International Journal of Advances in Engineering and Management (IJAEM)
Volume 5, Issue 6 June 2023, pp: 891-899 www.ijaem.net ISSN: 2395-5252

Exosomes and Their Role in Cancer

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Date of Submission: 20-06-2023 Date of Acceptance: 29-06-2023

ABSTRACT
Exosomes from extracellular vesicles deliver proteins, lipids, nucleic acids, and other substances to recipient cells, where they can activate or inhibit different signalling pathways. Exosomes are also thought to have a variety of roles in the growth and development of tumours derived from various tissue origins, including remodelling of the tumour microenvironment, increasing angiogenesis, metastasis, and invasion, as well as controlling the immune escape of tumour cells. However, it is still unknown exactly how exosomes interact in these many activities at the molecular level.In this review, we outline the state of the study on the role of exosomes produced by tumour cells in the development of cancer.Further the potential uses of exosomes are also discussed.As a result, information on the function of exosomes in malignant cancer will help to design new diagnostic and therapeutic techniques.

KEY WORDS: Exosome, Tumor, Angiogenesis, Metastasis, Therapeutic techniques

I. INTRODUCTION

Cancer is still one of the diseases that endangers the lives of many individuals all around the world. It is the world's second biggest cause of mortality, after only cardiovascular disease. Cancer cells have distinct traits such as rapid proliferation, self-renewal, cancer stem cell (CSC) characteristics, metastasis, and the capacity to flip between multiple biochemical pathways to build treatment resistance. Novel therapies, such as nucleic acid medicines and anti-cancer medications, have been created based on these features to target cancer cells and restrict their development. Furthermore, innovative approaches, such as the use of nanoparticles, have been used for the targeted delivery of medicines to cancer cells. Exosomes are nanosized vesicles that are actively released by almost all cell types, including fibroblasts, endothelial cells, epithelial cells, neuronal cells, immunological cells, and cancer cells. Exosomes, which are rich in bioactive substances such as nucleic acids, proteins, lipids, and metabolites, have the potential to convey signals between cells. Exosomes have been found in a variety of bodily fluids, including bile, blood, breast milk, urine, cerebrospinal fluid, and saliva, indicating that exosomes have diverse functions in regulating physiological responses. Exosomes' pathophysiological impacts on illnesses, particularly malignancies, have recently been discovered. Tumor-derived exosomes are thought to play a role in cancer malignancy development by stimulating cancer proliferation, forming a premetastatic niche, and controlling treatment resistance. Exosomes have been highlighted clinically as diagnostic indicators, therapeutic targets, and even anticancer drug-delivery vehicles due to their distinct biological and pathological properties. We present a thorough overview of exosomes in cancer cell biology and describe how exosome-based intercellular interactions influence cancer growth and metastasis. Furthermore, we summarise the significance of exosomes in therapeutic applications in terms of their molecular and biological properties.

II. ORIGIN OF EXOSOMES:

The early sorting endosomes (ESEs) are generated by invagination of the cell membrane. The early endosomes are then converted into late sorting endosomes (LSEs) under the supervision of the endocytosis sorting complex and other transport-related proteins. After a second indentation, LSEs develop into multivesicular bodies (MVBs). The contents inside the cells are released to the outside in the form of vesicles when MVBs fuses with the cell membrane. These are exosomes. Figure 1 depicts exosomes' biological genesis. Exosome formation is complex. Currently, further studies are being conducted on ESCRT-dependent and ESCRT-independent pathways.However, it has recently been revealed that other elements, including lipid rafts and proteins with four transmembrane domains, are also involved in the creation of some exosomes. Therefore, there is still debate over the actual process.

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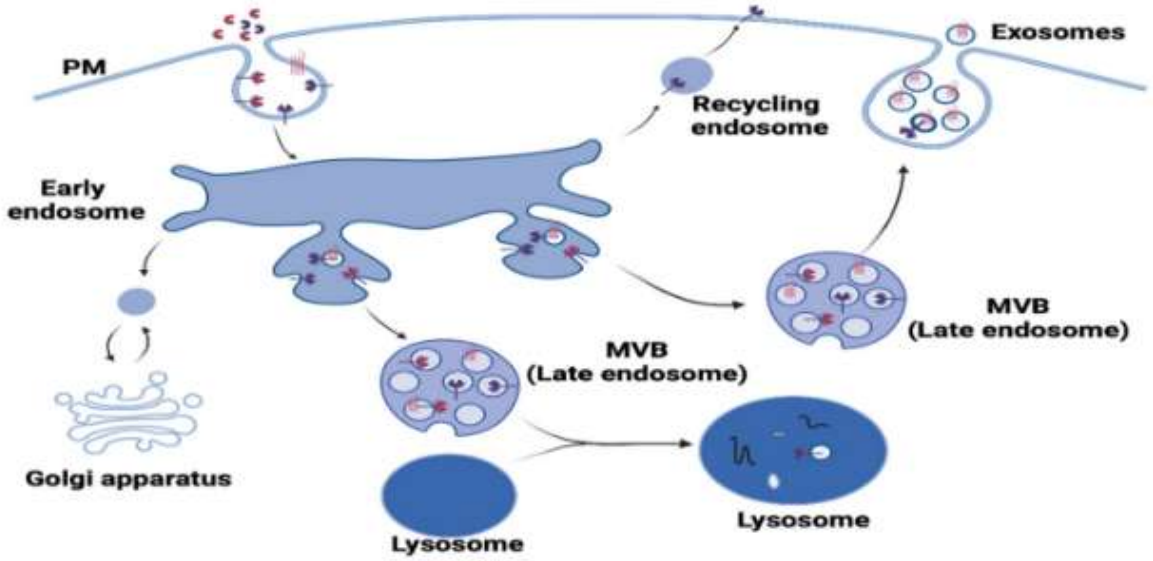

Figure 1: Biogenesis of exosome

III. EXOSOME STRUCTURE:

Exosomes are vesicles with a lipid bilayer and a diameter of around 100 nm that may be broadly divided into membrane components and molecules that have been enclosed (Fig. 2). Like a conventional cell membrane, the components of the membrane are made up of lipids and proteins. According to some reports, the cell that makes the exosomes determines the lipid makeup of the membrane. The outer side of exosomes has higher concentrations of phosphatidylserine, sphingolipids, and cholesterol than the inner side of the cell membranes do. Tetraspanins—proteins with four transmembrane domains—like CD9, CD63, CD81, etc.These included MHC molecules, which are proteins involved in the presentation of antigens and include four transmembrane domains, as well as the cell adhesion molecule integrin. Integrin is implicated in exosome tropism, and tetraspanin is employed as a reasonably specific exosome marker.

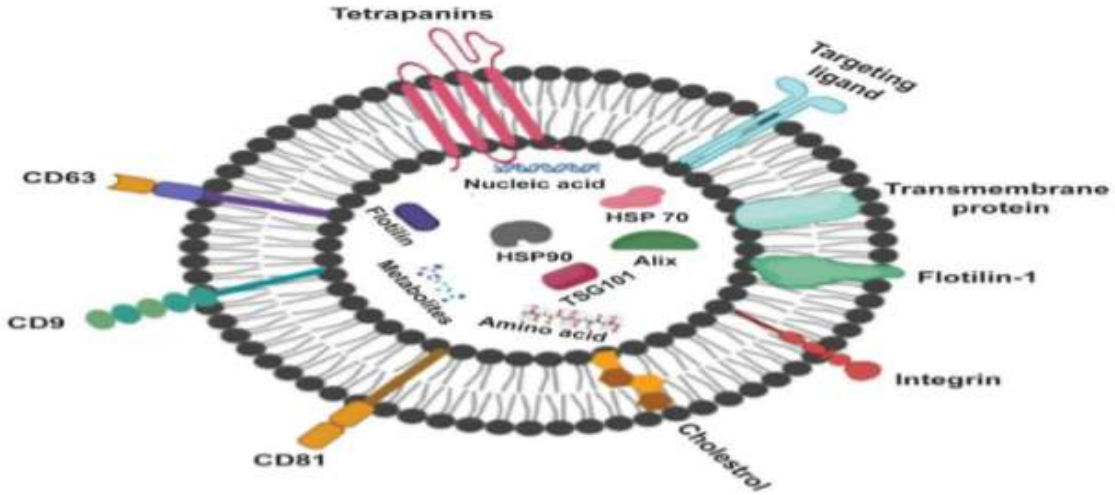

Figure 2: structure of exosome

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IV. CLASSIFICATION OF EXOSOMES:

Exosomes can be classified as either natural or designed exosomes depending on whether they have undergone artificial modification. Later, natural exosomes are separated into exosomes generated from animals and exosomes derived from plants. Animal-derived exosomes are further separated into normal exosomes and tumour exosomes due to the fact that exosomes are generated in both normal and tumour situations.

The human umbilical vein endothelial cells, mesenchymal stem cells (MSC), T cells, B cells, macrophages, dendritic cells (DC), and natural killer (NK) cells are only a few examples of the typical cell types that may create exosomes. For instance, mesenchymal stem cells (MSCS) are pluripotent stem cells with the ability to differentiate in several directions and self-renew. In addition to their ability to adapt to the tumour microenvironment, MSCs also exhibit potent paracrine activity and produce a significant quantity of exosomes.Exosomes generated from food also have promising growth possibilities. Exosome-like nanoparticles (ELN) produced from plants have been discovered in recent years to resemble mammalian exosomes structurally. Particles made from ginger have the ability to prevent the onset of liver-related illnesses, while ELN made from grapes, carrots, grapefruit, and ginger has anti-inflammatory properties and the capacity to maintain intestinal homeostasis.

Exosomes are currently grouped mostly according to their origins. The properties and practical uses of the various exosome kinds are not thoroughly studied in this categorization. Future subdivisions based on the characteristics of organophilicity, biological dispersion, and immunogenicity may be taken into account.

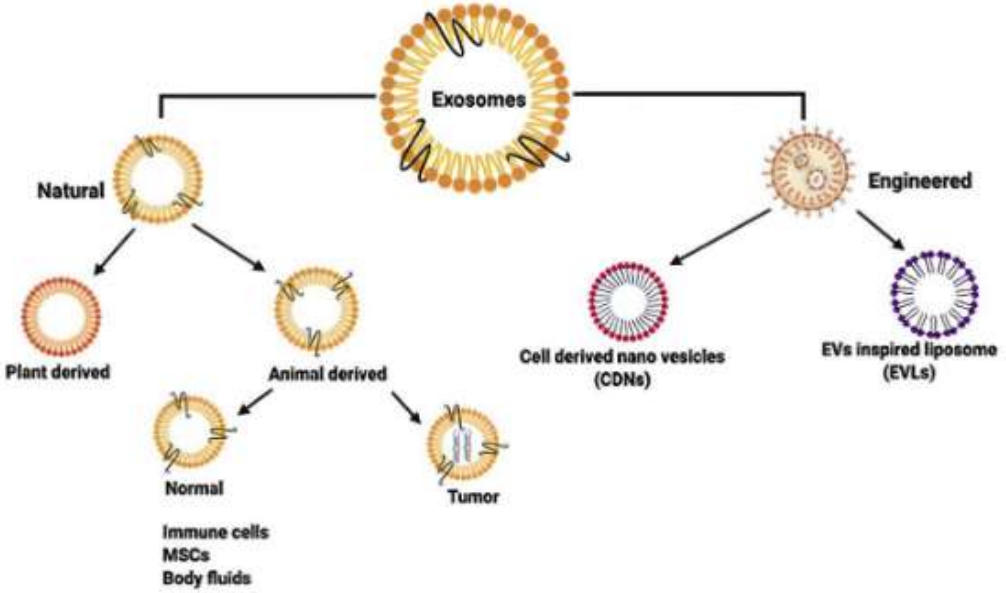

Figure 3: Classification of exosomes

V. EXOSOMES CELL-CELL COMMUNICATION:

In order to maintain physiological homeostasis and control disease symptoms, cell-to-cell communication is essential. Exosomes are emerging as crucial mediators in inter- and intracellular interactions both locally and remotely, replacing direct cell-cell contact and the production and absorption of extracellular signalling molecules such cytokines, growth factors, hormones, and extracellular matrix. Exosomes offer a wall of protection for weak biological molecules inside the lipid bilayer-membrane. It is true that the exosomal membrane structure encloses and shields proteins or miRNAs from being broken down by RNases or proteinase, respectively. Numerous investigations have shown that exosomal molecules' biological activity really modifies recipient cells' biological processes and cell signalling events.

The oncogenic receptor EGFR vIII may be transferred from aggressive brain cancer cells to cancer cells missing this oncogenic receptor activity using tumor-derived microvesicles, commonly known as oncosomes. Additionally, the sharing of lncRNAs by gastric cancer cells via

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exosomes promotes the growth of the disease. Exosome-mediated cell-cell communication has been demonstrated both locally and remotely in the tumour microenvironment, indicating that it is not just a feature of cancer cells. Transforming growth factor beta (TGF-), which induces the differentiation of fibroblasts into myofibroblasts, may be delivered to healthy fibroblasts via tumor-derived exosomes. In contrast, exosomes produced by cancer-associated fibroblasts (CAF) influence the metabolism of cancer cells by preventing the mitochondrial oxidative phosphorylation pathway.

In terms of the role of exosomes in the long-distance transfer of biological molecules between cells, malignant cancer cells, such as breast or pancreatic cancers, secrete exosomes containing bioactive molecules, such as telomerase activity or macrophage migration inhibitory factor, to the distant tumor-associated microenvironment, where they contribute to the formation of premetastatic niches.

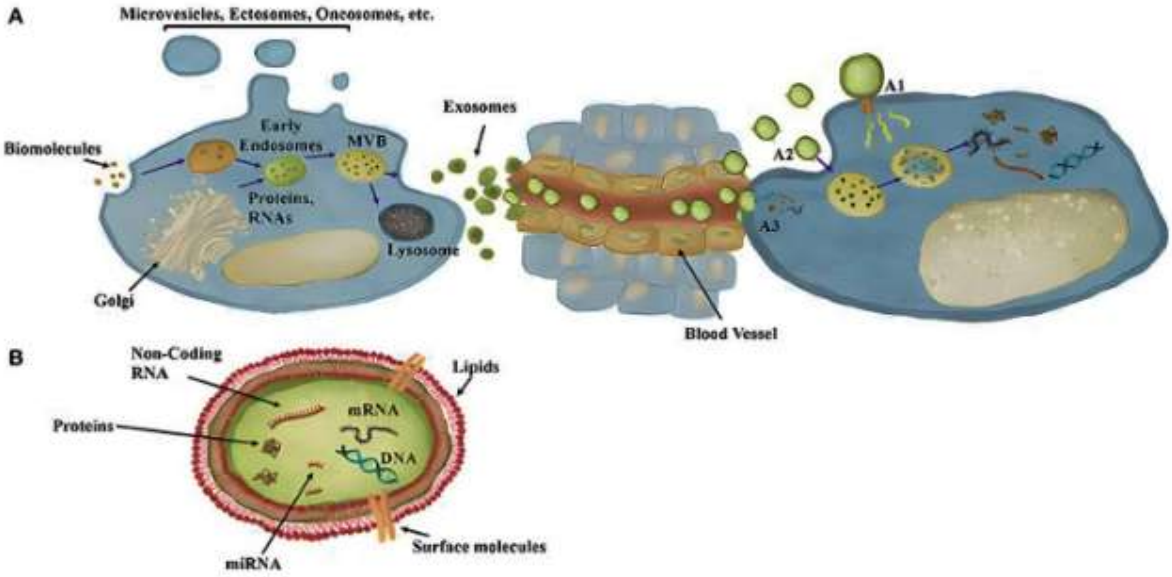

Figure 4: Cell- Cell communication of exosomes

Different pathways enable exosomes to mediate cell-cell communication. Exosomes may lodge at the target cell's plasma membrane and trigger intracellular signalling through ligand-receptor interaction (A1). (A2) Exosomes can be internalised through phagocytosis, micropinocytosis, or receptor- or raft-mediated endocytosis. After fusing with the delimiting membrane of an endocytic compartment, their contents are released into the cytoplasm of the recipient cells. (A3) Membrane fusion has the potential to directly take up exosomes, releasing their contents into the cytoplasm. (B) An exosome is a double-layered lipid membrane vesicle that contains all of the fundamental cellular biomolecules, including DNA, mRNA, proteins, and miRNA.

VI. EXOSOMES IN TUMOR PROGRESSION:

Cancer advancement is a dynamic and multistep process in which various well-studied signalling events contribute in the orchestration of cancer malignancy growth. Tumor-derived exosomes have been shown to actively affect cancer progression through autocrine/paracrine oncogenesis, stromal cell reprogramming, immune system modulation, and angiogenesis.The transfer of oncogenic chemicals within oncosomes between primary tumours causes morphological alteration as well as an increase in anchorage-independent proliferation in recipient cancer cells. Similarly, tumor-derived exosomes promote cancer growth by exerting antiapoptotic effects of TGF-1 signalling in an autocrine manner. ZFAS1 lncRNA is transported from malignant malignancies to ZFAS1-negative cancer subpopulations to promote the growth of ZFAS1-negative cancer subpopulations.Tumor-derived exosomes influence endothelial angiogenic responses by stimulating the creation of endothelial tubule networks, which may lead to cancer malignancy.

Exosomes produced from tumours also promote the differentiation of mesenchymal stem cells (MSC) into pro-angiogenic and pro-invasive myofibroblasts. Differentiated MSCs stimulate

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cancer proliferation and invasion by secreting growth factors and matrix-regulating factors. Cancer cells require adequate oxygen and nutrients to grow and thrive. Tumor-induced angiogenesis delivers oxygen and nutrients while also eliminating waste. By upregulating angiogenesis-related genes, Tspan8 and other surface tetraspanins on tumor-released exosomes can remotely stimulate resting endothelial cells, sprout endothelial cells, and mature endothelial cell progenitors. In addition, tumor-derived exosomes harbouring miRNA clusters like the miR-17-92 cluster enhance endothelial migration and tube formation.

Exosomes may have a role in facilitating communication between cancer cells and immune cells such as macrophages, neutrophils, natural killer (NK) cells, dendritic cells, and T cells, according to mounting data. Indeed, tumor-derived exosomes influence macrophage polarisation. In a SOCS3/STAT3 signal-dependent manner, macrophages that have received miR-222-3p inside exosomes can induce polarisation towards tumor-promoting M2 macrophages. Furthermore, tumor-derived exosomes promote carcinogenesis and cancer development by increasing the differentiation of bone marrow-derived neutrophils and their recruitment to cancer cells. Exosomes isolated from liquid biopsies of individuals with acute myelogenous leukaemia reduced natural killer cell cytotoxicity, which was ascribed to an increase in Smad phosphorylation and a decrease in NKG2D receptor expression.This research implies that tumor-derived exosomes aid cancer growth by suppressing immune responses. Furthermore, tumor-derived microvesicles impact myeloid cell capabilities by inhibiting monocyte differentiation into dendritic cells, which reduces T-cell proliferation and anticancer cytolytic functions.

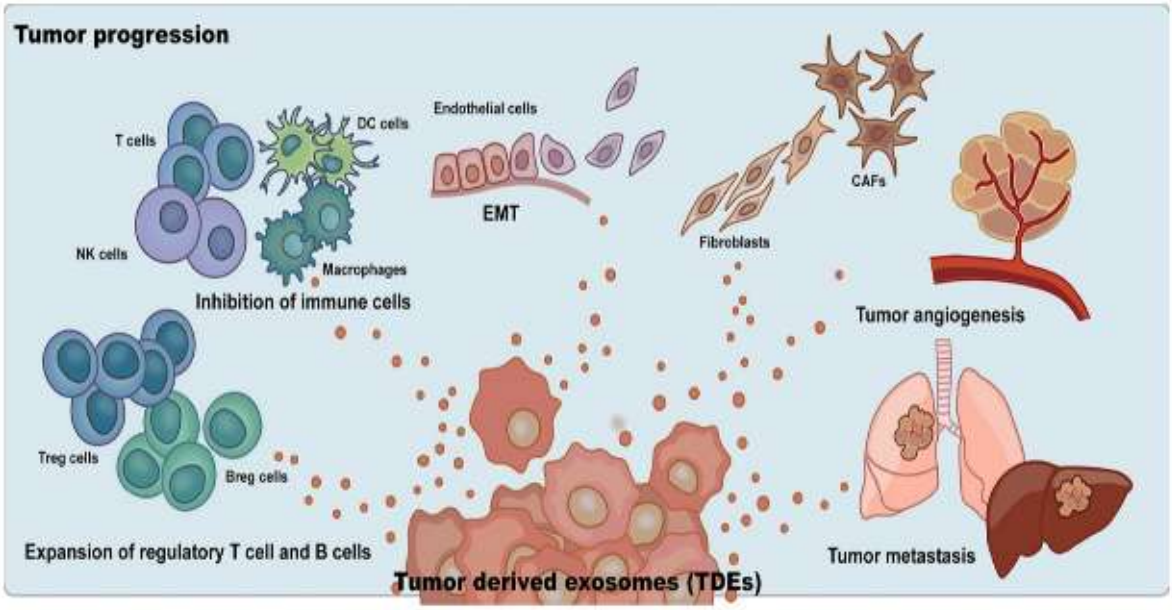

Figure 5: Tumor progression in exosomes

VII. EXOSOMES IN CANCER METASTASIS:

The functional impact of tumor-derived exosomes on the capacity of malignancies to invade is highlighted by their pathological importance to cancer metastasis. For exosome-mediated cancer invasion, invadopodia formation and exosome secretion are unquestionably necessary together. Rab27a knockdown dramatically inhibited the development of mature invadopodia as well as extracellular matrix digestion by inhibiting exosome synthesis or secretion. Exosome secretion is crucial for invadopodia, which raises the intriguing possibility that exosomes work in concert to control invasive activity. Additionally, miRNAs from metastatic cancer cells may be transferred by tumor-derived exosomes to less metastatic cells, altering the gene expression of less metastatic cells and promoting metastasis.

The most common cause of illness and mortality in cancer patients is brain metastases. The blood-brain barrier (BBB) is very selectively permeable, yet metastatic cancer cells can nevertheless enter the

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central nervous system (CNS). Recent research has demonstrated that the BBB's structure and operation can be disturbed by exosomes produced by metastatic cancer cells. Vascular endothelial cells take up miRNAs from cancer exosomes such miR-105 and miR-181c, which then cause the aberrant localization of the cytoskeleton or target tight junction proteins to cause the degradation of vascular endothelial barriers. The damaged vascular endothelial barriers allow cancer to spread to the brain as a result.

VIII. EXOSOMES IN CLINICAL APPLICATION:

Exosomes provide distinct bioactive chemicals necessary at different stages of cancer formation, contributing to the pathophysiological development of malignancies. This suggests that exosomes have the potential to be used as diagnostic biomarkers and therapeutic targets. Exosome-related drug resistance is a new phenomena that is showing up in a variety of malignancies. Determining the processes underlying exosome-mediated cancer treatment resistance might thus be useful knowledge for developing precision cancer medicines. Exosomes have also been employed as a delivery vehicle for anticancer medications since they are nonimmunogenic in nature and have a membrane structure that is comparable to that of the majority of human cells.

8.1 EXOSOMES AS TUMOR BIOMARKERS:

The need for precise new biomarkers is of utmost relevance in patient identification, diagnosis, and prognosis, and the developing field of exosomal biomarkers has considerable potential, particularly in cancer. Exosomes could be a great biomarker for tracking the development, spread, and prognosis of cancer as well as the effectiveness of various treatment modalities. Exosomes have been shown in a few studies to be easily detectable in tumour tissue and numerous body fluids, and they may also be discovered in larger amounts in cancer patients' serum and plasma as well as tumour tissue.There have been a number of publications that have found potential exosomal biomarkers in patient samples in addition to other research that have characterised putative exosome biomarkers in cell lines.

Through the discovery of a disease-specific EGF receptor transcript, the presence of nucleic acid in exosomes has been characterised as a biomarker in glioblastoma patients.Exosomes from melanoma patients exhibit significant quantities of the proteins Caveolin-1 and CD63, whereas eight microRNAs that can be utilised to discriminate between benign and malignant illness have been found in an examination of ovarian cancer patients. Exosomes from patients with prostate cancer and non-small cell lung cancer have been characterised as containing markers in other research. It's interesting to note that examination of the lipid profile of prostate cancer exosomes showed specific lipid signatures that might potentially be used as biomarkers. Even though the investigation of exosomes for cancer biomarkers has produced a large number of potential candidates (especially microRNA), none have shown enough promise to be used in clinical settings. Before exosomes be used clinically as a biomarker for either diagnosis or prognosis, more research on the dynamic expressional profile of their contents throughout tumour growth and therapy, along with improved collecting techniques, is required.

8.2 EXOSOMES IN DRUG RESISTANCE:

Drug efflux-dependent mechanisms in tumour exosomes cause drug resistance in cancer by expelling chemotherapeutic drugs from cancer cells. Drug-sensitive cells' gene expression is altered as a result of the intercellular transfer of exosomal proteins and miRNAs between drug-resistant and drug-sensitive cells. When exposed to the medication, this alteration in gene expression gives the sensitive cells an antiapoptotic ability—a property also seen in drug-resistant cells. Such a phenomenon was seen in tumours resistant to docetaxel that release exosomes carrying P-glycoprotein, a protein that functions as a drug efflux pump. Cancer cells that were drug-sensitive ingested these exosomes, and it was shown that these cells had drug resistance.

Additionally, exosomes from breast tumours that overexpress HER2 show active HER2 protein, which controls how sensitive a patient is to the anticancer medicine trastuzumab. Additionally, exosome-derived activated HER2 protein is involved in oncogenic signal-mediated cancer malignancy. According to other studies, tumor-derived exosomes can shield target cells by carrying a large number of the proteins that medications target and counteracting the effects of the drug on the target cells. Similar to this, tumour microenvironment cells also produce exosomes that reduce cancer cell treatment resistance. It has been demonstrated that stroma-derived exosomes influence NOTCH3 and STAT1-dependent antiviral and radiation sensitivity in cancer cells. These research collectively provide information on a variety of exosome-mediated drug resistance

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mechanisms, including pumping anticancer medications out of cells or transporting bioactive chemicals.

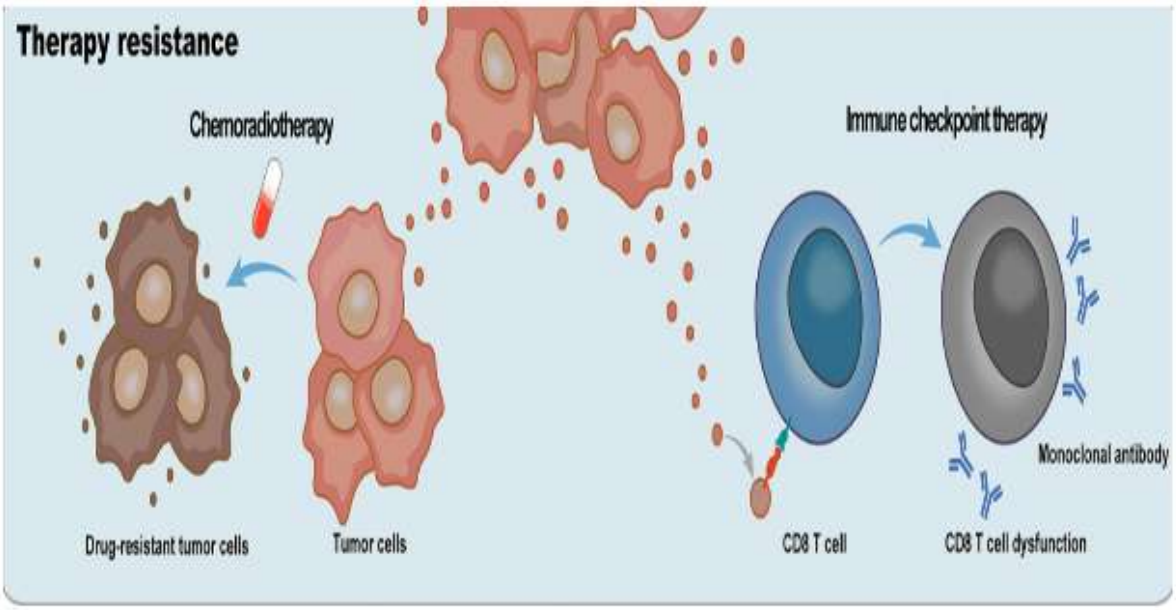

Figure 6: Drug resistance in exosomes

8.3 ROLE IN DRUG DELIVERY:

Naturally produced exosome vesicles, which resemble liposomes, have drawn a lot of interest as drug delivery systems. First off, the exosomes' nanometric size makes cell-to-cell communication simple. A protected habitat for bioactive compounds from degradation in the extracellular milieu is provided by the lipid bilayer-membrane structure of exosomes, which is the second benefit. Third, compared to other drug delivery methods, exosomes exhibit decreased immunogenicity and toxicity. Finally, exosomes with certain surface proteins, such integrins, can target themselves to particular organs. These characteristics of exosomes suggest that they can be effective drug-delivery vehicles for the administration of proteins, siRNAs, or anticancer drugs.

Exosomes have been acknowledged as innovative cell-free vaccinations in immunotherapy on an intrinsic level. In patients with advanced non-small-cell lung cancer, tumour antigens loaded into exosomes produced by autologous dendritic cells promote anticancer immune responses (i.e., induced natural killer, NK, cell effector activities). Exosomes from interferon-mature dendritic cells were employed in later research to speed up NK and T cell antitumor immune responses. Advanced non-small-cell lung cancer patients showed increased NK cell activity and a longer progression-free survival rate. These findings collectively showed that exosomes might be used as cell-free vaccinations or drug delivery systems for anticancer treatments.

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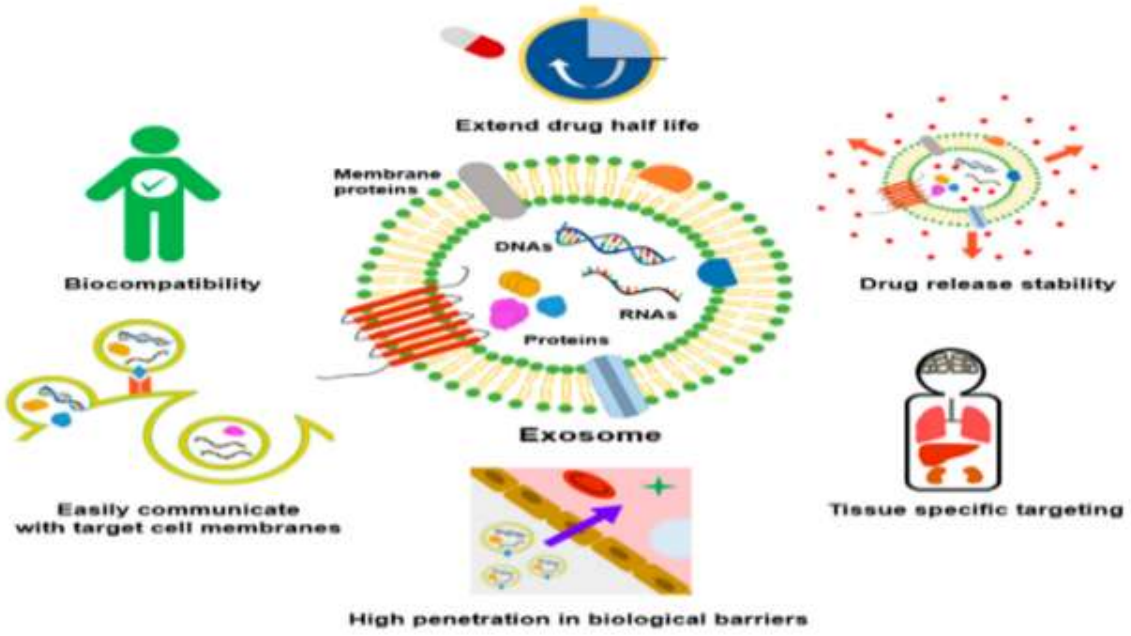

Figure 7: Exosomes as a drug delivery system

IX. CONCLUSION:

Exosomes and their involvement in the development of cancer are briefly discussed in this review.Though both in vitro and in vivo studies clearly illustrate the tumor-modulating potential of exosomes, the extent to which these signalling pathways determine carcinogenesis in patients is still far from being fully known. Scientists are just now starting to understand the intricate activities of exosomes.Exosome-mediated cell-to-cell communication has become a crucial regulator of drug resistance, carcinogenesis, and metastasis in cancer.Regardless of the contribution, the motivation behind exosome research—the considerable potential of exosomes as a non-invasive biomarker, as well as a means of drug transport and drug resistance—has generated a sizable body of work studying these messengers. Despite this, there are still a lot of technological obstacles to be removed before exosomes may be used as a biomarker, biological target, or medication delivery system.Exosomes may out to be the most effective biological effector for cancer so far found and may eventually offer feasible therapy approaches and biomarkers due to these reasons, as well as the numerous other ones covered in this article.

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