling pathways and miRNAs, while the latter covers the remodeling of ECM by exosomes and the ECM modification led by the interaction between exosomes and other cells. Besides, Tumor-derived exosomes can inhibit and activate immune cells which cause tumor cell immune escape, inhibit anti-tumor immunity, and promote the killing ability of immune cells. This review summarized the function of exosomes secreted by tumor cells that it may have a significant impact on the development of tumors for interfering with the functioning of immune cells, endothelial cells, and epithelial cells, and gave some prospective exosome-based therapy methods.

Keywords: Tumor Exosomes; Endothelial Cells; Epithelial Cells; Immune Cells.

1. Introduction

Tumor development process were investigated for very long time. In the last decades, attention has been focused on the accumulation of driver mutations and suppression gene dysfunction in cancer cells. However, the microenvironment of developing tumors acts as a natural selector, leading to the expansion of optimally adapted ("better fit") clones over time. It is very recently recognized that the interaction among individual tumor cells, the normal cells of the original tissue and their abiotic environment is critical to tumor development.

Among various cellular crosstalk pathways, extracellular vesicles obtained more and more notice because of their emerging importance discovered by recent researches. The growth factor in the vascular endothelial-VEGF receptor (VEGF-VEGFR) signaling route can be the target with the greatest potential for angiogenesis., because it plays a key role in angiogenesis and tumor growth. The exogen secreted by tumor cells is one of the dominating mechanisms for inducing angiogenesis. A host of evidence have revealed that EMT regulatory factors liberated by tumor cells can induce the onset of EMT and malignant transformation of epithelial cells and EVs (including exosomes and macrovesicles) play a momentous part as mediators. For example, Xiang Li and colleagues found that exosomes produced by rat alveolar macrophages can act on tracheal epithelial cells to promote EMT, and explained that the exosome miR-21-5p drives the process by means of the TGF- β 1/SMAD signaling channel targeting SMAD7[1].Marc A Antonyak's team demonstrated that the macrovesicles of two distinct human cancerous cells-MDAMB231 breast carcinoma cells and U87 glioma cells-can transmit transformed cancer cell features to normal fibroblasts and epithelial cells (e.g., independent anchor growth and improved survivability.)[2].Some experiments prove that

tumor-derived exosomes can affect tumor cells by affecting the role of immune cells. Lundholm and his team confirmed that when exosomes are released from prostate cancer cells, they can promote the escape of tumor immunity by down-regulating NK cells. This review will focus on the role of exosomes in the interplay of the tumor with endothelial cells, epithelial cells and immune cells, respectively.

2. Endothelial cells are involved the formation of an important component of tumor microenvironment as well as promote tumor angiogenesis

Primary tumor location includes the primary tumor lesion as well as the environmental cellular environment, tumor microenvironment. The tumor microenvironment contains a variety of malignant bystander cells, including endothelial cells, immune cells, and cancer cells with fibroblasts, additionally extracellular matrix as well as other important factors secreted into tissues[3]. Tumor formation, growth and metastasis are closely related to the internal and external environment of tumor cells. This includes not only the structure, function and metabolism of tumor tissues, but also the internal environment of the tumor cells themselves. Tumor cells can modify and regulate their own conditions for survival and growth through autocrine and paracrine and promote tumor growth and development. Tissues in the body can also limit and influence the formation and growth of tumors through changes in metabolism, secretion, immunity, structure and function. Heterogeneity of tumor cells can be enhanced by the heterogeneity of the tumor microenvironment. The primary tumor site is regulation by tumor-induced interactions between cancer cells, cancer cells and the tumor microenvironment[4].

Exosomes derived from cell lines or plasma cancer types from various human cancers, including glioblastoma, pancreatic and nasopharyngeal carcinomas, are known to be potent inducers of angiogenesis in vitro and in vivo[5]. Tumor cell derivation exosomes transport a number of important miRNAs and lncRNAs into the microenvironment of cancer cells, generally composed of fibroblasts, endothelial cells, macrophages, as well as epithelial cells. This results in impaired cell acquisition, infiltration, angiogenesis of tumor cell phenotypes, as well as tumor innervation.

Endothelial cells interact with cancer cells to promote angiogenesis around cancer cells. The angiogenesis characteristics of human umbilical vein endothelial cells will be enhanced and promoted by exogenous epithelial ovarian cancer cells. When human umbilical vein endothelial cells carrying related lung adenocarcinoma transcript 1 are transfected from these cells (leptin, basic fibroblast growth, angiogenesis, IL-8, placental growth factor, epithelial-derived neutrophil activator 78 and VEGF-D), they will have the effect of stimulating the expression of vascular endothelial growth factors[6]. Furthermore, human umbilical vein endothelial cells can internalize miR-25-3p that exists outside the colon cancer cell membrane, resulting in reduced expression of KLF2, which inhibits angiogenesis, and KLF4, which maintains endothelial cell barrier integrity[7]. Tumor release to tumor cell external miR-221-3p enhances lymphatic formation as well as lymph node metastasis of cervical squamous cell carcinoma by targeting human epithelial endothelial cells leading to activate the signal axis—serine/threonine protein kinase Akt/miR-221-3p-angiogenesis-1 extracellular signal regulatory kinase[8].

In particular, under hypoxia conditions, the exosomes from tumor cells promotes the production of blood vessels by regulating the characteristics of endothelial cells. Exosomes bearing tetraspanin may promote tumor growth by increasing angiogenesis[9].

Then to summary the downstream effect of the interaction between tumor and endothelial cells, the pathway can be concluded as when exosomes activate the cell response of endothelial cells, they give reaction to promote tumor cells migration and invasion in different ways. All in all, they can be classified into vascular sprout, elongation and tumor cells intravasation, which are dependent on the molecules inside the exosomes.

2.1. Adhesion-associated molecules

Exosome-transported soluble E-cadherine heterodimerized with vascular endothelial cadherine in endothelial cells to activate β -catenin and NF- κ B signaling for angiogenesis[10].

Furthermore, several reports have suggested that adhesion-related molecules on the surface of exosomes, such as tetraspanins, glycoproteins, and integrins, determine which cells receive the exosomes[11]. TSPAN8- α 4 integrin (CD49d) in exosomes promoted the binding and uptake of exosomes by endothelial cells, thus promoting angiogenesis [12].

2.2. cytokines

Exosomes can release their own cytokines outside the cell and act on endothelial membrane surface receptors, leading to angiogenesis and promoting tumor migration. Exosomes derived from tumor cells contain cytokines such as angioauxin, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), which promote tumor vasculature formation in various ways.

VEGF contained in exosomes promotes the mitosis of vascular endothelial cells by activating the formation of phosphatase C and the second messenger. It can induce the expression of fibrinolytic enzymeogen actives, so that extracellular protein hydrolysis and the degradation of the basement membrane, thus promoting the migration and hyperplasia of vascular endothelial cells. VEGF can also increase the permeability of blood vessels, cause fibrinogen and other leakage, forming a matrix for the growth of vascular endothelial cells. FGF promotes the regeneration of blood vessels by stimulating collagen formation, or enhances the ability of vascular endothelial cells to resist apoptosis, and studies have found that FGF and VEGF have synergistic effects[13].

2.3. miRNAs

The exosomes of malignant melanoma cells contain miRNA-9, which can promote angiogenesis by activating the JAK-STAT pathway after being ingested by endothelial cells. After miRNA transmitted from the exosomes of human leukemia tumor cells is ingested by umbilical vein endothelial cells, it can lead to increased tumor cell migration and the formation of vascular cavities. The study found that the exosomes secreted by human nasopharyngeal carcinoma C666-1 cells can promote angiogenesis. After the exogen is swallowed by human umbilical vein endothelial cells, it changes the corresponding proteins in endothelial cells, suggesting that the exogen may promote angiogenesis by changing the expression level of endothelial cells[14].

On the other hand, exosomes can open tight junctions to increase tumor cell intravasation. Breast cancer exosomes containing MiR-105 reduce the expression of ZO1 in endothelial cells, thereby disrupting tight junctions between endothelial cells[15].

2.4. Pathway-activating molecule

Endothelial tip cell exosomes with a huge number of delta-like-4 protein, which hyperplify nearby capillaries by activating the Notch pathway of the vascular endothelial cells around them[16].

To summarize, so far, more and more literature shows that exosomes play an important role in promoting angiogenesis and inhibiting angiogenesis, phenotypic changes and migration of tumor endothelial cells.

3. The roles of exosomes on epithelial cells

Epithelial cells are immotile polarized cells, and their intercellular junctions composed of key protein complexes are of great significance for maintaining the structural integrity and function of epithelial cells. Loss or instability of key proteins in the intercellular junctions can easily lead to EMT and tumor metastasis. Most of the tumors are drawn from epithelial tissues, and their morphology and function are closely related to the evolution of tumors. Plentiful studies have implied that exosomes can target epithelial cells to foster the invasion and spread of tumors through inducing EMT process,

principally including the direct effects of inducing factor, signaling pathways and miRNAs and the indirect effects on ECM regulation.

3.1. Exosomes directly promote the occurrence of Epithelial–mesenchymal transition (EMT)

EMT is a physiological or pathological process defined by the transformation of epithelial cells into mesenchymal phenotypic cells in a specific manner. On the grounds of the certain biological circumstance of its origin, EMT can be split into three types. Related to the normal development and repair of body damage, Type I and type II are necessary for physiological activities of the human body. Type III is manifested in a pathological state that tightly linked with tumor metastasis. EMT is characterized by inhibited epithelial cellular markers (e.g., E-cadherine and cytokeratin) and enhanced mesenchymal cellular markers (e.g., vimentin and N-cadherine). Changes in the expression of these markers will bring about a reduction in the cellular junction between transitional cells and adjoining epithelial cells, and increase the release of enzymes that break down the extra-cellular matrix, resulting in the abrogation of epithelial cell polarity and the acquisition of mesenchymal phenotypic traits that possesses the capacity to migrate and invade [17].

The emerging EMT is under the domination of multiple pro EMT factors (e.g., TGF- β , HIF-1 α , TNF- α (NF- κ B), catenin β 1) and signaling pathways (e.g., SMAD and WNT signaling pathways). Exosomes from tumor cells or other sources can secrete inducible factors and modulate major transcription factors (e.g., SNAIL, TWIST and ZEB) through corresponding signal pathways to change the gene expression to raise or diminish the expression of relevant cell markers and eventually trigger EMT, thereby enhancing the capability of tumor invasion and metastases, and facilitating the tumor progression as well.

TGF- β is one of the critical EMT promoting cytokines secreted by exosomes. The key effectors induced by TGF- β are the transcriptional repressors of E-cadherine (e.g., SNAIL1, SNAIL2 (also known as SLUG), ZEB and TWIST). It can participate in the induction of EMT via SMAD or non-SMAD pathways (such as PI3K/AKT, MAPK signaling pathway), and also directly affect the EMT associated factors by other signaling pathways (such as NOTCH, WNT, INTEGRIN, STAT3 pathway etc.) [18].

In the SMAD signaling pathway, SMAD2 and SMAD3 are activated by tetrameric complex receptors (TbRI and TbRII) and then combined with Smad4 to form a compound, which regulates pro EMT transcription factors (e.g., SNAIL and SLUG) to coordinate epithelial and mesenchymal cell markers, consequently contributing to the EMT process. For example, LPS stimulates exosomes produced by macrophages to activate TGF- β /SMAD2/3 signal, which subsequently increases EMT related proteins vimentin, alpha smooth muscle actin (α -SMA) and type 1 collagen (Col1) in human type II alveolar epithelial A549 cells to promote EMT of cells [19].

In the non-SMAD pathway, TGF- β is able to take control of the transcription factors by mediating PI3K-AKT-mTOR signaling pathway to reach the effects of EMT. Researchers have made it clear that by means of a crosstalk between the AKT/PKB and TGF- β signaling, PI3K/AKT signaling induces TWIST1 phosphorylation to cause EMT and tumor metastasis [20].

Acted as a vital regulator of EMT, HIF-1 α can up-regulate EMT transcription factors to suppress the e-cadherine expression that is to the benefit of the EMT genesis. In nasopharyngeal carcinoma, the oncogene LMP-1 increases the level of HIF-1 α in exosomes secreted by relevant cells to adjust the representation of EMT markers and ultimately drive the EMT to occur [21].

The Wnt/ β -catenin signaling pathway is one of the most common target pathways to initiate EMT by activating transcription factors involved with EMT like SNAIL, SLUG and TWIST. In the context of WNT signaling, GSK-3 β is blocked and unable to phosphorylate catenin β and SNAIL, hence prompting the course of EMT and the survival rate of tumour cells during diffusion and invasion [22]. Exosomes secreted by human adipose-derived mesenchymal stem cells can give rise to the migration phenotype of breast cancer epithelial cells through Wnt signaling pathway [23].

Carcinogenic microRNAs (miRNAs) contained in exosomes, such as miR-128-3p and miR-193a-3p, are also capable of achieving the effect of regulating EMT by increasing or decreasing correlative

cell markers through SMAD, STAT3 pathway and other mechanisms in an analogous method. Researchers have brought to light that the exosome content miR-128-3p conditions EMT in colorectal cancer cells by straightforwardly restraining the downstream target gene FOXO4 to enable TGF- β /SMAD and JAK/STAT3 signaling[24]. MiR-193a-3p, miR-210-3p and miR-5100 of exosomes can provoke EMT through STAT3 signaling pathway and sequentially impel cancer cell invasion[25]. Furthermore, exosomes secreted by CD103-positive cancer stem cells (CSCs) transport miR-19b-3p into clear cell renal cell carcinoma (CCRCC) cells to repress the expression of PTEN and in turn elicit the progress of EMT, conferring the higher metastatic capacity of CCRCC[26].

3.2. Exosomes take part in the regulation of ECM components leading to EMT

Extracellular matrix (ECM) is a noncellular substance existing between cells, whose major components encompass glycosaminoglycan and proteoglycan, collagen and fibronectin. As the basic composition of tissues, it is a secreted product of cell life activities and normally exists in the form of fiber network. On account of its complicated and diverse constituents, ECM is involved in various fundamental physiological activities, such as cell morphology, proliferation and differentiation, migration, communication, recognition and adhesion. In the meantime, it is also associated with the pathological process, particularly the invasion and metastasis of tumor cells in the progress of tumorigenesis and development. A multitude of studies have demonstrated that exosomes accelerate tumor metastasis via remodeling ECM, especially for epithelial cell-derived tumors. The active proteases (MMPs etc.) contained in exosomes are able to degrade ECM components (collagen, etc.), and accordingly result in the deficiency of epithelial cell phenotype and the obtainment of mesenchymal cell phenotype (EMT), which is favorable for the invasion and migration of tumor cells. MMP13 can change the components of ECM, and thus exosomes comprising MMP13 conduce to the metastasis of nasopharyngeal carcinoma under the influence of ECM degradation[27]. CD151 and Tspan8 positive exosomes from ASML recruit integrins and proteases (MMP9 and MMP13 etc.), and degrade collagen and fibronectin to modify ECM, meanwhile enhancing cell invasion[28]. Exosomes originated from lung CSCs upregulate the levels of associated matrix metalloproteinase (MMP-9 and MMP-1), modifying the corresponding cadherine proportions to favour EMT and invasiveness of lung cancer cells[25].

In addition, exosomes can also interact with cancer-associated fibroblasts (CAFs), endothelial and other cells to remodel ECM and stimulate the process of EMT. The phenotype of fibroblasts will be altered after interacting with tumour cells. And this sort of fibroblasts, termed as cancer-associated fibroblasts (CAFs), gain a new capacity of promoting tumor development, which can transform ECM contents and structures to mediate the migration and invasion of tumor cells. CAFs amend ECM through matrix metalloproteinase (MMP), RhoA, ROCK, MyoII, and palladin to generate a microenvironment that supports tumor cell invasion and migration[29]. MiRNAs in tumor exosomes play a significant part in the formation of CAFs. MiR-27a in exosomes derivatives of stomach cancer cells regulates the conversion of fibroblasts into CAFs, enabling them to perform the function to assist remodeling the ECM[30]. MiR-9 and miR-200s (miR-200a etc.) has a similar effect[31, 32].

4. Interaction with each other between exosomes coming from tumor and immune cells

Immune cells and cytokines in human body play a vital element in the occurrence and progression of tumors. Tumor derived exosomes (TEX) have reactions of different sort on immune cells, and there are many ways to influence them: inhibiting immune cells activities and promoting their proliferation, regulating the expression of related cytokines, promoting tumor immune escape, activating the immune system, and playing an essential role in the development and occurrence of human tumors. Studies have confirmed that when exosomes come from nasopharyngeal carcinoma cells, these exosomes can recruit CD4⁺T (CD4⁺T is a kind of lymphocyte) to induce them to differentiate into regulatory T cells. The induced adaptive regulatory T cells are nearly related to the

emergence of autoimmune diseases, and their improper expression can lead to autoimmune diseases, and then participate in the peripheral immune tolerance of tumors, so that nasopharyngeal carcinoma cannot be recognized by the immune system, and then nasopharyngeal carcinoma can develop[13].

Lundholm and his research team confirmed that when exosomes are released from prostate cancer cells, exosomes can inhibit the cytotoxic reaction mediated by NKG2D and promote the escape of tumor immunity by downregulating the expression of NK cells (an important immune cell in the body) and the activation receptor of CD8⁺ T cells - NKG2D (a ligand that can bind to a variety of lymphocyte subsets). The research of Huang Shaohong's team proved that exosomes produced by non-small cell lung cancer contain a large number of EGFR (epidermal growth factor receptor), and regulatory T cells are induced by these exosomes, which have a strong inhibitory effect on tumor specific CD8⁺ T cells. Therefore, TEX exist the function of anti-tumor immunity, and thus TEX play a vital function in the growth and progress of tumor.

4.1. TEX regulates gene expression in target cells

One of the mechanisms by which TEX change the gene expression of cells is to change the cytokine and chemokine expression profile of macrophages, activate NF-κB pathway, affect the gene expression of macrophages, and promote the immune escape of tumor cells. Melanoma follows this mechanism, and tumor cells escape immune monitoring and thus proliferate indefinitely. TEX can also induce resting regulatory T cells to express high levels of CD39 and adenylyate, up regulate the expression of immunosuppressive genes in activated terg, and promote the latter to rapidly translate into inhibitory proteins, up regulate TG-β、 the function of immunosuppressive molecules such as IL-10 and COX-2, as well as the up regulation of inhibitory gene expression in CD4⁺ T cells, the loss of CD69 expression and the decline of CD4 + T cell function, will affect the cytoactive of CD4 + T cells and lead to the loss of their immune activity[33].

4.2. TEX promotes the activation and proliferation of immunosuppressive cells

The formation and shaping of tumor microenvironment (TME) are involved by myeloid derived suppressor cells (MDSCs) and Tregs with immunosuppressive function. Among the exosomes secreted by tumor cells, the exosomes produced by glioma (GDE) can inhibit the differentiation of MDSCs and promote their proliferation; In addition, miR-10a and miR-21 carried by GDE pass RORA/IκBα / NF-κB pathway and PTEN / PI3K / AKT pathway promote the activation of MDSCs, thereby enhancing their immunosuppressive effect, and may interfere with the normal differentiation of other immune cells, thus inhibiting anti-tumor immunity. The exosomes secreted by nasopharyngeal carcinoma cells promote the proliferation of Treg and enhance its ability to inhibit the proliferation of Treg, thus inducing tumor cells to develop immune tolerance, thus promoting the growth of tumor cells and endangering human health[33].

4.3. Immune activation of TEX

However, TEX can also promote the activation of host anti-tumor immunity. For examples, exosomes produced by heat treatment of tumor cells are rich in HSP70 (a protein that cooperates with immunity), and under the action of IL-6, Treg is transformed into Th17 (T cell subpopulation) to exert anti-tumor effect. When doxorubicin and melphalan are combined to treat multiple myeloma, they can induce the body to produce more exosomes and carry il-15ra and IL-15. In the presence of exogenous IL-15, exosomes are able to promote the activation, proliferation and maturation of NK cells and enhance the immune surveillance ability of NK cells. For example, exosomes produced by oral tumor cells are abundant in Nap1, which is able to facilitate the proliferation of NK cells, increase the release of perforin and granzyme M through IRF3 (interferon regulatory factor) pathway, and promote the expression and phosphorylation of IRF3, thereby enhancing the killing ability of NK cells[33].

4.4. Application of TEX in tumor immunotherapy

There are some successful examples utilizing TEX as carrier for bioactive molecules to treat diseases. As a natural vector, Tex delivers CRISPR / cas9 plasmid to ovarian cancer cells and inhibits the expression of PARP-1, leading to tumor cell apoptosis, enhancing the sensitivity of tumors to cisplatin, showing synergistic cytotoxicity, showing the potential of exosomes for tumor therapy. Wang and his team realized targeted drug delivery through exosome editing. As a drug delivery carrier, exosomes have strong targeting ability to tumor cells and high cell uptake efficiency, which can significantly improve the anti-cancer effect of drugs. Normal cell-derived exosomes deliver ptenp1 to bladder cancer cells and inhibit the progression in patients with bladder cancer by promoting cell apoptosis and reducing its invasion and migration ability. Exosomal miR-302b can pass through TGF- β RII / ERK pathway inhibits the proliferation and migration of lung cancer cells and is a potential therapeutic target for lung cancer. IEX (immune cell-derived exosomes) also exerts a certain effect in tumor treatment. For example, macrophage derived exosomes transfected with miR-21 inhibitor are transported to gastric cancer cells, and inhibit the progression of gastric cancer by blocking the initiation of PDCD4 gene. It shows stronger anti-tumor ability and less cytotoxicity than traditional methods[34].

5. Conclusion

This review discussed the downstream function of tumor-derived exosomes on endothelial cells, epithelial cells and immune cells. Exosome roles that exist increasingly amounts in angiogenesis manifest that microvesicles shoulder functional instrument in solid tumors when inhibiting the migration and phenotypic modification of endothelium cells and vessel germination. In epithelial cells, exosomes mainly facilitate tumor invasion and metastasis through EMT, which involves a variety of mechanisms (EMT inducing factor, signaling pathways, miRNAs and ECM remodeling). Tumor-derived exosomes(TEX) primarily pass through some ways to control immune cells, the first one is that TEX regulates physiological activity of immune cells. The second one is that TEX can promote the activation of host anti-tumor immunity.

There are some ongoing researches about exosome application in cancer therapy.

Exosomes can contain bioactive substances such as proteins, nucleic acids and lipids. Exogenes can promote drug resistance, invasion and metastasis of cancer cells. Therefore, bioactive molecules contained in exosomes can be used as targeted therapy for tumors. Clinically, significant progress has also been made in diagnosing diseases and evaluating the prognosis of patients by using exogenes in body fluids. However, despite a large number of research and literature reports on exogenes, translating this basic scientific research into clinical applications remains a huge challenge. The effect of most exogenes on tumor development or immunity is mainly determined by "functional acquisition" experiments, which may not fully represent the mechanism of exogenes in tumors. Secondly, as a biomarker of tumor diagnosis and prognosis, exogene extraction is still a cumbersome task. How to extract them efficiently, quickly and in large quantities remains a problem that needs to be solved. In addition, as a treatment, the biosafety of exogenes still needs to be carefully studied. The next step is to reduce the cost of extracting exogenes, improve the safety of exogenes in clinical applications, and develop a method for producing exogene simulation vesicles.

In the future, to develop such strategies, standardized techniques must be established to achieve consistent extraction protocol for exosomes. It is essential to explore exosomes of cancer origin that are ought to be targeted by any treatment regimen. The fields of cancer vaccines and immunotherapy also use exosomes as cell-free therapies. Only the combination of bioscience and biotechnology can set the stage to the prospective practice of exosomes across multiple clinical trials.

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