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Review

Exosomes and Urological Cancers

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HIGHLIGHTS

- Various new strategies for cancer therapy have been developed, but this field still needs more improvements.
- Exosome-based remedies can probably lead to cellular treatment's effects, this novel approach will overcome cell-related disadvantages.

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ABSTRACT

Cancer is still a fatal disease compelling all communities to encounter its unfavorable burdens. Not only there is no exception for urological cancer, but also these types of cancers have an increasing trend which puts them in the top ten most common kinds of tumors. Besides, the recent COVID-19 pandemic, by interrupting medical care cancer plans, caused more cancer-related problems to emerge. Although various new strategies for cancer therapy have been developed, this field still needs more improvements. Among them, cell-based treatment has great promising potential, while it has not been found completely safe. Furthermore, some evidence declares that cells' desirable effect mainly occurs via secreting tiny vesicles which are later called exosomes. Consequently, although exosome-based remedies can probably lead to cellular treatment's effects, this novel approach will overcome cell-related disadvantages. In addition, nowadays, enormous literature is indicating different aspects of abnormal exosome trafficking in many pathological states, confirming that more effort should be undertaken for studying and applying this mentioned structure in future cancer management and specifically, urological cancers.

Keywords: Photodynamic Therapy; Cancer Treatment; Photosensitizer

Introduction

Fundamentally, cancer emerges when normal cells find unhealthy features and unlimited cell growth occurs (1). Notwithstanding that cancerous tissues all have that mentioned property in common; various disorders are subsumed in this category. In other words, many different tissues could be affected, and the tumor could be in situ or developed, which spreads in the whole organism's body to invade other organs. Subsequently, this process takes lots of energy, and nutrients initially acquired from the organism's system are required. As a result, consuming all the host nutrients can lead to death, making these masses noteworthy (2, 3). Exosomes are tiny bilayer spherical vesicles released by unhealthy and healthy cells. Previous evidence demonstrated that these vesicles could play a role in cancer development and metastasis. Accordingly, here we are going to review related literature to investigate exosomes and cancer, specifically urological ones, collaboration (4, 5).

Cancer and its Burden

Some factors are accused of cancer emergence, including genetic properties and carcinogens, putting people in high-risk situations (6) . Following the development, cancer is known as one of the lethal diseases which enforces huge burdens worldwide with a rising trend due to an aging and growing population. In 2020, about 19 and 10 million new cancer cases and cancer-related deaths were globally considered, respectively. Unfortunately, its growing pattern could cause even 50% more burden in

2040 than in 2020 (7). At the same time, timely cancer diagnosis and treatment could enlarge the cancer survivor population (8, 9). Regardless, the recent COVID-19 pandemic has unluckily restricted access to medical care cancer programs, leading to disturbed early detection and proper treatment (10). Although distinct cancers are identified as the most common types in different countries depending on socioeconomic factors, urologic cancers are responsible for significant burdens across all. Accordingly, the National Cancer Institute classifies urological cancers, including prostate, bladder and kidney, and renal pelvis, as the top ten most common types of cancer (11). Testicular and penile cancer are two other urological cancers.

Nevertheless, their incidence is estimated to be low and not much remarkable. The increasing urological cancer incidence could be explained by industrialization, harmful food intake, health care, and public consciousness shortage. Meanwhile, it seems that rural areas are less affected either in incidence rate or in mortality rate; however, among urological cancers seen in both sex, bladder and kidney cancers, it is revealed that the male population is commonly more affected (12, 13).

Cancer Treatment

Nowadays, however, many substantial developments have occurred, but cancer management is still not without challenges. Admittedly, there is no exception for urological cancers, and advanced ones need doubtlessly good remedies (1, 14). Although cell-based therapies are a promising treatment, they are not safe, and an inauspicious immunological-related reaction and its consequences should always be considered (15). Besides, real-world usage is further limited due to invasive collecting techniques and ethical problems. Additionally, the qualified stem cell donor is currently an essential step, even as the quantity and quality of the cells are satisfying (16). Although cell-based treatments are promising, several genetic and epigenetic variations in these cells may appear, leading to complications such as tumorigenesis and emboli production in the host body (16, 17).

Importantly, plenty of recent studies demonstrated that stem cells' propitious action occurred through paracrine pathways, specifically by releasing various small-scale functional vesicles (17-19). Although Trams et al., first 1981 explained exosomes as the tiny isolable products shed by healthy and unhealthy cells in 1983, these structures were introduced during research on reticulocytes transporting transferrin receptors (20, 21). Ultimately, Johnstone et al., six years later, was the man who chose the name exosome for the mentioned interesting vesicles (22, 23). Exosomes were introduced as cellular garbage exporting waste products for a while until it was revealed in 2007 that these vesicles are intercellular messengers with decisive duties (4, 20, 24).

Exosome utilization is known as superior to cellular treatments due to cellular unfortunate probable reactions. Some examples are the genesis of emboli, tumor arising, and graft versus host disease (GVHD) (16). Moreover, their nanoscopic scales allow them to cross various biological barriers easily; for instance, the blood-brain barrier (BBB) is not impenetrable anymore (25). Furthermore, these vesicles cannot carry significant histocompatibility complex (MHC) type one or two proteins (16). Thus, as mentioned in numerous papers, the exosomes are described as particles without immunogenicity and toxicity in contrast to cell transplant procedures (26, 27).

Exosome Definition, Isolation, and Characterization

Exosomes with 50-120 nanometer-size and a cup-shaped appearance are classified as a subset of extracellular vesicles. Many procedures for reaping exosomes are proposed, including ultracentrifugation, ultrafiltration, antigen-antibody interaction, precipitation, and microfluidics-dependent methods. Each technique has its advantages and disadvantages. Accordingly, the procedure should be selected based on the examination's aims and equipment (23, 28).

Subsequently, reaped exosome must be confirmed to lessen clinical adverse effects. Several techniques are applied for exosome characterization. Electron microscopy is the gold standard for evaluating particle size and morphology (28). Also, exosome component assessment and molecular profiling are available through western blot and flow cytometery performance (25). Harvested exosomes can additionally be maintained in vitro for almost half a year at -20 oC. Exosomes naturally are such stable structures that they do not become inefficient, nevertheless a long refrigeration course, which makes them a more capable tool for therapeutic employment (16).

Two other significant subgroups of extracellular products are microvesicles and apoptotic bodies, which generally have been recognized as larger and heterogeneous (16). Interestingly, prostate epithelial cells released another particular extracellular vesicle, prostatosome taking action on spermatozoa mobility in addition to its protection (14, 29, 30). These extracellular vesicles naturally vary in biogenesis. While microvesicles and apoptotic bodies originated from the cell membrane and programmed cell death, respectively, exosomes are derived from the multivesicular body (MVB) (16).

Exosome Formation, Cargo, and Data Conveying

For exosome formation, firstly, the plasma membrane buds inward to generate endosomes which later, using their inward sagging, change to MVB. Then two elegant destinies for MVBs are suggested: either export their vesicles into body fluids as exosome structures through merging with the host cell membrane or degrade their products when choosing fusion with lysosomes (Figure 1) (25, 28).

Almost all mammalian living cells exchange

exosomes, but their contents are highly variable in each cell line (21). Exosomes carry thousands of biologically active molecules, including diverse proteins, lipids, coding and non-coding ribonucleic acid (RNA), and small deoxynucleic acids (DNA) (26, 31). Surprisingly, these vesicles are wrapped with non-random ribonucleic acids (RNAs), and a precise mechanism carefully sorts specific ones into exosomes (27, 31). Messenger RNAs (mRNA) loaded within exosomes are single-stranded RNA transcribed from a string of deoxynucleic acid (DNA) sequence, which after translation, manipulates receiver cell bioactivities on arrival (4, 19). On the other hand, exosomes packed micro RNAs (miRNA), which are tiny non-coding RNA regulating posttranscriptional gene expression mainly through binding to messenger RNA in recipient cells (15, 31). Besides, depending on the donor, cell classification, differentiation state, and surrounding conditions, the exosome RNA amount varies tremendously. The miRNA content is generally reported to be scant unexpectedly (19, 32). A study evaluating the effect of exogenous normal exosomes on the bone defect showed a dose-dependent manner for this cell-free treatment (16). Lastly, the exosome is a supportive hemispherical lipid bilayer vesicle preserving its cargo from extracellular degradation operating by ribonucleases and proteases (4, 14).

Exosomes alter recipient cell biological function through three potent pathways following the transition in body fluids. Firstly, exosomes can alter cell function through ligand-receptor interactions, making data conveyed non-accidental. The second and third pathways involve exosome internalization via endocytosis or directly merging with the recipient plasma membrane (Figure 1) (21, 24). Exosome entry to the cell requires energy and is not considered a passive process (27).

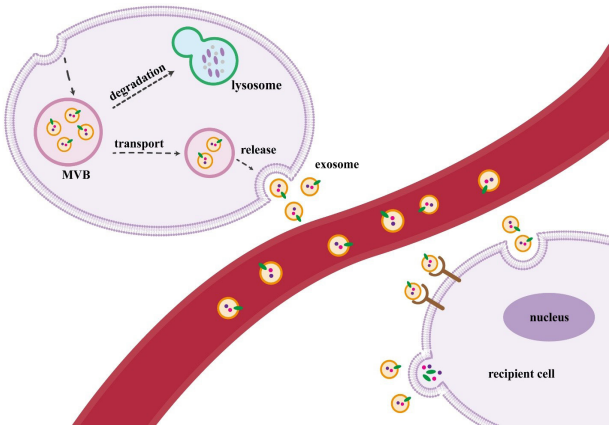

Figure 1. Schematic diagram of the biogenesis of exosomes, microvesicles, and apoptotic bodies. Exosomes are endosome-derived membrane vesicles, microvesicles are derived from the budding of the plasma membrane, and apoptotic bodies arise from blebbing of apoptotic cell membrane

Exosome Uptake

A study undertaken a few months earlier by Linxweiler et al., disclosed that extracellular vesicles (EV) uptake occurs so quickly, and malignant cells derived EVs entrance is done more perfectly than those produced by benign cells. Another critical finding discussed in this literature was factors influencing different organs' EV absorption. Although organotropism declared malignant cancers select some favored organs for metastasis, EV uptake is organized in various values but is not entirely organ-specific; possibly, EV uptake is not the only underlying agent.

In addition, these different EV acceptance levels are clearly determined by parent cell lines secreting EV (33).

However, the analysis showed organ EV admission to various extents, but some organs are recognized as pioneers. For example, it is established that EVs vastly go to the spleen, followed by the liver, lung, and kidney, respectively. Oppositely, organs like the heart and muscles are not interested in EV uptake (34). Furthermore, EV origin may interfere with the EV level accepted by the organ, as is found about brain EV uptake from different parent cells (33). Besides, since exosomes are considered endogenous resources, their half-life in the body's circulatory system is generally enormously satisfying (27).

Multiple reasons could be applied hypothetically to elucidate the cause of different amounts of EV admission by the recipient organ. One of the significant factors is probably EV external markers. The organ blood vessel architecture is the second known impressive factor. Apart from those interpretations, the injection route must be considered carefully, which can modify the organs order EV crossing through. Afterward, circulating EVs were not used by own original organs preferentially, confirming why urothelial carcinoma is frequently seen multiregional than multiple identical metastases from the primary mass (33).

Cancer and Exosome

Indeed, multicellular creatures are dependent on cooperation and intracellular communication. Various processes for cell-to-cell information shuttling are suggested, like straight cell-to-cell contact, paracrine, endocrine, neuronal electrical signals, etc. (23). Another practical method could be exosome trafficking. These structures are cell information transporters to adjacent or distant cells independent of direct contact between parent and target cells (28, 31).

Exosomes have been accused of cooperation in cancer prognosis and metastasis. For instance, several investigations demonstrated that exosome expression differs in kidney cancer individuals compared to the average population (4). Admittedly, numerous distressed conditions contribute to exosome production stimulation,

Table 1. Exosomes in different urological cancers

Year	Organ	Exosomes' Role
2020	**Prostate**	Prostate cancer cells overcome a nutrient deficiency state by receiving surrounding exosomes, resulting in tumor growth continuously (23).
2012	**Prostate**	Exosomes may assist in bone metastasis mainly happens following an ominous cycle caused by osteoblasts, osteoclasts, and prostate cancer cell interactions. Intriguingly, exosomes loaded with a transcriptional factor, Ets1, have been recognized to be expelled by DU145 and PC3 hormone-refractory prostate cancer cells. Secreted exosomes are greatly associated with osteoblast differentiation promotion and consequently metastasis (44).
2017	**Prostate**	Ye et al., investigated the impact of exosomal miR-141-3p released by prostate cancer cells on osteoblasts. Thereafter, data revealed these exosomes clearly increase osteoblast activity and modulate the microenvironment of skeletal metastases (45).
2016	**Prostate**	Karlsson et al. represented prostate tumor shed exosomes trigger pathological management of bone cell production via manipulating osteoclast transformation and fusion significantly (46).
2016	**Prostate**	Exosomes secreted in a hypoxic condition contribute to intensifying prostate cancer cell invasiveness and stemness via impairing adherens junction structures (47).
2016	**Prostate**	Hosseini-Beheshti et al. reported exosomes shed by prostate tumoral cells, LNCaP or DU145, can dramatically diminish caspase 3 and 7 activity of LNCaP treated cells, though only exosomes released by DU145 could remarkably decrease apoptotic activity in a benign epithelial prostate cell line, RWPE-1, following treatment (48).
2012 & 2014	**Prostate**	It is established that prostate tumors transfer exosomes to alleviate host immune response in addition to providing drug tolerance such as Docetaxel resistance (49, 50).
2015 & 2019	**Prostate & Bladder**	Exosome-mediated data conveying can cause cell proliferation and fibroblast differentiation in bladder and prostate cancer (24, 32).
2014 & 2020	**Bladder**	Bladder cancer cells may utilize the exosome for anti-metastatic molecule efflux, i.e. miR23b, wisely (23, 51).
2013	**Bladder**	Jeppesen et al. particularly discovered multiple proteins in bladder carcinoma cell derived exosomes assisting in the EMT pathway (52).
2015	**Bladder**	Franzen et al. intriguingly collected exosomes of bladder cancer to treat urothelial cells and their results indicated mesenchymal marker overexpression like Snail in contrast to epithelial marker down expression like E-cadherin were happened (53).
2017	**Bladder**	The study displayed the role of hypoxic exosomal long non-coding RNA urothelial cancer-associated 1, lncRNA-UCA1, in cancer development through EMT phenomenon (54).
2016	**Bladder**	Muscle invasive bladder cancer cells are found to generate periostin-containing exosomes to induce cell aggressiveness, leading to poor clinical prognosis (55).
2014	**Bladder & Kidney**	High-grade bladder cancer shed exosomes can even motivate new vasculature formation similar to functions related to RCC-derived exosomes (56).
2016	**Kidney**	In advanced renal cell carcinoma management, sunitinib tolerance is an eminent issue. Accordingly, Qu et al. reported a long non-coding RNA (lncRNA) packed in exosomes contributing to this vicious event (57).
2019 & 2021	**Kidney**	Importantly, RCC is identified as a greatly vascularized cancer and for angiogenesis occurrence, endothelial cells must be activated to release exosomes enriched with various growth factors such as vascular endothelial growth factor (VEGF) (27, 58).
2011	**Kidney**	Admittedly, RCC stem cells with CD105 marker secret microvesicles stimulate new blood vessel formation in addition to premetastatic niche organizing (59).
2013	**Kidney**	Zhang et al. precisely disclosed that RCC cell EVs promoted tubular structures through upregulation of VEGF mRNA and protein expression (60).
2021	**Kidney**	Two separated studies showed the role of exosomal microRNA in RCC angiogenesis (61, 62).
2017	**Kidney**	Carbonic anhydrase 9 (CA9) loaded exosome produced by RCC cells can promote angiogenesis in the microenvironment (63).
2020	**Kidney**	Exosome effect in RCC is not only detected in blood vessel formation but also identified in metastasis manifestation via the EMT process which is modulated by Apolipoprotein C1 (ApoC1) harboring exosome exchange simultaneously (64).

including acidic status, hypoxic state, radiation, temperature change, oxidative stress, etc., rationalizing the observation in which cancerous cells take up exosomes more efficiently compared with healthy ones (1, 24).

Moreover, unhealthy exosomes can make premetastatic niches ready by altering microenvironments in their neighboring or remote areas and, consequently, result in tumor emergence, development, invasiveness, and immune resistance (14, 25, 33). Meanwhile, they play even a key role in cancer metastasis. Hence, exosomes are communicators between cancer and stromal (normal) cells and between unhealthy cells (21). Exosomes produced by cancer cells incredibly convert local and distal microenvironments cells to promote cancer evolution and establish premetastatic niches (33). Stephan Paget described a seed-and-soil hypothesis to elucidate why metastasis is not a random system. Here cancerous cell is the seed that is trying to discover a fertile distant organ as the soil. Parent cells make signaling by producing and transferring exosomes to selected cells, and their bidirectional interaction illustrates which microenvironments support cancer cells for metastasis. Without exosome translocation, abnormal cells cannot find the proper organ for invasion, and they lose the opportunity to survive in the novel soils (21, 33). On a molecular basis, the exosome is employed by the abnormal cells to achieve angiogenesis ability, epithelial-mesenchymal transition (EMT), escape from apoptosis, drugs, and host immune reactions, which are necessary for tumor progression (24).

Targeted therapy in tumor treatment might be an active or passive phenomenon arranged to enhance the potency of the remedial process. In the first action, the drug is actively specified by various molecules. Contrarily the passive one is regulated by the recipient subject (25). In other words, the cancer vasculature is not entirely flawless, and its highly penetrable layers offer the particles an absolute chance to extravasate much more effortlessly (35). In addition, its flawed lymphatic drainage system cannot appropriately eliminate these drugs from the tumor's microenvironment. Subsequently, exogenous healthy particles can be trapped in the tumor surroundings regardless of simply passing through healthy tissues (25, 36). More specifically, the exosomes' role in different urological cancers is summarized in Table 1.

Although former evidence revealed the exosome influence in multiple cancers such as breast cancer, many other pathological states are related to exosomes. Some associated samples are cardiovascular, neurodegenerative, autoimmune, and infectious problems (4, 27). Meanwhile, their interventions in diabetic Mellitus type one and two, including lack of insulin sensitivity and glucose endurance, have been detected (57, 58).

On the other hand, MSC-derived EVs employment has illuminated their intrinsic potency in improving non-physiological status. For example, this product can inhibit hepatoma growth or help ameliorate renal function after acute kidney injury (AKI) (24, 29, 59).

Subsequently, although exosomes are applicable in enormous clinical situations as drug delivery machines, biomarkers, and vaccines for cancers, healthy ones can also be used for cancer treatment (14, 60). In other words, any barriers to abnormal exosome production, secretion, circulation, and uptake are possible effective tumor management. That is why decreasing the systemic cancerous exosome level can restrict this inauspicious crosstalk and, accordingly, be introduced as a cancer remedy (20, 31)

Conclusion

However, it has been found that exosomes play a crucial role in cancer progression, but blocking cellular cross-talk via modifying pathological exosomes is also a novel strategy for cancer management. The possible options could be removing unhealthy vesicles from the circulation system or adding normal ones, known as promising cancer treatments with fewer adverse effects and advantages like nanoscopic size and lack of immunogenicity and toxicity. Furthermore, healthy exosome usage for combination therapy or as a drug carrier should also be noticed.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethical statement

Not applicable.

Data availability

Data will be provided by the corresponding author on request.

Abbreviations

AKI	Acute kidney injury
BBB	Blood-brain barrier
DNA	Deoxynucleic acids
EV	Extracellular vesicles
MVB	Multivesicular body
RNA	Non-coding ribonucleic acid

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