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REVIEW ARTICLE

Exosome and Breast Cancer

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ABSTRACT:
Breast cancer is responsible for the death of millions of women worldwide every year. It is widespread in the world and Iraq that become a genuine problem for public health**.** Several clinical, diagnostic and pathological techniques have been introduced to get early detection of breast tumors. The uses of current known tumors markers have many limitations. New technique for diagnosis of breast cancer involve detection of extracellular vesicles (EVs) exosomes and its phosphoproteins as a product of cancer cells which represent a non-invasive liquid biopsy that may replace the invasive surgical method.

KEYWORDS: Breast cancer, Exosomes, Endosomes, Extracellular vesicles, Endosomal sorting complex required for transport (ESCRT) machinery.

INTRODUCTION:
Breast cancer is the most common cancer among women worldwide[1], comprising 23% of the 1.1 million female with cancers which newly diagnosed each year[2,3]. American Cancer Society estimated that 252,710 invasive breast cancer discovered in women in the United States in 2017 and there were 40,610 deaths, making this fatal second only to lung cancer as a cause of cancer death in women[4,5]. In Iraq, breast cancer is the common type of malignancy in females and there is a general direction towards an increase in the frequency of breast cancer as well as increase incidence in younger age group, also Breast cancer rates in Iraq region were generally stable between 2000 to 2009, but newer data from the Iraqi Cancer Registry reveal rising rates since 2009 with women after age 50 making the major contribution to the increase incidence of breast cancer. Patients fewer than 30 years old age formed about 5% of cases, whereas about 75% of the cases signed in women with women 40-60 years and the rest 20% represented women older than 60 years. The highest number of cases is between 40-50 years old age groups[6].

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Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk[7,8]. Cancers developing from the ducts are known as ductal carcinomas, while those developing from lobules are known as lobular carcinomas[9,10]. About 5–10% of cases are due to gens inherited from person's parent, including BRCA1 and BRCA2 among others[11].

In the late 1980s, the term 'exosomes' was first coined to characterize small endosomal-origin nanosized vesicles which are released during the maturation of reticulocyte with rich activity of 5'-nucleotidase, reflecting a particular subtype of secreted membrane vesicles[12]. "For the next 10 years, exosomes still not subjected to profound studies given that in early 2003 less than 20 PubMed-referenced articles using the term "exosomes" were released[13]. In endosomal compartments called multivesicular endosomes, exosomes are formed which contain internal vesicles that stack and store molecules in membrane-bound structures[14].

Endosomes are normally known as an intermediate compartment between the plasma membrane where extracellular molecular endocytosis occurs and the lysosomes that considered as the compartments in which the releasing and degradation of these molecules take place[14]. At the same time, studies of in vitro isolated exosomes from tissue cultures (immune cells, but also epithelial and tumor cells) began to demonstrate that exosomes released by one cell could be received by

another cell and information passed to the latter cell[15].

WHAT ARE EXOSOMES:

Exosomes are endocytic origin extracellular vesicles (EVs) with a size ranged from 30 to 120nm that produced in both pathological and physiological conditions[16]. The composition of exosomes represents the cell of origin and contains proteins, lipids, messenger and micro RNA, that have the ability to pass from donor to target cells[17]. The content of exosome may cause functional modifications in target cells that facilitate metastatic expansion, including a contribution to the creation of pre-metastatic niches[16]. For this reason, as potential biomarkers and therapeutic targets for cancer, cancer-secreted exosomes and their molecular material have gained considerable interest[18].

Compared with non-cancer cells, cancer cells secrete a significant amount of exosomes . Exosomes produced from cancer cells enhance the growth and mobility of cancer cells and the response of immune cells to cancer invasion and metastasis[19]. So Exosomes could be used as a source of biomarkers to assess metastatic dissemination, selective drugs delivery, cell-free vaccination of antitumor and gene therapy[19]. Exosomes have been shown to control metastasis in breast cancer through controlling stem cell activation, apoptosis, immune suppression, and drug resistance[20]. Exosomes are secreted by T-cells in a non-neoplastic context to modify the body's immune response to viral infections [21].

Biological function of exosoms:

Antigen presentation, immune modulation, tissue differentiation and remodeling, and cell-cell interaction are the biological functions of exosomes[22]. Exosomes, including proteins, metabolites, RNAs (mRNA, miRNA, long non-coding RNA), DNAs (mtDNA, ssDNA, dsDNA) and lipids, play an essential role in cell-to-cell communication[23,24]. In addition to controlling normal physiological processes, this communication also plays a vital role in pathological processes of the initiation of many diseases such cancers[24].

Exosomes likely affect other physiological processes, in addition to the immune system. Exosomes showed a wide variety of potential functions as they are secreted from muscle, neural, epithelial, and stem cells[7]. Exosomes, upon contact, cause physiological modifications in recipient cells. Since the initial definition of exosomes was in immune cells, a significant amount of information is available on the immunological effects of exosomes, which depend very strongly on the physiological condition of the cells that secrete them[25]. As such, mature dendritic cells secrete exosomes carrying antigens or peptide complexes of MHC-class 11 and trigger antigen-specific immune responses (especially in the context of anticancer) by other dendritic cells[26].

Target cell acquisition and internalization of exosomes may modify target cell functions by directly releasing their cargo into the cytoplasm or by activating juxtracrine signaling via receptor-ligand interactions[27]. As demonstrated in the diagram (1). In most cell types, exosomes are secreted and released into body fluids such as urine, plasma, saliva and breast milk[12].

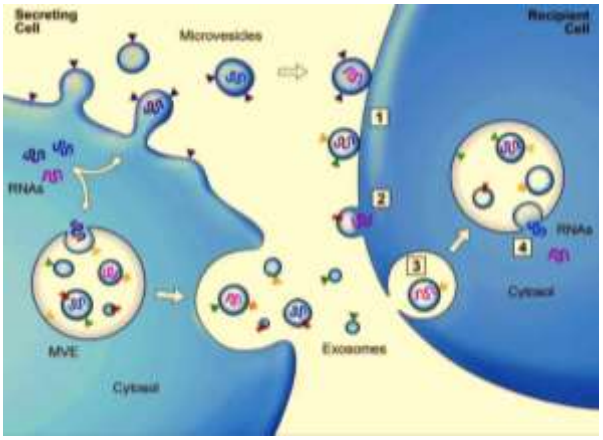

Figure (1): Exosome mediate cellular changes in recipient cells (Role of exosome in cellular communications)

Exosom biosynthesis:

Various kinds of EVs have been described and several species of secreted vesicles may be formed by the same cell. These various vesicle types are produced and demonstrated at separate subcellular locations[28]. Three forms of EVs (exosomes, microvesicles, and microvesicle clusters (MC)) have specifically been studied with regard to their biogenesis. Exosome biogenesis is characterized first by an endocytic event on the plasma membrane, and then by the maturation of early endosomes to late endosomes[29]. If shown in diagram (2). There are several forms of secreted vesicles and they may vary by size, biophysical and biochemical features, sub - cellular origin, pathway of biogenesis, processes of cargo uploading, and molecular content[17].

Exosomes are formed as intraluminal vesicles (ILVs) through the endocytic pathway and budding into early endosomes and multivesicular bodies (MVBs)[17,30]. MVBs are defined by the presence of small, cytosol-containing ILVs that are formed from the limiting membrane of late endosomes[31]. The fate of MVBs is either fusion with lysosomes for cargo degradation or fusion with the plasma membrane for releasing ILVs to the extracellular milieu as exosomes[17] (Fig.2). One of the well-known mechanisms that describe the formation of ILVs and cargo sorting involves the endosomal sorting complex required for transport (ESCRT) machinery[32,33]. ESCRT comprises four complexes (0, I, II, and III)[33].

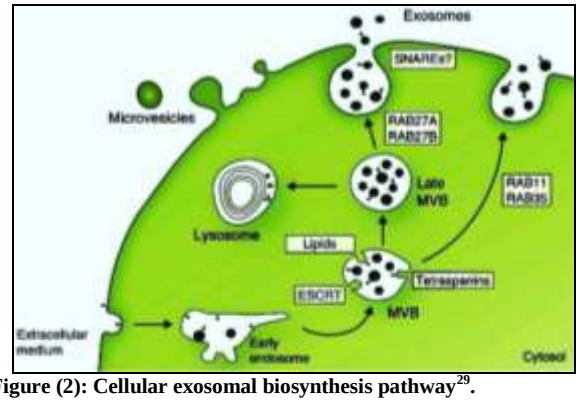

Figure (2): Cellular exosomal biosynthesis pathway[29].

ESCRT 0 involves cargo clustering by recognizing and sequestering ubiquitinated transmembrane proteins in the endosomal membrane. ESCRT I and II induce membrane deformation into buds with sorted cargo, and ESCRT-III drives vesicle scission. However, it should be noted that not all proteins are required for ubiquitination for their sorting into MVBs, and that ESCRT-independent mechanisms have been found to support that MVBs and ILVs can form in the absence of ESCRT function as inactivation of key proteins in the four different ESCRT complexes cannot block MVB formation. On the other hand, other subsets of ILVs release cargo to the cell's exterior in the form of exosomes, which appear to be ceramide biosynthesis-dependent and ESCRT-independent[34].

It remains to be investigated how cancer cells, as opposed to normal cells, package exosomes and regulate the sorting (degradation in the lysosome vs. release of exosomes) of vesicles within MVBs[31]. Special sorting mechanisms that target tumor-suppressing elements containing ILVs to the lysosome, as well as direct oncogenic-elements containing ILVs to the plasma membrane, are probably present in invasive cancer cells [27,34].

Isolation and Detection Techniques for Exosomes:

A-Isolation of Exosomes):

With the growing interest in EVs in research protocols, various isolation and detestation techniques have recently been developed[35].

1- Density-based isolation:

As the name suggests based on their density, particles are separated upon centrifugation[36].

2- Size-based isolation:

With exosomal size being known (<200nm), EVs can be separated from cells and large debris by using nano-sized membrane filters[37].

3- Affinity-based isolation:

To isolate EVs and study their relationship with cancer, new isolation techniques utilizing microfluidics are being developed, based on immunoaffinity capture with antibodies specific to EVs[38].

B- Detaction of exosoms:

Novel detection methods are required to explore the physical characteristics and biology of exosomes and EVs. To analyze them many techniques needed, including electron microscopy, light scattering, fluorescence, and molecular profiling[39]. So exsomes detected by one of these methods:

1- Size characterization:

Size and morphological information can be obtained from high-resolution imaging with electron microscopy utilizing transmission electron microscopy (TEM), scanning electron microscopy (SEM), or atomic force microscopy (AFM). The light scattering techniques determine the relative size distribution in a solution and the concentration of the particles[40].

2- Enzyme-linked immunosorbent assay (ELISA):

ELISA-based techniques provide information on the presence of surface markers and could be an indirect method to quantify exosomal proteins. Recently, various commercially available ELISA kits were used to validate EVs protein content (including exosome). This is a highly sensitive method for the quantitative analysis of exosomal proteins[38].

3- Western blotting (WB):

Western blotting is a convenient method to show the presence of exosomal protein. Surface markers include tetraspanins (CD9, CD63, CD81, and CD82), MHC molecules, and cytosolic proteins or cytoskeletal proteins[41].

The Weakness of Existing Tumor Biomarkers and the Promising Role of Plasmatic Exosomes as a tumor marker:

Currently the diagnosis and follow-up of cancer patients suffering the absence of specific biomarkers[42]. In fact, clinical oncologists often reliable screening test and tools that leads to mis- or overdiagnosis[43]. A clear example is one of the most used tumor biomarker CA 15-3 as show above, it increase in many malignant tumors other than breast cancer, also may elevated in number of benign tumors and other disease[44].

This should be also true for all the existing clinical tumor biomarkers which display a low level of specificity, while showing some sensitivity, but not discriminating patients at early stages of disease (false negatives), or detecting those with no disease (false positives)[45]. Recent studies have shown the potential use of circulating exosomes as biomarkers for predicting and monitoring a number of complex diseases, including cancers[46-48].

Because tumor cells actively shed tens of thousands of vesicles a day, it has been estimated that hundreds of billions of vesicles can be found in a milliliter of plasma [49]. So It has been reported that circulating exosomes may carry valuable information (DNA, RNA, and proteins) from their parental tumors, which make them ideal biomarkers to detect very early cancer stages, as recently shown in patients with breast cancer[50,51]. As a result, cancer derived exosomes may offer the potential of being the most sensitive and specific biomarker than currently available clinically used tumor biomarkers as they carry the cargo reflective of genetic or signaling alterations in cancer cells of origin[52,53].

EXOSOMES AS LIQUID BIOPSY:

The advent of next-generation sequencing technologies has proven their value in the search for novel, more comprehensive and less invasive biomarkers in order to truly realize the goals of cancer precision medicine, Such minimally invasive tests, known as a "liquid biopsies"[54,55]. Which gained plenty of traction in the last few years and the method was even recently listed as a top ten technology breakthrough in 2015 by the MIT Technology Review[56].

As tumors shed parts of themselves into the circulation, analyses of circulating tumor cells, circulating tumor DNA, and tumor-derived exosomes, often referred to as "liquid biopsies" may enable tumor genome characterization by minimally invasive means[56,57]. So, Exosome based liquid biopsy merits consideration over conventional tissue biopsy for following reasons:[58]

It provides the convenient and non-invasive way of diagnosis over tissue biopsy that required surgery[19].

The small sample size of tissue biopsy cannot provide the detailed information of genetic heterogeneity within the primary tumor or metastasized secondary tumors. exosomes shed from heterogeneous cancers can be collected at once and provide the dynamic information from the tumors at the time of blood drawing[19].

Surgical biopsy procedure is hampered by limited repeatability, patient age, comorbidity, costs, time consuming and potentially leading to clinical complications[56].

As a result, EVs (exosomes) offer all the same attractive advantages of a liquid biopsy, but without the sampling limitation and complications[59].

Role of Exosome in Breast Cancer:

Much of the pioneering work on EVs in cancer has focused on breast cancer, possibly because breast cancer remains the most common type of cancer affected women[60]. Currently, it is not possible to accurately predict the risk of developing metastatic disease or the response of patients to treatment, and this is reflected in up to 20% of patients who ultimately die of metastatic breast cancer[5]. While tumor cells are classically described to communicate via direct cell-to-cell contact and by release of soluble factors, such as cytokines and growth factors[61]. Alternative mechanisms have recently been described. That is by exosomes, which contribute significantly to the intercellular communication and subsequent reprogramming of the tumor microenvironment[25].

These findings provide novel insight into the tissue-specific outcomes of breast cancer-derived exosome which accumulation in breast cell and contribute to immune suppression and promotion of metastases[5]. Tumor recurrence and metastasis are important factors that reflect the prognosis of patients. Compared to breast cancer in situ, patients with an invasive tumor have a higher risk of recurrence and metastasis and should be monitored more frequently[62]. There are many methods to evaluate such risk factors, such as gene detection, but by now only a small number of genes have been identified (for example, gene screening for familial breast cancer patients) and the cost is relatively high[63].

Compared to gene assessment, exosome biomarkers are easier to be tested with less cost because those markers are mostly proteins and RNAs, which can be detected by regular western blot, FCM and PCR assay[64].

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