International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 08 Issue: 03 | Mar 2021 www.irjet.net p-ISSN: 2395-0072

# Exosomes: Nanoscale Cancer Immunotherapy

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**Abstract -** *Exosomes are the nano-vesicles that are secreted by almost all the cells. Exosomes are an important form of the intercellular communication. Exosomes are always being recognized as potential therapeutics as they have the ability to evoke potent cellular responses in vitro and in vivo. Exosomes hold significant promise for creating exciting methodologies in drug delivery and the cancer immunotherapy. The ability to develop these exosomes in the lab holds tremendous promise. Bioengineered exosomes are in effect effectively conveyed to convey intense tumoricidal drugs (siRNAs and chemotherapeutic compounds) especially to cancer cells. (Malam Y, 2009)*

*Recent advances have made viral and non-viral methods to prepare the parent cells in the lab to secrete the modified exosomes or alternatively to directly duplicate exosome content following the secretion. The majority of research evidence has given much promising results, with the decrease in tumor cell invasion, migration and proliferation, along with that immune response is enhanced, cell death and sensitivity to chemotherapy observed. The studies in this review paper will highlight the exciting potential of the use of exosomes as therapeutic vehicles for the treatment of cancer. (Ristorcelli E, 2008)*

***Key Words*: Cancer Nanomedicine, Immunotherapy, Tumoricidal drugs, Drug delivery, Bioengineered.**

## 1. INTRODUCTION

Cancer is a leading cause of death worldwide, decreasing the life expectancy of the people. Although patient survival rates for some kind of cancers are high due to medical advancement in treatments but still the search for effective cancer treatment protocol remains the ultimate aim of researchers and doctors. Traditional treatments for cancer include radiotherapy, the use of chemotherapeutic drugs and interventional surgery. Recent research suggests the huge application of Tumor Cell-derived Exosomes and Dentritic Cell-derived Exosomes could emerge as nanoscale immunotherapy treatments.

Exosomes are nanoscale membrane vesicles which were first briefed by Rose Johnstone in the 1970s. Although its exact biological function and mechanism is yet to be know but it was postulated that they are involved in cell to cell communication. It has shown to have lipid composition which is rich in spinghomyelin, cholesterol and ceramide. (Grivennikov SI, 2010)The research in the field of exosomes has greatly been increased in the past few years which lead to the creation of online databases such as Exocarta.Exocarta is an encyclopedia dedicated to provide original research finding about exosomes and the proteins associated with them. The main protein makers are Alix,TSG101 and Tertraspanins and is able to mediate a biological immune response by activating Natural Killer Cells via NKG2D ligand binding and T lymphocytes via antigen presentation.

## 2. Isolation and purification of exosomes:

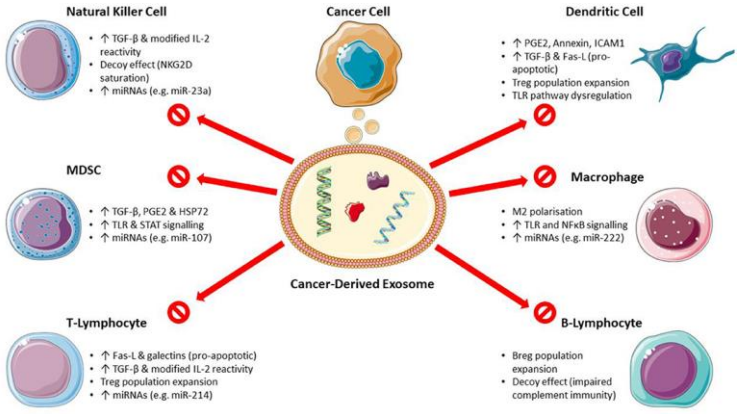


Fig.1.1 Exosomes

There are several methods which have been investigated for the isolation and then purification of exosomes from the various biological fluids. Filtration, centrifugation, microfluidic isolation and immunological separation can effectively be used in the laboratory research as well as clinical medicine. Differential ultracentrifugation is one of the most important techniques for the isolation of the exosomes. This technique consists of several centrifugation steps which helps to remove the cells and large vesicles at lower centrifugation speeds. But the efficiency of this method reduces when plasma and serum are used due to high viscosities of the fluids.

Scientists have explored that specific binding of antibodies to the receptors that are present on the surface of the exosome. Ultrafiltration has also been investigated for the exosomes to be separated from the various proteins but the efficacy of this method is not clearly known. Polymer-facilitated precipitation which is most commonly using Polyethylene glycol is employed for the extraction of exosomes. (Temchura VV, 2008)

### 3. Cancer Immunotherapy:

A cell becomes cancerous if it gains an oncogenic function, lose its tumor suppressor function and become immortalized. Within the surface of the tumor cells there is high interaction between the immune cells and cancer cells and these cancer cells may escape the field where immune system works by sudden expression of antigen, absence of B7 molecules and release of various immunosuppressive factors such as IL-10 and TFG(Beta). However, one question still remains unanswered as why and how the immune system tolerates these cancer cells. (Koos D, 2010)

Dendritic Cells are powerful Antigen-Presenting Cells (APCs) which would always be activated after experiencing a foreign agent and would interact with it using T cells to activate an antigen-specific immune response. Mature dendritic cells are powerful antigen-presenting cells than immature dendritic cells. (Xie Y, 2009) So, when immature dendritic cells are activated upon stimulation by foreign antigens then they become mature dendritic cells. This inturn releases chemokines to attract T cells. Traditional use of monoclonal antibodies in cancer immunotherapy causes various side effects like immunosupression ad hypersensitivity reactions due to stander effect. But dendritic cell-based immunotherapy could be alternative cancer treatment because the immune system mounted is more specific. Recent trends in this field and research has given an evidence that artificial antigen-presenting cells systems are also emerging as powerful techniques for immunotherapy and this is much more safer than traditional method. This has made the researcher to attract for cancer vaccine development. (Sasada T, 2010)

### 4. Search for a Cancer Vaccine:

There is a huge clinical advancement that has been made in the treatment of various types of cancer using the human immune system. Use of donor lymphocyte infusions is one of the best examples which are very useful in treating chronic leukemia. Bone marrow transplantation has also paved a way towards treating haematological cancer. However, the need and search for a cancer vaccine remains the main objective of all the researchers and oncologist. However, current treatment for cervical cancer involves vaccination with either Gardasi or Cervarix, which is useful against cancer causing variants of HPV-Human Papillomavirus.

A modified method has also attracted researchers which uses long synthetic HPV oncopeptides and this has demonstrated that both $CD4^+$ T- and $CD8^+$ cell responses can be mounted in vivo and these are capable of inducing complete protection against vulvar cancer. These results were encouraging because it was the first time an antiviral or tumor vaccine has successfully eradicated many known tumors. But this is not the true cancer vaccine. In the way of finding a true cancer vaccine, researchers have found some interesting approaches that have been adopted by targeting

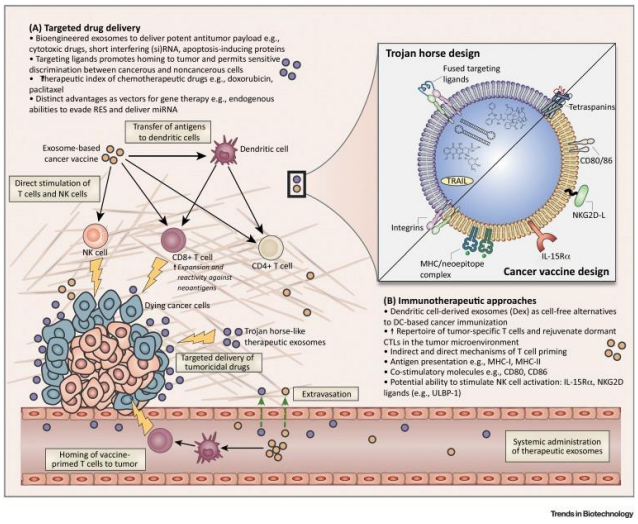


Fig. 1.2: Targeted Drug Delivery

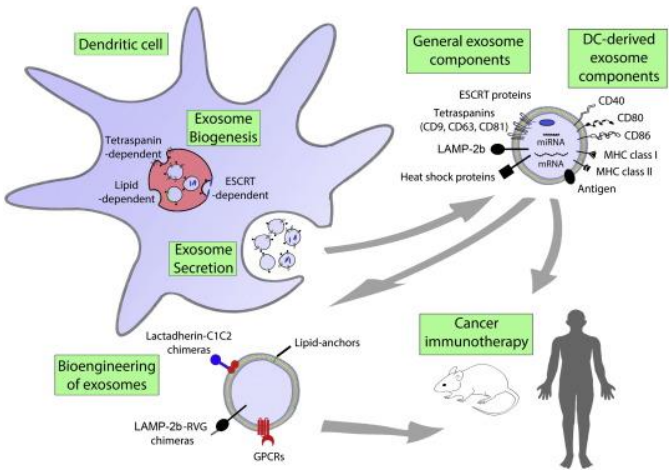


Fig. 1.3 Nanoscale Cancer Immunotherapy

self proteins on cells that which are expressed at only some particular sites for specific time frames. In addition to all these, Hepatitis B vaccine protects against Hepatitis B virus and this virus is associated with liver cancer. (Zitvogel L, 1998)

In the year 2010, the FDA approved the use of Provenge with the content sipuleucel-T in the treatment of advanced prostate cancer. It was the first true therapeutic cancer vaccine which stimulated the body to kill the cancerous cells by invoking a biological immune response. This process involves merging dendritic cells along with prostatic acid phosphatise containing fusion protein in order to make the immune system of the patient to recognize and kill those prostate cancerous cells. Research evidence has also shown that loading and merging dendritic cells with tumor antigens resulted in much higher response rates in cancer patients which increase antitumor-specific immunity than compared

to other types of vaccine formulations. This could also be the future of the cancer vaccines which is much more effective than other vaccines.

**5. A nanoscale and Cell-free cancer vaccine:**

A true cancer vaccine should always be able to activate the immune system of the humans to identify the specific tumor antigen and then release an appropriate immune response towards cancerous cells without damaging the neighboring cells. Clinical trials for such vaccine yielded less than satisfactory results.

Exosomes interact rigorously with the cells of the immune system and research evidence has shown that these exosomes activate the dendritic cells and thereby activating the immune system to recognize it and kill the cancerous cells. Exosomes are basically derived by the number of centrifugation steps.

TEX is the exosomes purified from cancer cells. TEX mainly contains the tumor antigens and research evidence has shown to stimulate the cells of the immune system and reduce the growth of the tumor. There is also scientific evidence pointing towards TEX as tumor and RNA transporters which could safely serve as a useful diagnostic tool and biomarkers. Furthermore, evidence also shows that membranous bound Hsp70 TEX are much more efficient than cytoplasmic Hsp70 TEX. When dendritic cells are attacked with cancer antigens or else tumor peptides then DEX has been shown to improve the immune system towards the cancerous cells. This upregulates the specific antibody release and cytokine production. Evidence has shown that intradermal injection of DEX is much more efficient than subcutaneous which leads to the fact that there are more dendritic cells in the area of intradermal than subcutaneous area. (Hao S, 2006)

**6. Future directions:**

Although the results in clinical trial that exosomes can safely be administered, their ability to activate the appropriate immune responses to kill the cancerous cells still leaves much to be desired. Furthermore, exosomal immunotherapy relies on the immune system but there remains a need to address on this issue of cancer patients whose immune system is suppressed due to chemotherapy and radiotherapy and therefore this method alone cannot destroy the cancerous cells.

Carbon Nanotubes which are allotropes of carbon can also be utilized in delivery systems of cancer vaccine. There is research evidence that suggest CNTs when attached to tumor antigens, imparts a specific antitumor response in animals. (Fadel TR, 2008)

**7. Conclusion:**

The application of immunotherapy revolutionizes the development of cancer treatment. Utilization of exosomes in APCs which involved dendritic cells are now emerging as a more powerful technique to activate the immune system of the person in order to recognize and diminish the cancerous cells and eradicate the known tumors. Combining the use of exosomes with nanobiotechnology will likely be the future for the development of nanoscale cancer vaccines.

**ACKNOWLEDGEMENT:**

I would like to thank my friend Anushka Bhandari for giving me confidence during the course of work for this paper.

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## BIOGRAPHIES

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