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Emerging approaches to genetic therapy in treatment for breast cancer

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Abstract

Breast cancer is one of the leading causes of death among women, which implies an urgent need to explore further alternative therapeutic strategies than conventional surgery, chemotherapy, and radiotherapy treatments. Thus, prevention should be highlighted through early genetic screening, not only among patients with clear risk factors but also among the general population in order to discover predisposition and intervene earlier.

The current therapeutic innovations are focused on improving such treatments by devising less invasive and more specific approaches. Examples include gene repair, such as halting tumor growth by restoring functionality to damaged genes using CRISPR and similar technologies. MicroRNAs have also shown much promise in controlling major cancer processes such as metastasis and cell division. Besides, nanoparticle-based drug delivery allows for more effective release of drugs. Consequently, there is lesser development of side effects. Suicide gene therapy is also commanding more attention against breast cancer as a less aggressive and hence more effective therapy with the appearance of selective killing of cancerous cells.

Keywords: Breast cancer; Gene therapy; Nanoparticle; mRNA vaccination

1. Introduction

Breast cancer is a genetically complex and heterogeneous disease, and essentially all tumor suppressor genes have been implicated-especially high-risk genes such as BRCA1, BRCA2, PALB2, CHEK2, CDH1, PTEN, STK11, and TP53. Several other genes including ATM, BARD1, BRIP1, CASP8, CTLA4, CYP19A1, FGFR2, H19, LSP1, MAP3K1, MRE11A, NBN, RAD51 and TERT have also been implicated as conferring an increased risk of breast cancer when mutated [1]. Of these, one of the most promising methods includes gene correction, where tumor growth is stopped by restoring the function of a gene through editing genetic material using tools like CRISPR. Because these genetic regulators can act both as tumor suppressors and oncogenes, miRNAs are increasingly being ascribed with therapeutic pertinence. This allows for intervention in key disease processes, including metastasis, cancer cell proliferation, and treatment resistance in breast cancer. Another extended strategy is the use of nanoparticles for drug administration, wherein systemic toxicity is reduced by allowing a more regulated and selective delivery of medication right to the tumor tissue. A more non-invasive method of fighting cancer cells, suicide gene therapy also makes use of genes that drive the tumor cells to undergo programmed cell death. These new approaches have started the change in the concept of breast cancer treatment options by improving the quality of life of the patients and increasing the efficacy of treatment, thus turning to a personalized and non-aggressive direction.

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2. Gene correction

Gene correction is a very modern therapeutic approach targeted at genetic mutations responsible for the onset and development of cancer. This method primarily focuses on the replacement of a mutated gene with a functional counterpart, bringing about the normalization of the cellular function and resulting in the loss by cancer cells of properties of malignant transformation.

Regarding breast cancer, in this context, the TP53 gene encodes a transcription factor and an oncosuppressor protein, p53, that regulates several intracellular metabolic pathways related to DNA damage repair, cell cycle arrest, apoptosis, and senescence. Most often, changes including mutations of the TP53 gene disrupt these pathways, leading to tumor development [2].

Recent progress n genome manipulation technologies took us closer, especially CRISPR/Cas9, to therapeutic gene editing for the treatment of cancer and hereditary diseases [3]. Thus, this gene, through mutations, leads to various cancers; hence, it's importance. This results in loss of their function due to mutations in these genes, leading to cells growing out of control, and causing tumor progression. This tumor development can be stopped by the correction of genes through various gene editing techniques like CRISPR-associated protein Cas 9, which enable us to edit genomes of a wide range of organisms in a fast and efficient manner. This effectively can be delivered to stop the multiplication of cancerous cells by the initiation of apoptosis, reducing the size of the tumor, thereby preventing metastasis.

While preclinical studies promise a great future for gene correction, gene correction alone is poorly effective in treating breast cancer; however, there is evidence that with common treatment options like chemotherapy or radiation therapy, gene correction significantly improves the therapeutic results [4].

3. Targeting miRNA

MicroRNAs are small ribonucleic acid (RNA) molecules that do not encode proteins, they have been widely investigated in the last few years due to their role in gene expression regulation and involvement in diseases, such as cancer [5]. Changes in the levels of certain miRNAS in blood plasma or tumor tissues are linked to cancer progression, as miRNAS influence key cellular processes such as cell growth, differentiation, DNA repair and apoptosis, they can also interact with the tumor microenvironment leading to causing an impact on tumor growth, metastasis and resistance to treatment.

These miRNAs can either function as either oncogenes (oncomiRNAs) or tumor suppressors. OncomiRNAs such as miR-21, miR-29 and miR-155 are shown to promote tumor growth, metastasis and survival by preventing events such as apoptosis. We see these miRNAs are often overexpressed in breast cancer and have been considered to be associated with a more aggressive disease.

On the other hand, miRNAs like miR-34 and let-7 act as tumor suppressors, inhibiting cancer cell growth and division [3]. When these tumor-suppressing miRNAs are down regulated, it can lead to uncontrolled tumor growth. Giving their different roles they are being investigated, by either inhibiting harmful oncomiRNAs or restoring the function of tumor suppression miRNAS, thus targeting miRNA can offer us a promising avenue for developing new breast cancer therapies.

4. Nanoparticles-based drug delivery

Nowadays, nanotechnology is already improving the health care system. Professionals are using nanoparticles in many ways, such as drug delivery systems, for targeting tumors and giving early diagnoses. Cancer treatments like nanoparticles-based drug delivery are multifunctional, they can both find tumor cells and carry drugs, objectively for controlled release and less aggressive treatment. One of the main interests in this approach is the reduction of harmful side effects associated with well-known cancer therapies available to most of the population [6].

There have been clinical trials using Nanoparticle Albumin Bound Paclitaxel highlighting the advantage of this treatment. The multicenter phase II trial that was performed in 2010, evaluated the efficacy and safety of weekly nanoparticle albumin-bound paclitaxel with carboplatin and weekly trastuzumab as first-line therapy for 32 women with HER2-overexpressing metastatic breast cancer. Only 10 patients (31%) of the 32 (100%) enrolled in the study had died. The other 22 patients were still alive at the time of analysis [7].

5. Lipid nanoparticle-based RNA therapy for the treatment of breast cancer

One of the great advantages provided by these nanoparticles is to offer a precise approach, good biocompatibility, toxicity and reduced adverse reactions [8].

Therapeutic messenger RNA (mRNA) has the ability to initiate protein expression in the cytosol without the need for nuclear transport, however, it is exposed to in vivo challenges, such as its rapid degradation by nucleases and low cell uptake due to its size and negative charge. Lipid nanoparticles (LNP) are not exposed to these challenges and provide a solution to this problem since they allow effective cell uptake and a powerful administration of mRNA in the body [9].

A recent study by El-Mayta et.al showed that C12-200 mRNA-LNP lipid nanoparticles have an mRNA encapsulation efficiency of 92.3% [10]. Meanwhile, Zhang et al. developed PTX aminolipid nanoparticles (PAL) that integrate chemotherapy with mp53RNA, achieving a high carrying capacity and encapsulation efficiency, as well as an antitumor effectiveness in triple negative breast cancer worlds in mice [11]. These discoveries open up new possibilities to combine chemotherapy with personalized medicine in the treatment of TNBC [12].

6. mRNA vaccination in breast cancer

Immunotherapy has transformed the treatment of breast cancer by focusing specifically on the tumor, which reduces side effects in patients due to its low toxicity. The main objective of this therapy is to activate an immune system response that reduces the tumor in a less aggressive way compared to other traditional treatments.

Over time, various drugs have been used in immunotherapy against breast cancer, and vaccines are currently being developed with innovative strategies in this field. These vaccines seek to activate the immune system so that it can identify and attack tumor cells by presenting tumor-specific antigens [13].

Among the most promising alternatives are nucleic acid-based vaccines, such as mRNA vaccines. This type of vaccine has become a promising alternative to traditional vaccines. mRNA, discovered between 1947 and 1961, acts as an intermediary between genes and proteins. Towards the end of the 1980s, in vitro transcribed mRNA began to be developed, and the first animal tests in 1990 resulted in improvements in its stability and a reduction in unwanted immune responses. Unlike DNA vaccines, mRNA vaccines allow temporary protein expression without the risk of causing DNA mutations. In addition, they are versatile, as they can be designed to encode different proteins and peptides, enhancing both cellular and humoral immune responses. Although these vaccines have been shown to be safe and well tolerated, clinical experience with them is still limited, and their short- and long-term side effects, which may include local or systemic inflammatory reactions [14].

The mRNA structure has a cap flanked by untranslated regions 5' UTE, 3' UTR, an open reading frame encoding cancer antigens in mRNA vaccines and a Poly A col. All these structures are modifiable with the aim of obtaining more stable, more efficient vaccines with more immunostimulatory properties. There may be 3 approaches to the design modification and optimization of mRNA components, these include, the design and optimization of the coding region where the aim is to add GC content to improve translation, in the same way it can be optimized by incorporating chemically marked nucleosides so that immunogenicity is reduced and translation efficiency is improved, modifications in nucleosides such as 5-methylcytidine, 1-methylpseudouridine and pseudouridine are where modifications are preferred in this case. Other forms of design and optimization are that of the non-coding region where the objective is to optimize the 5' and 3'-UTR elements to increase the efficiency and half-life of the mRNA and the design and optimization of the administration formats where there are two main ways to administer these mRNA vaccines [15].

To improve delivery, mRNA delivery platforms are being investigated that are more efficient and safer, allowing prolonged expression of antigens in the body. Some mRNA vaccine formulations have been shown to be able to induce strong immune responses without the need for additional adjuvants [16].

The whole mechanism of mRNA vaccines has been evolving over time and has been increasingly improved. One of the most recent clinical trials by Xinhui Li et al sought to identify the differences between the molecular subtypes of breast cancer in order to select patients most likely to benefit from immunotherapy, while ongoing research into the personalization of treatment according to the molecular subtypes of breast cancer opens a new perspective for immunotherapy in the future, promising an even more precise and efficient approach for each patient [17].

7. Suicide gene therapy

This therapy was introduced into the medical world in 1984 [18]. It consists of the administration of genes intended to encode enzymes that will activate non-toxic prodrugs into cytotoxic metabolites responsible for the death of the transfected cancer cells [19]. Although this approach has exhibited considerable clinical advances and is very promising for the treatment of cancer, it has not reached the expected clinical relevance so far.

There are several enzyme/prodrug systems in which mechanisms of action, protein strategies to improve stability, enzyme affinity, and chemical modification techniques for drug potential must be given important consideration [18]. Therapy can be approached in two ways: by a toxin gene that causes direct tumor cell death or by genes that activate prodrugs, releasing toxic metabolites into the tumor (GDEPT). Besides, for this therapy to be effective, some requirements need to be fulfilled. One of these is an administration system that ensures the toxin or the enzyme activating the prodrug is expressed only in the tumor cells and in a quantity sufficient to reach at least an effective concentration of its action, be it toxic or enzymatic. Another requirement is that in complex tumors where cancer cells may express the suicide gene at different levels, a "spector effect" is desirable, which allows a spread of the enzymatic activity to nearby unmodified cells, thus inducing toxicity. From the above, it is generally deduced that toxin agents may become more effective for direct action, while prodrug activating genes may facilitate the "spector" effect [19].

This is in regard to talking about the operationalization of suicide gene therapy for cancer [18], enhanced by the activation of small molecule pharmacological agents that may eliminate cancer cells within the tumor beyond the cells that are successfully translocated. This is possible through the spread of cytotoxic antimetabolites from the transduced cells expressing the transgene into the tumor, thereby able to significantly reproduce a tumor mass without needing to transduce a high percentage of cells [17]. One of the main limiting factors of this process has been the generally low transduction efficiency of the vectors, especially in solid and dense tumors, whose inner layer cells are difficult to reach [18].

The experience accrued during the last decades clearly shows that cancer is a multivariegated and continuously evolving disease, requiring an approach which combines traditional treatments with new strategies [20-23]. Within SGTC in particular, mention can be made of a specific strategy to apply, which minimizes damage to healthy tissue and eliminates only tumor cells; it is based on the administration of suicide agents using microbubbles that are destroyed by ultrasound, which allows for a less invasive intervention [18]. In addition, a structured approach, coupled with continued support in research and development, is quite necessary to tackle effectively the overall challenge of cancer gene therapy; and upon an evaluation of these terms, it can be carefully determined whether this technique and general therapy can be consolidated as a viable therapeutic option in cancer treatment or not.

8. Conclusion

The therapeutic approaches presented provide innovative strategies in the fight against cancer, each addressing unique aspects of tumor biology to improve treatment outcomes. Genetic correction is bases on reactivating mutations from their origin, although with the aim of restoring normal cellular functions and preventing malignant transformations. Targeting miRNAs is a method to modulate gene expression involved in cancer progression, employing both oncogenic and tumor-suppressing miRNAs to control cell growth and apoptosis. The drug delivery system with nanoparticles provides a better way of transporting therapeutic drugs to cancerous cells efficiently and minimizes side effects, hence increasing the efficacy of treatment. In breast cancer, RNA therapies and mRNA vaccines based on lipid nanoparticles emerge as promising tools in delivering personalized medicine and turning on immune responses. Suicide gene therapy offers a much more precise way to induce programmed cell death in cancer cells, having potential applications when combined with advanced delivery. While all these techniques are promising, problems with gene delivery, specificity of treatment, and long-term effects persist. The combination of such strategies with conventional treatments may yield better outcomes and open new perspectives towards more selective and effective cancer therapies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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