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REVIEW

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Tissue engineering applications in breast cancer

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ABSTRACT

In Iran, breast cancer (BC) is the most prevalent cancer among women. The standard treatment for this cancer is partial or total removal of breast tissue, followed by chemotherapy and radiation. Tissue engineering (TE) has made new treatments for tissue loss in these patients by creating functional substitutes in the laboratory. In addition, cancer biology combined with TE provides a new strategy for evaluation of anti-BC therapy. Several innovations in TE have led to the design of scaffold or matrix based culture systems that more closely mimic the native extracellular matrix (ECM). Currently, engineered three-dimensional (3D) cultures are being developed for modelling of the tumour microenvironment. These 3D cultures fulfil the need for *in vitro* approaches that allow an accurate study of the molecular mechanisms and a better analysis of the drugs effect. In the present study, we review recent developments in utilising of TE in BC. Moreover, this review describes achievements of Iranian researchers in the field of breast TE.

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1. Introduction

In Iran, breast cancer (BC) is the most prevalent cancer among women, with comprising 24.6% of all cancers with age-standardised rate (ASR) of 22.6 per 100,000 [1]. This cancer is the first cause of death in less developed countries (324,000 deaths, 14.3%), and the second in more developed countries (198,000 deaths, 15.4%) [2]. The majority of cases in Iran are diagnosed at early stages, and the prevalence of advanced stage (stage III) is reported to be 17% [3]. For this cancer, the standard treatment is Lumpectomy (partial removal of the breast tissue) or mastectomy (total removal of the breast tissue), followed by chemotherapy and radiation [4,5].

Tissue engineering (TE) has made new treatments for tissue loss in these patients by creating functional substitutes in the laboratory. In addition, different innovations in the context of TE also provided new technology platforms to study mechanisms of tumour cell growth and tumour cell spreading in cancer research. TE models of cancer attempt to mimic cancer tissues by including cells and extracellular matrix (ECM) in a three-dimensional (3D) arrangement [6,7]. These 3D cultures fulfil the need for *in vitro* approaches that allow an accurate study of the molecular mechanisms of cancer initiation and a better analysis of the drug effect [8,9]. In the present study, we review recent developments in utilising of TE in BC. Moreover, this review describes achievements of Iranian researchers in the field of breast TE.

2. Tissue engineering and breast reconstruction

Breast reconstruction is a valuable option to any woman undergoing surgery. However, there are different complications. A majority of breast reconstructions are performed by using silicone-based implants or autologous tissue transplantation [8]. It is known that reconstruction using implants leads to the formation of a stiff fibrous tissue surrounding the implant over time and give the unusual appearance to the breast. Since breast implants also have a cosmetic function, its need a variety of factors to achieve an ideal surgical outcome [8,9]. Reconstruction using autologous tissue is also associated with long-term resorption and tissue necrosis [10,11]. Research is therefore focussed on breast TE. This field combines engineering, cell

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biology, biomaterials and plastic surgery in order to reconstruct breast following mastectomy [12]. Adipose-derived stem cells (ADSCs) are rapidly becoming the standard cell source for TE. These cells are suitable for breast reconstruction due to their characteristics such as proliferative and differentiation capacity along with stromal support of cancer cells and delivery of growth factors. These cells can be easily isolated from subcutaneous adult adipose tissue after liposuction by enzymatic digestion and culture of the stromal vascular fraction (SVF). However, the oncological safety of implanting ADSCs into patients with BC due to the risk of cancer recurrence remains to be fully elucidated [10,11].

In a study, Wu et al. [12] prepared self-assembling RADA16-I peptide hydrogel scaffold loaded with tamoxifen for breast reconstruction. The ADSCs isolated from liposuction were attached to the scaffold. The results suggested that this scaffold provide support for ADSCs cells attachment/proliferation and retain cytotoxic effect on MCF-7 cells, which might be a promising therapeutic breast tissue following lumpectomy. Schusterman et al. [13] reported a novel method of breast reconstruction using a 3D absorbable mesh scaffold and subsequent autologous fat grafting (AFG). Twenty-two patients underwent reconstruction and all patients were satisfied with final breast shape and size. Postoperative mammogram and magnetic resonance imaging revealed robust adipose tissue in the breast with a gradually resorbing mesh and no oil cysts or calcifications. Recently, Baldwin et al. [14] developed a novel tannic acid-collagen type I injectable bead scaffold material for breast reconstruction post lumpectomy in an *in vivo* rat model. Tannic acid is a polyphenol with anticancer and antibiotic properties. After 12 weeks, implants showed incorporation into native tissue with no fibrous encapsulation. Despite the presence of inflammatory cells in the remaining beads, fat tissue growth and collagen redistribution were observed within the beads over 12 weeks, showing incorporation within native subcutaneous tissue and indicating good biocompatibility and bioactivity of the implant.

3. Scaffold-based tissue engineering in breast cancer

The innovative in TE was application and fabrication of scaffolds that are needed in tumour microenvironment engineering for effective cell seeding. Scaffolds that have been used in TE adipose tissue can be divided by origin into natural or synthetic and by structure into solid scaffolds or hydrogels [15]. Some materials, such as Matrigel, collagen, fibronectin, gelatine, alginate, chitosan and silk fibroin are derived from natural resources, whereas others are generated from synthetic materials using polycaprolactone (PCL), poly lactic-co-glycolic acid (PLGA), poly ethylene glycol (PEG) and hydroxyapatite (HA) [16]. Different scaffolds that are used in BC study are listed in Table 1.

The environment-mimicking 3D cultures have shown advantages in the studies of tumour cell biology. 3D scaffolds can mimic the ECM of connective tissues and provide architectural support for TE and regeneration with selecting of cell types [31].

4. Tissue engineering and breast cancer therapy

Cancer biology combined with TE provides a new strategy for evaluation of anti-BC therapy. BC initiation and progression require interactions between mammary epithelial cells and their surrounding microenvironment, including the ECM [32,33]. In BC, major changes are observed in the ECM structure in comparison to normal breast tissues (Table 2). Woodward et al. [53] proposed that the drug therapy sensitivity of BC can increase by changing the ECM components. Moreover, the matrix composition can be used to deliver drugs. Mårlind et al. [54] showed that antibody-mediated delivery of interleukin-2 (IL-2) to the stroma of BC strongly increases the potency of chemotherapy and treatment with IL-2 synergised with paclitaxel therapy can repress tumour growth.

Currently, in the field of TE, increasing interest is emerging in artificial ECM as an applicable scaffold that can mimic native ECM [55]. Therefore, artificial ECMs should be designed by adopting the real chemical complexity and structure of a native ECM. Moreover, in recent years, drug delivery systems are rapidly evolving for cancer therapy. In a study by Subia et al. [56], a 3D silk fibroin scaffold based co-culture model was designed to observe the interactions of the BC cells within the bone microenvironment. The effects of targeted delivery of doxorubicin loaded folate conjugated fibroin nanoparticles (NPs) on the cancer cell growth in co-culture construct were observed. The co-culture of cancer cells with the osteoblast-like cells displayed the decreased population of the cancer cells, invasiveness and angiogenesis after the treatment.

Table 1. Different scaffolds that are used in breast cancer (BC) study.

Type of scaffold	Application
Polyurethane (PU) foam scaffold [17]	To reproduce a bone biomimetic microenvironment, useful for the co-culture of human osteoblasts/BC tumour-initiating cells and to investigate their interaction
Nanoclay-based [18]	To study mechanisms governing the later stage of cancer pathogenesis in bone
Human decellularised adipose tissue scaffold (hDAM) [19]	To provide BC cells with a biomimetic microenvironment *in vitro* that more closely mimics the *in vivo* microenvironment and thus can provide vital information for the characterisation of cancer cells and screening of cancer therapeutics
Porous PLGA/PLA microparticles [20]	To use as a model system for preclinical evaluation of the cytotoxic effect of anticancer agents
Silk scaffold [21]	To provide an important first step for bioengineering an informative human breast tissue system to study normal breast morphogenesis and neoplastic transformation
Collagen coated gelatine nanofibrous matrix (CCGM) [22]	To use as a tissue-like 3D model for studying BC metastatic events *in vitro*
Photocrosslinked PEG scaffolds [23]	To provide insight into the potential for oncogene-transformed cells to migrate within and colonise tissues of varying stiffness
Hydroxyapatite (HA) nanoparticle-containing scaffolds [24]	To study cancer biology and to define design parameters for non-tumorigenic mineral-containing or mineralised matrices for bone regeneration
Electrospun polycaprolactone–chitosan nanofiber scaffolds [25]	BC stem-like cells (BCSC) populations are enriched in cells cultured on electrospun poly(ε-caprolactone)-chitosan nanofibers, scaffolds that may provide a useful system to study BCSC and their response to anticancer drug treatment
3D printed nanocomposite matrix [26]	To study metastasis and assessing drug sensitivity in BC
Multi-walled carbon nanotube scaffolds [27]	To use *in vitro* metastasis studies of BC cell lines
Poly(ε-caprolactone) (PCL) fibres [28]	To study how the 3-D microenvironment affects the behaviour of BCCs
Free agarose hydrogels [29]	To allow for the formation of more differentiated, estrogen-responsive structures that are a more relevant system for evaluation of oestrogenic compounds than traditional 2D models
Human-fibronectin (MB-FN3VEGFR2) scaffold [30]	To use in ultrasound molecular imaging (USMI) of BC neoangiogenesis

Table 2. ECM components in breast cancer (BC) in comparison to normal breast tissues.

Collagens	Increased accumulation of fibrillar collagens I, III and V, and decreased of type IV collagen in BC [34,35]
Fibronectin	Upregulation in cancer cells [36]
Laminins (LM)	Loss of expression of LM-111 in BC [37]
Hyaluronan (HA)	Increased in BC in comparison to normal breast tissues [38]
Versican	Increased accumulation within the ECM of peritumoural stroma [39,40]
Decorin	Increased expression in the normal mammary gland and reduced expression in BC [41,42]. Decorin is tumour suppressor [43].
Lumican	Low lumican expression is associated with poor overall survival in BC. Lumican is tumour suppressor [44].
Syndecan-1 (SDC-1)	Expression of SDC-1 in the stroma of BC predicts poor overall survival [45].
Glypican-1 (GPC1)	Increased expression in BC in comparison to normal breast tissues [46]
Tenascin C (TNC)	Very low expression in healthy mammary glands while highly up regulated in BC especially at invasive fronts [47,48]
Periostin (POSTN)	Increased expression in BC compared to normal human breast tissues [49]
Secreted protein, acidic and rich in cysteine (SPARC)	Increased expression in BC compared to normal breast tissue. Expression of SPARC is also linked to poor clinical outcome [50,51]
Thrombospondin (THBS)	In BC models, THBS1 leads to inhibition of primary tumour growth [52]

5. Tissue engineering and breast cancer research

One of the challenges in cancer research is to develop *in vitro* models of human tumours. One special focus that has emerged from TE research is the development of nanoscale drug delivery systems using liposomes and nanoparticles (NPs) to facilitate the rational delivery of chemotherapeutic drugs in the treatment of malignant diseases. Recent developments have led to multifunctional NPs capable of targeting and controlled release of therapeutic and diagnostic agents. Among the published methods, short-peptide-based molecular hydrogels formed by biocompatible methods have been claimed to hold a potential for TE and controlled drug delivery [57,58].

In addition, one of the novel clinical approaches to tackle BC is the engineering of dormant stage. Dormancy has been implicated with cell cycle arrest and drug resistance [59]. Primary breast tumours can transform to invasive BC and this transformation is also known as epithelial–mesenchymal transition (EMT) [60]. During EMT, the BC cells lose their polarity

and specialised E-cadherin-based cell–cell contacts, and they acquire a migratory phenotype, which is associated with an increase in metastatic potential [61]. It is established that dormant tumour cells can stay in a non-dividing level for many years with chemo resistance and radiation resistance characteristics [62]. There is a growing need to understand this mechanism of dormancy in order to develop therapies to target these cells [63,64]. In recent years, several researchers have demonstrated 3D models of cancer cell dormancy [28,65,66]. For example, Marlow et al. [65] fabricated a 3D co culture model by culturing mesenchymal stem cells (MSCs) together with endothelial cells (ECs) and BC cells in a 3D collagen matrix. BC cells in co cultures proliferated less than in monocultures and appeared to be cell cycle arrested. Recently, Cui et al. [67] reported engineering a novel 3D printed vascularised tissue model for investigating BC metastasis to bone. They demonstrated that the 3D printed tissue construct by incorporating multiple cells and various ink matrices can provide a suitable model for studying the interaction between these cells in a complex vascular microenvironment. Therefore, it will be helpful for the screening of novel anticancer drugs.

6. Breast tissue engineering in Iran

Currently, many universities and research institutes in Iran are conducting active research in the field of TE. The most studies are in the fields of bone and neural TE [68]. However, in recent years, Iranian researchers had achievements in the field of breast TE including breast reconstruction and tumour models for anticancer therapy.

Nafisi et al. [69] published a paper describing the use of acellular dermal matrices (ABDMs) in implant-based breast reconstruction. They conclude that the application of ABDMs has promising outcomes for breast reconstruction to provide total coverage without the need for breast expansion before implant placement. In a study by Mahmoudzadeh and Mohammadpour [70], the impact of cultured 4T1 cancer cells, which mimics stage IV of human BC, was examined in a 3D collagen–chitosan scaffold. Their study indicated that collagen–chitosan nanoscaffolds provide a suitable model for tumour studies. In a study that was conducted by Maroufi et al. [71], the potential application of compritol was investigated as a major scaffold into nanostructured lipid careers to highlight myricetin efficiency in treatment of BC cells along with codelivery of docetaxel (DXT). Their results represented that the nanostructured lipid carriers (NLCs) delivery system could be a promising strategy to improve the effect of anticancer agents such as DXT on BC. Researchers from Shiraz University of Medical Sciences investigated the expressions of insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF) and CXCL8 (IL-8) in BC cells and ADSCs isolated from breast tissue of women with BC. Their results showed that the presence of resident ASCs within the scaffold of breast tissue may support breast tumour growth and progression through the expressions of tumour promoting factors [72].

7. Conclusions

TE provides a promising mean to further understand BC aetiology. A model that can mimic different stages of BC metastasis might be a potential option for future studies. This model will provide a platform for analysing the different stages during disease progression. Another future interesting direction would be design biomimetic scaffolds that align scaffolds with biomolecules for investigating BC biological processes.

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Disclosure statement

The authors report no conflicts of interest.

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