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Recent advances in peptide-based therapeutic strategies for breast cancer treatment

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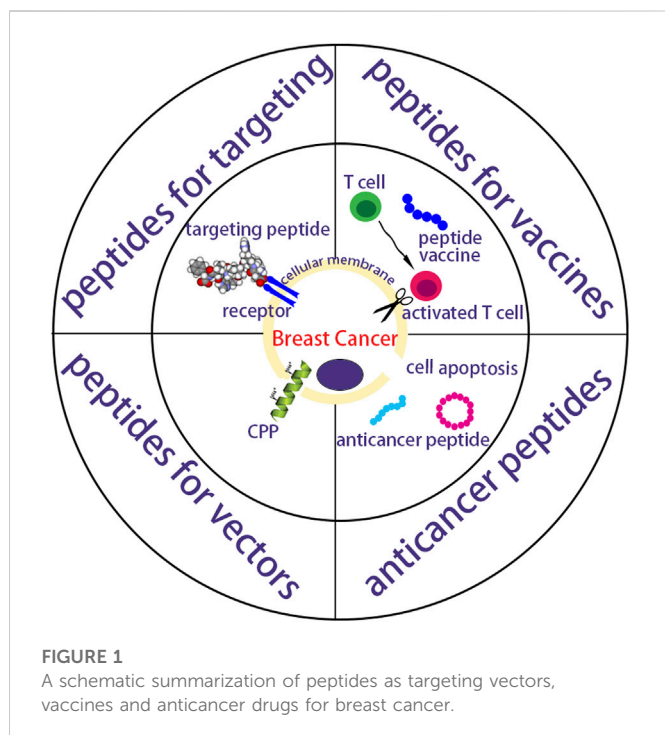
Breast cancer is the leading cause of cancer-related fatalities in female worldwide. Effective therapies with low side effects for breast cancer treatment and prevention are, accordingly, urgently required. Targeting anticancer materials, breast cancer vaccines and anticancer drugs have been studied for many years to decrease side effects, prevent breast cancer and suppress tumors, respectively. There are abundant evidences to demonstrate that peptide-based therapeutic strategies, coupling of good safety and adaptive functionalities are promising for breast cancer therapy. In recent years, peptide-based vectors have been paid attention in targeting breast cancer due to their specific binding to corresponding receptors overexpressed in cell. To overcome the low internalization, cell penetrating peptides (CPPs) could be selected to increase the penetration due to the electrostatic and hydrophobic interactions between CPPs and cell membranes. Peptide-based vaccines are at the forefront of medical development and presently, 13 types of main peptide vaccines for breast cancer are being studied on phase III, phase II, phase I/II and phase I clinical trials. In addition, peptide-based vaccines including delivery vectors and adjuvants have been implemented. Many peptides have recently been used in clinical treatments for breast cancer. These peptides show different anticancer mechanisms and some novel peptides could reverse the resistance of breast cancer to susceptibility. In this review, we will focus on current studies of peptide-based targeting vectors, CPPs, peptide-based vaccines and anticancer peptides for breast cancer therapy and prevention.

KEYWORDS

peptides, breast cancer, targeted vector, CPP, Cancer Vaccines, anticancer drugs

1 Introduction

Cancer is a common cause of death, especially in the developing countries (Dissanayake et al., 2017). It resulted in over 9.95 million human deaths in 2020 provided by GLOBOCAN. Among female cancer patients, breast, lung, colorectal, cervical, and gastric cancers are the most common types of cancer. In these cancers, breast cancer is the second major cause of cancer-related fatalities worldwide in female (DeSantis et al., 2014) and has been the commonest cancer diagnosed in clinic until December 2020, according to statistics released by the International Agency for Research on Cancer (IARC). According to the data reported by Siegel et al., there were approximately 279,110 breast cancer patients in women and men, and about 48,530 *in situ* breast cancer cases in the United States alone (Siegel et al., 2020). The average 5-year survival rate of progressed metastatic breast cancer patients is only 22% (Terjung et al., 2014). However, the 5-year survival rate of patients with breast cancer in China has a gap of approximately 8%



compared with those of the United States and Europe (Ma et al., 2021). Based on the estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor-2 (HER2) status, there are three breast cancer subtypes: HER2-positive, hormone receptor-positive and triple negative subtypes (Parise and Caggiano, 2014). Among all the breast cancer, hormone receptor-positive breast cancer constitutes approximately 60%–70% (Hart et al., 2015), while the proportion of triple negative breast cancer (TNBC) is about 15%–20% (Marra et al., 2019), and the remainder are HER2-positive breast cancer subtype. Although breast cancer is a major cause of cancer-related fatalities in female (Loftus et al., 2021), it may well be cure if it is early diagnosed and appropriately treated.

There are several traditional treatments for breast cancer: targeted therapy (Gilbert et al., 2021), radiotherapy, chemotherapy, surgery (Riis, 2020), and hormone therapy, often together or in various combinations which depend on the breast cancer subtype. Among these treatments (Blanco et al., 2011; Hou et al., 2019), chemotherapy plays a basic role for treating breast cancer in clinic (Pérez-Herrero and Fernandez-Madarde, 2015; Parikh et al., 2017) and will keep up integration as a backbone in the treatment of breast cancer for the near-future (Maeda, 2015; Claessens et al., 2020). However, the high dosage of chemotherapy drugs ultimately leads to serious side effects and multi-drug resistance (Fan et al., 2016; Suo et al., 2016). Thus, the goal is to reduce or even avoid toxic side effects and resistance (Suo et al., 2017).

Peptides exhibit scalable production, good safety and adaptive functionalities, and are important for delivering different anticancer drugs like biopharmaceuticals and chemical drugs (Deming, 2016; Mazo et al., 2020). The drug-free neutrally charged peptide, containing a cationic peptide guanidinium-functionalized poly(L-lysine) and a pH-sensitive peptide poly(ethylene glycol)-b-poly(L-lysine)-graft-cyclohexene-1,2-dicarboxylic anhydride, exhibited similar efficacy against resistant MCF-7/ADR cells and MCF-7 cells *in vitro* (Yang et al., 2022). These neutrally charged peptides also circumvented *in*

in vivo instability and toxicity of cationic charged anticancer medicines. The phenylalanine dipeptide (FF) can self-assemble by π - π stacking (Reches and Gazit, 2003) into either vesicular structures or a nanotube structure at low concentrations (<7 mg/mL) or higher concentration (>10 mg/mL) respectively (Song et al., 2004). Wang et al. synthesized RAFF modified with polyethylene glycol (PEG-RAFF) self-assembled nanospheres for surviving siRNA delivery (Han et al., 2019). In the HER2 extracellular domain, antigenic peptide CH401 (YQDTILWKDIFHKNNQLALT) was expected to effectively activate both CD4⁺ and CD8⁺ and thus induce T cell response (Ishida et al., 1994; Miyako et al., 2011), and co-assembling vaccines composed of peptide CH401 and additional lipid chains had enhanced vaccine potency (Aiga et al., 2020). In this review, peptides working as targeted nano-vectors, cancer vaccines and anticancer drugs in treating breast cancer are highlights (Figure 1). Anticancer strategies involving peptides will show increasing clinical translation in the future.

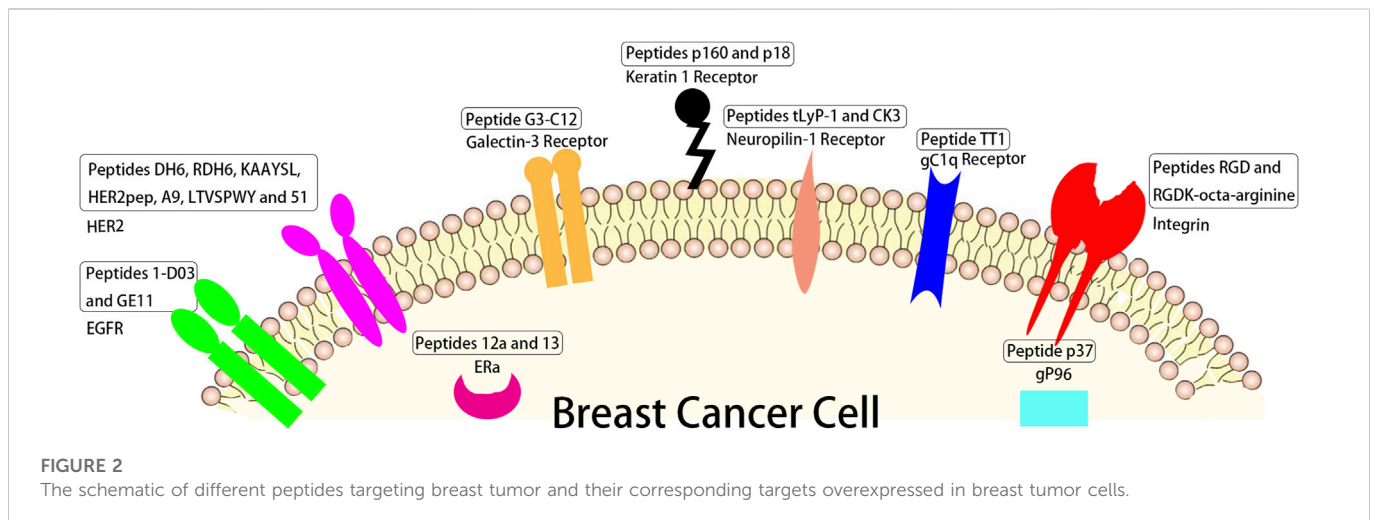
2 Peptides for anticancer drug vectors

Nucleic acid therapy appears to be a promising strategy of cancer treatment for its abilities to overcome many challenges such as metastasis, drug resistance, genetic alterations, tumor microenvironment heterogeneity, and tumor relapse (Jin et al., 2020). However, nucleic acid therapy containing small interfering RNA (He et al., 2014), microRNA, aptamers (Zhou et al., 2016), and immune adjuvant nucleic acids (Zhang et al., 2018), still faces several obstacles: low solubility, instability, weak permeability, uncontrolled drug release kinetics and lack of target specificity. Some organic materials including liposomes (Eckstein, 2014), polymersomes, micelles, peptides and dendrimers work as nanotechnology vectors for protecting nucleic acids and targeting tumor cells (Chan et al., 2009; Pan et al., 2017). Among these targeting vectors, peptides (Shukla et al., 2014; Numata, 2015) have attracted a lot of attention due to the ease of manipulation and inherent biocompatibility (Zhao and Jiang, 2018; Liu et al., 2019). In addition to good biocompatibility (Singh et al., 2018; Cummings et al., 2019), peptides (Tai and Gao, 2017; Yang et al., 2018) with desirable sequences (Wang et al., 2018; Zhang and Lu, 2018) could further enhance the transfection efficacy (Li et al., 2018; Kuai et al., 2019).

2.1 Peptides for targeting breast cancer

Heat shock protein (HSP) gp96 (Hou et al., 2015), a molecular chaperone residing in the cell membrane of cancer cells, is usually used as a target in cancer treatment (Hou et al., 2015; Li et al., 2015). Peptide p37 (LNVSRETLQKHLLKLVIRKLVKTLDMIKKIADDKY), which can specifically recognize the N-terminal helix-loop-helix sequence of gp96, is able to disrupt intramolecular helix-helix interaction and inhibit gp96 conformational changes, thereby destroying its chaperoning function (Li et al., 2015; Qian et al., 2019). Liang et al. (Liang et al., 2021) modified cationic liposome CDO14 with p37 to form p37-CDO14 with gp96-targeted function and found that p37-CDO14 could specifically bind to gp96-overexpressed breast cancer cells on cytomembrane (Figure 2).

3-mer peptide RGD prepared by Pierschbacher and Ruoslahti from fibronectin (Pierschbacher and Ruoslahti, 1984; Garate et al.,



2015), can recognize several integrins, some glycoproteins composed of α and β subunits (Demircioglu and Hodivala-Dike, 2016; Cheng and Ji, 2019) which are overexpressed on the cancer cell membrane and involved in angiogenesis, tumor growth (Nieberler et al., 2017) and metastasis (Wu et al., 2019; Chen et al., 2021). Hazeri et al. (Hazeri et al., 2022) fabricated a targeting delivery system for doxorubicin (DOX) with mesoporous silica nanoparticles loaded with AS1411 aptamer and peptide RGDK-octa-arginine. The results revealed this targeting delivery system could obviously enhance the anticancer activity of DOX with single-dose administration *in vivo* (Figure 2).

Linear peptide TT1 (AKRGARSTA) was often used to modify the surface of liposomes for targeting protein p32 (Simón-Gracia et al., 2018; Simón-Gracia et al., 2018), known as a transmembrane gC1q receptor, which is overexpressed on the cellular surface of cancer and cancer associated cells, like active angiogenic endothelial cells (Rubinstein et al., 2004), cancer associated fibroblast (Fogal et al., 2008), and cancer associated macrophages (TAMs) (Agemy et al., 2013; Sharma et al., 2017). The cell results showed that the liposome modified with linear peptide TT1 had better interaction with 3D breast cancer spheroids than non-modified one and that 50% of the total nanovesicles were internalized in M2 primary human macrophages (d'Avanzo et al., 2021) (Figure 2).

Peptide tLyP-1 (CGNKRTR), a tumor homing ligand, can specifically target neuropilin-1 receptor overexpressed in breast cancer (Bielenberg et al., 2006; Zhu et al., 2018). Zhong et al. found that tLyP-1 peptide-functionalized chimaeric polymersomes showed well ability of loading of siNAC-1 (up to 14.4 wt. %) and potently inhibited MDA-MB-231 cell invasion and migration (Wang et al., 2020a). Peptide CK3 (CLKADKAKC) as described by Feng et al. (Feng et al., 2014) showed higher ability binding to MDA-MB-231 breast tumor cells than other breast tumor cells such as 4T-1, MCF-7 and MDA-MB-435 breast tumor cells (Figure 2).

Linear dodecapeptide p160 (VPWMEPAYQRFL) displays strong binding to MCF-7 and MDA-MB-435 breast tumor cells according to the target of keratin 1 receptor (Askoxylakis et al., 2005). Its analogue peptide p18 (WXEAAYQRFL), proteolytically stable in human serum, binds to keratin 1 receptor (Shahin et al., 2013), and DOX loaded P18-PEtOx-dioleoyl phosphatidyl ethanolamine (DOPE) nanoliposomes

designed for targeting AU565 cells elicited a strong antitumor response compared to free DOX (Bolat et al., 2021) (Figure 2).

Peptide G3-C12 (ANTPCGPYTHDCPVKR) specific binding to galectin-3 receptor, which is a 30 kDa protein and associated with cancer metastases and growth in breast cancer (Morris et al., 2004), was connected with 1,4,7,10-tetra-azacyclododecane-N,N',N''N'''-tetraacetic acid (DOTA) by a peptide GSG linker which was radiolabeled with ^{111}In for breast cancer targeting (Kumar and Deutscher, 2008). The results showed the peptide G3-C12 can significantly bind to human MDA-MB-435 (galectin-3) cells (Figure 2).

ERs contain ER α and ER β (Nilsson et al., 2011), in which ER α activated for proliferation of breast and uterine tissues (Frasor et al., 2003; Helguero et al., 2005) was overexpressed in more than 70% of breast cancers (Holst et al., 2007), thus ER α is the an important target for treating ER α positive breast tumor (Qin et al., 2018). Peptides 12a (HKIKHRLIQ) and 13 (Rcyclo (DILDap) RLLQ) as reported by Zhao et al. showed significant binding to ER α receptor (the value of KD were 118 nM and 85 nM respectively) (Zhao et al., 2016) (Figure 2).

The HER2 positive accounts for over 20% in all breast cancer patients (Schrama et al., 2006; Okines and Cunningham, 2010). This type of breast cancer has poor prognosis, strong invasiveness, and a high recurrence rate (Slamon et al., 1987), so drugs for targeted therapy of HER2 positive breast cancer are good for HER2 positive patients mostly in the early stages of their disease. Du et al. designed peptides DH6 (YLFFVFER) and RDH6 (REFVFFLY) conjugated with PEG that showed good metabolic stability and specially targeted HER2 positive tumors, while not HER2 negative tumors (Du et al., 2020). Stefanick et al. (Stefanick et al., 2015) reported targeting HER2 positive tumors with peptides HERP5, HRAP, KAAAYSL, and AHNP for cellular uptake, in which peptide KAAAYSL had the maximum tumor uptake. Kim et al. (Kim et al., 2020) prepared liposomal nanoparticles with DOX-lipid conjugates and HER2pep (selected form peptides reported by Stefanick et al. (Stefanick et al., 2015), the sequence is YCDGFYACYMDV) lipid conjugates, and the nanoparticles at 0.5% peptide density enhanced ~ 2.7 fold and ~ 3.4 fold the uptake of HER2 positive tumors with EG8 and EG18 linker over non-targeted nanoparticles, respectively. A9 non-peptide (WAVQNTDAV) site-specifically conjugated with diethylene triamine penlaacetic acid (DTPA) and radiolabeled with ^{111}In

TABLE 1 Summary of the major peptides against breast cancer with respective targets.

Peptide	Sequence	Target/Ref.
P37	LNVSRETQHQHKLKLVIRKLVKRLTLDMIKKIADDKY	gp96 Liang et al. (2021)
RGD/RGDK-octa-arginine	RGD/RGDK-octa-R	Integrin Garate et al. (2015); Hazeri et al. (2022)
TT1	AKRGARSTA	gC1q Simón-Gracia et al. (2018)
tLyP-1/CK3	CGNKRTR/CLKADKAKC	neuropilin-1 Zhu et al. (2018); Feng et al. (2014)
p160/p18	VPWMEPAYQRFL/WXEAAAYQRFL	keratin 1 Askoxylakis et al. (2005); Shahin et al. (2013)
G3-C12	ANTPCGPYTHDCPVKR	galectin-3 Kumar and Deutscher (2008)
12a/13	HKIKHRLQ/Rcyclo (DILDap) RLLQ	ER Zhao et al. (2016)
DH6/RDH6/KAAYSL/ HER2pep/A9/LTVSPWY/51	YLFFVFER/REFVFFLY/KAAYSL/YCDGFYACYMDV/WAVQNTDAV/ LTVSPWY/ATWLPVPPVVGFMASA	HER2 Du et al. (2020); Kim et al. (2020); Stefanick et al. (2015); Honarvar et al. (2018); Larimer et al. (2014)
1-D03/GE11	MEGSPKCCYSLALSH/YHWYGYTPQNVI	EGFR Larimer et al. (2014); Hailing et al. (2022)

(Honarvar et al., 2018) was conducted for non-invasive imaging of HER2 positive tumors, and the results showed that DTPA-A9 had sufficient *in vivo* stability. Martyna Michalska et al. (Michalska et al., 2016) designed peptide LTVSPWY functionalized alloyed CuInZnS₂+x quantum dots as a fluorescent nanoprobe of HER2-positive breast tumors, and peptide LTVSPWY worked for targeted binding to HER2. Peptide 51(ATWLPVPPVVGFMASA) selected by Larimer and Deutscher (Larimer and Deutscher, 2014) was used to target BT-474 human breast cancer and other HER2 positive cancers in order to reduce the non-target accumulation in other tissues (Figure 2).

Epidermal growth factor receptor (EGFR), a transmembrane receptor, is an attractive target for strategies of breast cancer treatment (Gonzalez-Conchas et al., 2018). Its overexpression is correlated with reduced overall survival and disease-free and poor prognosis in breast cancer patients (Herbst and Shin, 2002). Peptide 1-D03 (MEGSPKCCYSLALSH) selected from a phage microlibrary by Larimer et al. (2014) showed high specificity for only MDA-MB-435 cells according to EGFR. Peptide GE11 (YHWYGYTPQNVI) can specifically target EGFR and bind to one region of EGFR (Genta et al., 2017; Li et al., 2021). Hailing et al. synthesized GE11 modified poly(lactide-co-glycolic acid)/D- α -Tocopheryl polyethylene glycol 1,000 succinate nanoparticles for delivering salinomycin to breast cancer. The results showed that these nanoparticles potentially enhanced the therapy efficacy to EGFR overexpressed breast cancer (Hailing et al., 2022) (Figure 2).

Different sequences of peptides have been designed in order to treat breast cancer according to specific affinity to breast cancer overexpressed receptors in order to develop an ideal peptide for targeting breast cancer now. These overexpressed receptors mainly include HSP gp96, integrins, gC1q receptor, neuropilin-1 receptors, keratin 1 receptor, galectin-3 receptor, ERs, HER2 receptor and EGFR. These targeting peptides are numerous, so we selected some representative peptides to illustrate in Figure 2 and Table 1, such as peptide p37 targeting HSP gp96, peptides RGD and RGDK-octa-arginine targeting integrins, linear peptide TT1 targeting gC1q receptor, peptides tLyP-1 and CK3 targeting neuropilin-1 receptor, linear peptides p160 and p18 targeting keratin 1 receptor, peptide G3-C12 targeting galectin-3 receptor, peptides 12a and 13 targeting ERs, peptides DH6, RDH6, KAAYSL, HER2pep, A9, LTVSPWY and 51 targeting HER2 and peptides 1-D03 as well as GE11 targeting EGFR. They all showed high binding to their corresponding receptors.

There are also many challenges of targeting peptides including *in vivo* instability, low affinity to target, high non-target tissues uptakes and low internalization (Ahmadpour and Hosseinimehr, 2019).

2.2 CPPs for anticancer drug vectors

CPPs along with various drugs penetrating into cytomembranes by direct penetration or endocytosis (Zorko and Langel, 2005; Xu et al., 2019) enhance the anticancer efficacy of difficultly penetrable molecules for breast cancer therapy (Fukunaga et al., 2019; Tesaro et al., 2019). Nam et al. (Nam et al., 2021) developed a pH-activatable CPP dimer LH2 (monomer was LHHLCHELLHLLHLAG) to deliver paclitaxel into triple negative MDA-MB-231 cells on account of the weak acidic condition around the tumor, which was about pH 6.0 (Fan et al., 2016) tested the CPP C (GPGLWERQAREHSERKKRRRESECKAA) conjugated with peptide SP90 having breast tumor homing ability, especially for triple negative MDA-MB-231 cells. SP90-C revealed well targeted delivery function for anticancer drugs. Park et al. (2021) synthesized anticancer drugs targeting the weak acidic condition of the breast tumor by conjugating cyclic CPP (cCPP, CWRWRKWRWR) with a targeting peptide (TP1 or TP2) and anticancer drug cabazitaxel (CBT). TP1-cCPP-CBT revealed antiproliferative activity on MDA-MB-231 and MCF-7 cells. 5(6)-Carboxyfluorescein (FAM) used as a control for confocal microscopy and cellular uptake studies was conjugated with TP1-cCPP or cCPP. The CPP gH625 (HGLASTLTRWAHYNALIRAF) synthesized by Ben Djemaa et al. was used for CPP-capped stealth magnetic siRNA nanovectors (CS-MSN) to deliver siRNA for treating triple negative MDA-MB-231 cells. Peptide gH625 facilitated siRNA into the cell and promoted it escaping from endosomes (Ben Djemaa et al., 2019). Ben Djemaa et al. (Ben Djemaa et al., 2018) also developed CPP-capped stealth-fluorescent nanoparticles (CS-FNP) functionalized with gH625 and cationic polymers nanovectors to treat triple negative MDA-MB-231 cells; the MDA-MB-231 cells had higher uptake of optimized nanovectors than CS-FNP. CPP GALA (WEAALAEALAEALAEHLAEALAEALAEALAA) designed to interact with cytomembranes at acidic pH (Subbarao et al., 1987; Li et al., 2004) and the tumor homing linear pentapeptide (CREKA) modified redox-responsive complex co-delivered siRNAs for triple

TABLE 2 Summary of the major cell penetrating peptides as anticancer drugs vectors for breast cancer therapy.

CPPs	Sequence/Ref.
LH2	(LHHLCHLLHHLCHLAG) ₂ Nam et al. (2021)
C	GPGLWERQAREHSERKRRRRESECKAA Fan et al. (2016)
cCPP	CWRWRKWRWR Park et al. (2021)
gH625	HGLASTLTRWAHYNALIRAFK Ben Djemaa et al. (2019)
GALA	WEAALAEALAEALAEHLAEALAEALAEALAA Li et al. (2004)
tLyP-1	CGNKRTR Wang et al. (2020)

negative MDA-MB-231 cell therapy. The results showed that the CREKA and GALA modified with redox-responsive complex had excellent transfection efficiency and protected siRNA from the degradation of RNA enzymes (Zhang et al., 2021). Wang et al. (2020) designed tumor homing peptide tLyP-1 (CGNKRTR) which penetrated inside cells through the CendR pathway mediated by neuropilin-1 modified micelles to co-deliver chemotherapeutic and TRPA-1 inhibitor for treatment of triple negative MDA-MB-231 cells. The results revealed that peptide tLyP-1 improved the tumor-targeting delivery of micelles. The major CPPs are shown in Table 2.

The TNBCs are difficult to treat and chemotherapy drugs commonly have low internalization for the TNBCs cells (Jamdade et al., 2015; Jain et al., 2020). According to the above researches, we found that CPPs were more studied for enhancing the cell penetration of chemical drugs or siRNA to treat TNBCs. To increase the internalization, many CPPs such as peptide dimer LH2, peptide C, cCPP, peptide gH625, peptide GALA and peptide tLyP-1 were selected for delivering chemical drugs or siRNA to treat TNBCs. However, several inherent properties limit the clinical applications of CPPs (Nam et al., 2021). One limitation is that effective penetrating concentrations of CPPs are generally above micromolar and these concentrations are difficult for CPPs *in vivo* due to instability (Milletti, 2012; Guidotti et al., 2017). Another limitation is that some CPPs indiscriminately penetrate into almost all cytomembrane due to the electrostatic and hydrophobic interactions between CPPs and cell membranes inducing the CPP internalization (Reissmann, 2014; Shi et al., 2014). Therefore (Kim et al., 2018), targeting delivery and local administration have been selected for clinical applications of CPPs (Dissanayake et al., 2017; Pescina et al., 2018). Many studies selected pH-activatable CPPs as delivery vectors for targeting the weak acidic condition around the tumor or combined CPPs with targeting peptides for specific delivery of drugs to treat tumors with low side effects.

3 Peptide-based cancer vaccines

3.1 Peptide-based breast vaccines ongoing clinical trials

Therapeutic cancer vaccines are at the forefront of current medical development (Sobhani et al., 2022). There are several types of cancer vaccines including nucleic acid-based vaccines (both DNA and RNA vaccines), protein vaccines, inactivated patient-derived tumor cells and purified tumor antigens vaccines. For breast cancer, a total of

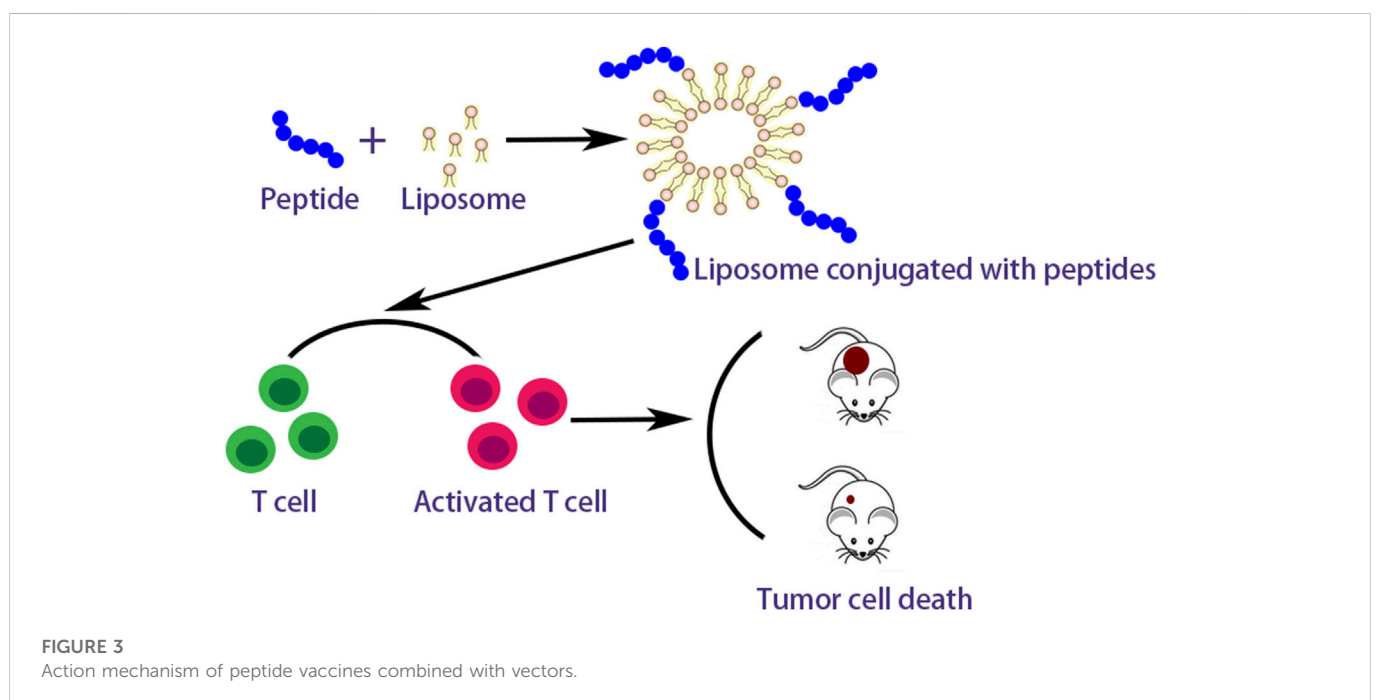
44 therapeutic cancer vaccines are currently being investigated with ongoing clinical trials as of 23rd June 2021 (Corti et al., 2022), of which, 30 clinical trials are open to TNBC patients, 21 clinical trials are enrolling HER2-positive breast cancer patients while there are only 15 trials with hormone receptor-positive breast cancer as inclusion criteria. Among these breast cancer vaccine ongoing clinical trials, peptide-based vaccines are in the majority (20, 45.5%). de Paula Peres et al. (de Paula Peres et al., 2015) reviewed 13 types of main peptide-based vaccines in breast cancer studied on phase III, phase II, phase I/II and phase I clinical trials, including peptides E75 (KIFGSLAFL), GP2 (IISAVVGIL), AE37 (LRMKGVGSPYVSRLGICL), P15 (FLAEDALNTV), P14 (NLMEQPIKV), P13 (YLIELIDRV), P7 (ILDDIGHGV), P5 (ALMEQQHYV), P4 (FLYDDNQRV), P3 (KLDVGNAEV), MUC1-KLH conjugate plus QS-21 (KLH-MBS-CVTSAPDTRPAPGSTAPPA HGVTSA PDTRPA), MFP (PDTRPAPGSTAPPAHGVTS) and L-BLP25 (STAPPAHGVTSAPDT RPAPGSTAPP) (Table 3). In addition, peptide vaccines including those of different delivery vectors and adjuvants have been implemented (Antonarelli et al., 2021) for the main reason of poor immunogenicity of single-peptide vaccines.

3.2 Peptide vaccines combined with vectors or adjuvants

Many researches on peptide-based breast cancer vaccines in combination with vectors or adjuvants are currently proceeding. Zamani et al. (2020) combined long multi-epitope peptide E75-AE36 (Ac-CGGGKIFGSLAFLAAAGVGSPPYVSRLGICL) with peptide PADRE (AKFVAAWTLKAAA) to form nanoliposomal vaccine and estimated its immunogenicity for the breast cancer of mice. The results revealed this nanoliposomal vaccine obviously enhanced the production of IFN- γ and responses of CD4⁺ and CD8⁺ T cells. Zamani et al. (2022) also studied another nanoliposomal-based peptide vaccine composed of peptide AE36 (Ac-CGGGKIFGSLAFL) and peptide PADRE conjugated with monophosphoryl lipid A (MPL) adjuvant. The results showed that an effective immune response was triggered by this peptide vaccine in breast cancer mice with the TUBO model and stimulated more robust Th1 immune responses. Peptide AE36 was also coupled with liposomes containing DOPE, 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) and cholesterol, by Barati et al. (Barati et al., 2022). Such formulations could effectively induce the responses of CD8⁺ and CD4⁺ T cells. Zamani et al. also investigated the combination therapies with peptide E75 (Ac-CGGGKIFGSLAFL) and DOX which could synergistically potentiate IFN- γ , CD8⁺, and CD4⁺ T cell responses (Zamani et al., 2020a). Peptide E75 also coupled with polyactin A (PAA) usually selected to treat impaired immunity in China could significantly increase positive rates of CD8⁺ and CD4⁺ T lymphocyte and potentiate IFN- γ production compared with pure peptide E75 (Wang et al., 2018). A nano-liposomal vaccine containing peptide P5, MPL, and peptide PADRE adjuvant showed prominent anticancer effects in HER2 positive breast cancer and effectively activated CD8⁺ T cell immune response (Zamani et al., 2019). Peptide P5 loaded in cationic nanoliposome composed of polyriboinosinic polyribocytidylic acid [Poly (I:C)] and DOTAP-cholesterol induced strong antitumor responses both *in vivo* and *in vitro* (Talesh et al., 2016). The peptide vaccines combined with

TABLE 3 Summary of the vaccination based on peptide clinical trials on breast cancer patients. (de Paula Peres et al., 2015).

Vaccine	Peptide	Gene	Sequence	Target(protein)
NeuVax™	E75(nelipepimut-S)	HER2	KIFGSLAFL	Her-2/neu
	GP2	HER2	IISAVVGIL	Her-2/neu
	AE37	HER2	LRMKGVGSPYVSRLIGICL	Her-2/neu
Depovax™ (DPX-0907)	P3	BAP31	KLDVGNAEV	BAP31/CDMproteinTopoisomeraseII a
	P4	TOP2A	FLYDDNQRV	Integrin β8subunitprecursorAbl-bindingprotein 3CTACE/ADAM-17
	P5	ITGB8	ALMEQQHYV	JunctionplakoglobinEDDRI
	P7	ABI_2	ILDDIGHGV	
	P13	ADA17	YLIELIDRV	
	P14	JUP	NLMEQPIKV	
	P15	DDR1	FLAEDALNTV	
	MUC1-KLH conjugate plus QS-21	MUC1	KLH-MBS-CVTSAPDTRPAPGSTAPPAHGVTSAPDTRPA	Mucin-1
Stimuvax	Oxidized mannan-MUC1 (MFP)	MUC1	PDTRPAPGSTAPPAHGVTS	Mucin-1
	L-BLP25	MUC1	STAPPAHGVTSAPDTRPAPGSTAPP	Mucin-1



vectors or adjuvants reveal the action mechanism as showed in Figure 3.

3.3 Novel peptide vaccines

Many novel peptides were studied as breast cancer vaccines except combining with vectors and adjuvants as shown in Table 4. Mahdavi et al. reported peptide 249 (GDLTNRCTMEEKPMEK) as a potential

peptide-based vaccine derived from insulin-like growth factor-1 (IGF-1) receptor in breast cancer (Mahdavi et al., 2017) and peptide 249 could excellently bind to Major Histocompatibility Complex (MHC) class II and I and T-cell. They also synthesized peptide 1412 (QPEQQETKKEEQ) and this peptide showed outstanding binding activity to most of the applied MHCs (Mahdavi and Moreau, 2016). Peptide E39 (EIWTHSYKV) (Vreeland et al., 2018) was combined with peptide E39' (EIWTFSTKV), an attenuated version of E39. Immune analyses suggested that the optimal

TABLE 4 Summary of the major peptide-based vaccines at early stage research for breast cancer therapy.

Peptides	Sequence/Ref.
249	GDLTNRCTMEEKPMEK Mahdavi et al. (2017)
1,412	QPEQKETKKEEQ Mahdavi and Moreau (2016)
E39/E39'	EIWTHTSYKV/EIWFSTKV Vreeland et al. (2018)
ErbB-2266-296/ OVA323-339	CGPSLLHCPALVTYNTDTFESMHNPEGRTYFGASCV/ISQAVHAAHAEINEAGR Wallis et al. (2020)
45A2L/QA2L/PPE15L/ PGRS	AGDAEYXRAYLXGECVEXLRXYLXLGNXTLLRXDXPKAHVTYHPRS/GPHXLRVYFXTAVXWPLVXPRFIXVGYVXDTQFV/ MDFGXLPEXNSXRMVAGXGAXPMAAXAAWNLAXELGTXAASY/LFXNGGAGGQGGXGGXGGXGGXGGXGMAGXPAGGTGGIGXIGGIG (the "X" represents any of 20 amino acids) Servín-Blanco et al. (2018)
MAG-Tn3	QYIKANSKFIGITEL Ganneau et al. (2017)

TABLE 5 Summary of the major peptides used for breast cancer therapy.

Peptides	Sequence/Ref.
melittin	GIGAVLKVLTGLPALISWIKRKRQQ Terwilliger and Eisenberg (1982)
iPep697Δ/iPep697/iPep682/iPep624/ iPep624W1ΔA/iPep624W2ΔA/iPep624ΔHEX	KKKRKVAPAAVYCTRYSDR/KKKRKVWPAWVYCTRYSDR/KKKRKVPLVWPAWVYCTRYSDRPS/ KKKRKVTDSSQQLVWPAWVYCTRYSDRPS/KKKRKVTDSSQQLVWPAWVYCTRYSDRPS/ KKKRKVTDSSQQLVWPAWVYCTRYSDRPS/KKKRKVTDSSQQLVWPAWVYCTRYSDRPS Beltran et al. (2014)
EN1-iPep/Mutant EN1-iPep	KKKRKVPLVWPAWVYCTRYSDR/KKKRKVPLVWPAWVYCTRYSDR/KKKRKVPLVWPAWVYCTRYSDR/ KKKRKVPLVWPAWVYCTRYSDR Sorolla et al. (2019)
[R5K]W7A	[R5K]W7A Mozaffari et al. (2021)
Nap-GFFpYK	Nap-GFFpYK Zhang et al. (2020)
P1/P2/P3/P4/P5/P6/P7	NmFARKGALRQ/FARKGALRQ/NmRFARKGALRQKNV/RFARKGALRQKNV/NmRKRTLRL/RKRTLRL/ NmNDSRSSLIRKR Gupta et al. (1996)
tetrapeptide	GFLG (Zhi et al., 2019)
T10-ERK	HAIYPRHGGCGMPKKKPTPIQLNP Sheng et al. (2016)
GFLG	GFLG Wang et al. (2020)
caPeptide	CLGIPEQEY Lingeman et al. (2014)
RAN-IP	CAQPEGQVQFK Haggag et al. (2019)
NT4	(ELYENKPRRPYL) ₄ Brunetti et al. (2016)
[F7,P34]-NPY	YPSKPDFPGEDAPAEDLARYYSALRHYINLITRPRY Bohme et al. (2016)
ERAP	11R-GGG-QMLSDLTLQLRQR Yoshimaru et al. (2013)
IF7	IFLLWQR Yu et al. (2015)
ASRPS	MTTKMRRRLRPSAPSLGQEAEVVEGCFPAVTETPFAPAYIKKRGRIWSSDPRSDGEH Wang et al. (2020)
AFPeq	cyclo(EKTOVNOGN) Jacobson et al. (2014)
Pasireotide	cyclo(Hyp(Unk)-Phg-WKY(Bn)F) Herbert (2008)
goserelin	XHWSYSLRP Parker and Schimmer (2001)

cytotoxic T lymphocyte population was induced by administering with E39 and E39' in turn. Peptide ErbB-2266-296 (CGPSLLHCPALVTYNTDTFESMHNPEGRTYFGASCV) binding to the native ErbB-2 protein by mimicking the pertuzumab for activating B cells and ovalbumin peptide OVA323-339 (ISQAVHAAHAEINEAGR) as a T cell epitope were connected as a liposomal system for inducing anti-ErbB-2 antibody response (Wallis et al., 2020). The mice tests showed that humoral immune response activated by peptides ErbB-2266-296 and OVA323-339

raised 7.3-fold and they also induced 96% tumor cell death *in vitro*. Servín-Blanco et al. developed a Variable Epitope Library (VEL) and identified long peptides 45A2L (AGDAEYXRAYLXGECVEXLRXYLXLGNXTLLRXDXPKAHVTYHPRS) and QA2L (GPHXLRVYFXTAVXWPLVXPRFIXVGYVXDTQFV) as well as their wild type peptides PPE15L (MDFGXLPEXNSXRMVAGXGAXPMAAXAAWNLAXELGTXAASY) and PGRS (LFXNGGAGGQGGXGGXGGXGGXGGXGMAGXPAGGTGGIGXIGGIG) (the "X" represents any of 20 amino acids) (Servín-Blanco

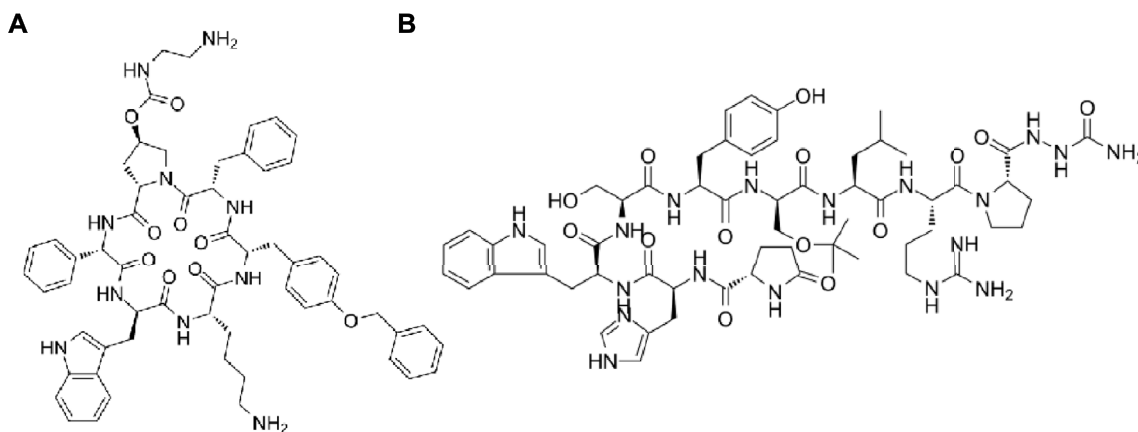


FIGURE 4
(A) The structure of pasireotide. **(B)** The structure of goserelin.

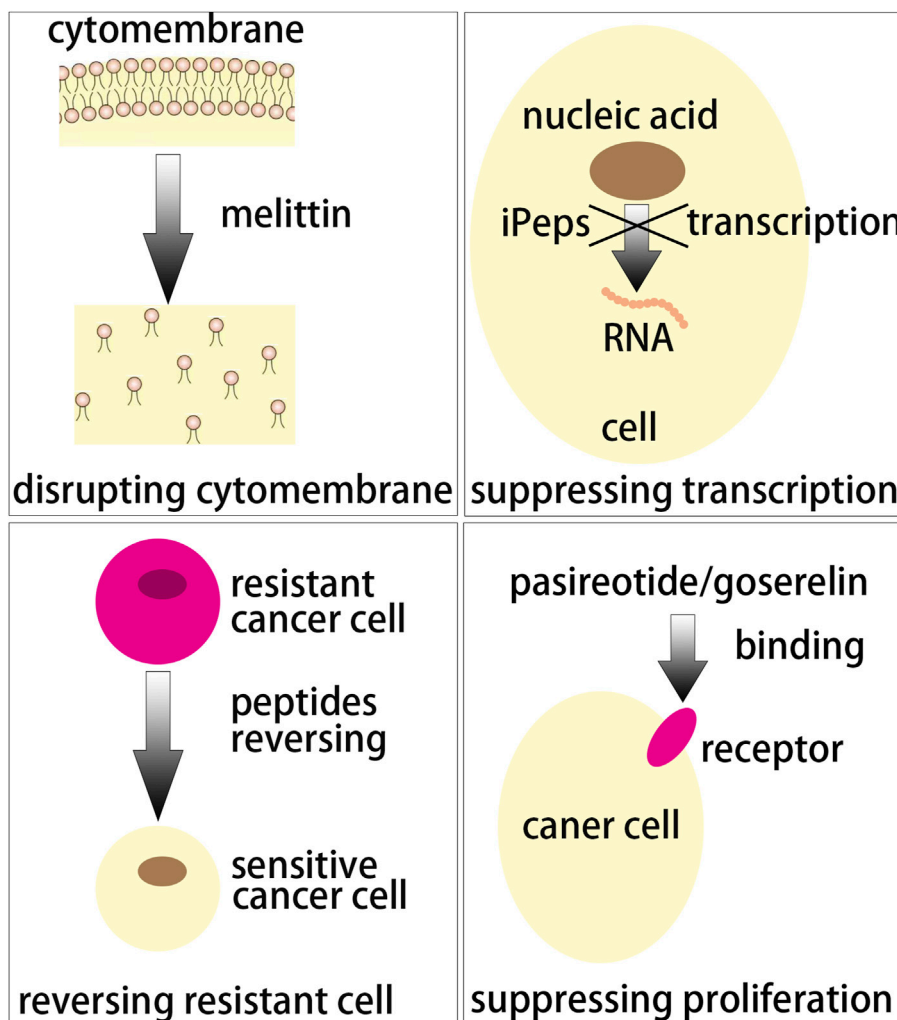


FIGURE 5
 Several action mechanisms of peptide-based anticancer peptides.

et al., 2018). They observed that 45A2L, QA2L, PPE15L, and PGRS significantly activated T cell for inhibiting tumors and reduced metastatic lesions in lungs of immunized mice. Ganneau et al. synthesized glycopeptide dendrimer MAG-Tn3 (containing peptide TT, its sequence is QYIKANSKFIGITEL) for an anticancer vaccine candidate for human use (Ganneau et al., 2017). They found that MAG-Tn3 induced Tn-specific antibodies that killed Tn-positive cancer cells of human and MAG-Tn3 was now being evaluated for cancer vaccine in breast cancer patients (phase I clinical trial).

Cancer vaccines should be tumor specific and well tolerated and they have well-known advantages over chemotherapy, so peptide-based cancer vaccines are promising for prevention and treatment breast cancer. The studies of main peptide-based vaccines such as E75, GP2, AE37, P3, P4, P5, P7, P13, P14, P15, MUC1-KLH conjugate plus QS-21, MFP, and L-BLP25 have been used on phase III, phase II, phase I/II and phase I clinical trials. In the last 2 decades, the researches of breast cancer vaccines showed poor clinical trial results and the immunogenicity of single-peptide vaccines was poor. However, breast cancer vaccines have been widely considered as candidates for the technological advancements by the COVID-19 vaccination campaign (Corti et al., 2021; Dafni et al., 2021). For inducing long-lasting immune responses, cancer vaccines could be combined with other treatment modalities (Dafni et al., 2021). Peptides connected with different delivery vectors and adjuvants as breast cancer vaccines have been widely studied. The delivery vectors are evolving towards non-degradable and polymeric nanoparticles, virus-like particles and lipid nanoparticles (Antonarelli et al., 2021), with liposomes showing superior performance in increasing cellular uptake to enhance vaccine immunogenicity and helping to deliver peptide-based vaccines to the lymph nodes (Watson et al., 2012). Peptide-based vaccine monotherapy has mainly focused on premalignant cancer or the (neo) adjuvant setting while peptide-based vaccines combined with anticancer drugs have been used in late-stage tumors. Peptide-based breast cancer vaccines have shown good prospects and further understanding of cancer vaccines as well as technological advancements in their preparation and use are important.

4 Peptides for anti-cancer drugs

4.1 Peptides disrupting the cellular membrane

Melittin (GIGAVLKVLTGTPALISWIKRKRQQ) constituting about 50% of dry weight of honey bee venom (Terwilliger and Eisenberg, 1982) showed good anticancer activity in breast cancer models by disrupting the cellular membrane. For the molecular mechanisms of melittin as anticancer agent, Duffy et al. demonstrated that melittin induced cancer cell death, especially in TNBC and HER2 breast cancers, by inducing that the EGFR and HER2 could not be phosphorylated in the cell membrane of breast cancer cells (Duffy et al., 2020). While melittin delivered in vectors is preferred due to its rapid lytic effects (Sorolla et al., 2020), Daniluk et al. designed melittin carried by nanographene oxide or nanodiamonds and found that nanographene oxide vector could increase the anticancer activity of melittin for breast cancer and nanodiamonds are able to protect normal cells from the destroy of melittin (Daniluk et al., 2019). Melittin complexed with micelles modified with estrone held steady against trypsin digestion and the micelles conjugated with estrone showed more than 6-fold increase in

uptake of ER positive MCF-7 cells relative to the TNBC cell line MDA-MB-231 as well as high anticancer efficacy (Raveendran et al., 2020; Motiei et al., 2021). For targeted co-delivery of melittin with miR-34a, Motiei et al. synthesized a nanocarrier composed of polyethyleneimine shell modified with folic acid, dextran sulfate as a complexing agent and polyglutamate grafted chitosan core (Motiei et al., 2021). The results revealed that the deaths of cancer cells were obviously increased by 54% by co-delivery of melittin and miR-34a. Melittin was used for treating breast cancer brain metastases (BCBM), by conjugating AMD3100, a small molecule antagonist of CXCR4 highly expressed in BCBM, with poly(lactone-co- β -amino ester) nanoparticles and melittin delivered *via* AMD3100 nanoparticles effectively inhibited tumor growth in mice of BCBM model (Zhou et al., 2020). In addition, melittin has good immunoregulatory activity such as augmenting Th1 cell function (Qiubo et al., 2000). Liu et al. prepared mutant interleukin-2 (MIL-2), one of the most successful cytokines for tumor immunotherapy and melittin to form a bifunctional fusion protein melittin-MIL-2 (Liu et al., 2016). The results showed that the melittin-MIL-2 could induce obvious antitumor and immune stimulation effects.

4.2 Peptides suppressing the activity of transcription factors

Interference peptides (iPeps), mutational transcription factor versions, are inert and able to inhibit the transcriptional program by sequestering their binding partners tight (Sorolla et al., 2020). Beltran et al. (2014) designed seven iPeps including iPep697 Δ (KKKRRKVAPAAVYCTRYSDR), iPep697 (KKKRRKVWPAWVYCTRYSDR), iPep682 (KKKRRKVPLVWPAWVYCTRYSDRPS), iPep624 (KKKRRKVTDSSQQLVWPAWVYCTRYSDRPS), iPep624W1 Δ A (KKKRRKVTDSSQQLVAPAWVYCTRYSDRPS), iPep624W2 Δ A (KKKRRKVTDSSQQLVWPAWVYCTRYSDRPS) and iPep624 Δ HEX (KKKRRKVTDSSQQLVGAAGAGCTRYSDRPS). These iPeps could target engrailed 1 (EN1) on account of their sequences which comprises the flanking protein sequences from the N terminus of the homeodomain (HD) and specific hexamotif of comprising EN1. The results showed that iPep624 and iPep682 rapidly mediated a strong apoptotic response in breast cancer cell line SUM149PT which overexpressed EN1. iPep697 and iPep697 Δ were internalized by cell in \sim 2 min and reached a high land 40 min later (Beltran et al., 2014). Sorolla et al. synthesized active EN1-iPep (KKKRVPLVWPAWVYCTRYSDR) as well as mutant EN1-iPep (KKKRVPLVAPAAVYCTRYSDR) and engineered two iPeps with four peptide RGDs including RGD1 (HGRGDLGRLKK), RGD2 (YTSGDQKTIKS), RGD3 (NLRGDLQVLAQ) as well as RGD4 (RGRGDLATIHG). EN1-RGD-iPeps was applied to functionalize the docetaxel nanoparticles for promoting tumor specific targeting. The results revealed that EN1-RGD-iPeps reduced cell viability and induced apoptosis in TNBC cells without showing toxicity and EN1-RGD-iPeps-mediated docetaxel nanoparticle increased tumor accumulation *via* integrins and intravenous injection (Sorolla et al., 2019). They also designed active EN1-iPep (KKKRRKVPLVWPAWVYCTRYSDR) and mutant EN1-iPep (KKKRRKVPLVAPAAVYCTRYSDR) (Sorolla et al., 2016). The *in vitro* cell toxicity assays showed high selective toxicity of EN1-iPep in human basal-like SUM149PT cells while not in MCF10A cells,

a normal breast epithelial cell line. Furthermore, EN1-iPep could improve the inducing apoptosis function of docetaxel by synergistic pharmacological action when they were co-delivered by poly(acrylic acid) modified poly(glycidyl methacrylate) nanoparticles.

4.3 Peptides for treating resistant breast cancer

The resistance of anticancer drugs is a critical problem limiting the extended use of chemotherapy drugs in breast cancer therapy (Cabeza et al., 2015). In almost every patient whose cancer shows resistance, it is inevitable that the relapse and metastasis of tumors appear after endocrine treatment (Mazumder et al., 2021). The two resistance mechanisms include the intrinsic resistance of tumors before administration of chemotherapy and the generated resistance during therapy of tumors previously suppressed by chemotherapy drugs (Wilson et al., 2006). The latter resistance is even more problematic due to its difficult predictability and multidrug resistance (MDR), many different chemotherapy drugs resisted simultaneously. There are many factors influencing drug resistance, including overexpression of ABC transporters, drug inactivation, changes in drug targets, apoptotic dysregulation, cancer stem cells and epithelial-to-mesenchymal transitions (Faruk, 2021).

The efflux mechanism in resistant breast cancer is usually achieved by overexpression of ABC transporters such as P-glycoprotein (P-gp) which can lower drug accumulation inside the cell by removing the anticancer drugs out of cells is the most popular resistance mechanism (Seelig and Gatik-Landwojtowicz, 2005). Correspondingly, many strategies are aimed at avoiding the P-gp efflux in order to overcome resistance. Mozaffari et al. synthesized conjugates [R5K]W7A-DOX and [R5K]W7C-S-S-DOX with a glutarate linker and a disulfide linker, respectively. They both contained DOX and [R5K]W7A, a peptide including linear W7A and cyclic R5K (Mozaffari et al., 2021). The anticancer results showed that [R5K]W7A-DOX conjugate had 16-fold higher activity against DOX-resistant breast cell line MDA-MB-231R compared to free DOX. The MTT results revealed that [R5K]W7A-DOX conjugate (5 μ M) had no significant cytotoxicity to heart muscle cells and kidney cells compared to free DOX (5 μ M) obviously increasing the cell apoptosis and destroying the morphology of the cells after 72 h of incubation. Prolonging intracellular retention is also important towards alleviating cancer cell MDR by suppressing the P-gp efflux. Nanocarriers have been showed to be an efficient approach to increase retention of anticancer drugs, both inside the tumor cells and in circulation (Yuan et al., 2015). Zhang et al. proposed a strategy based on the peptide Nap-GFFpYK covalently bound to etoposide in order to increase the intracellular retention and the water solubility (Zhang et al., 2020). Compared to free etoposide, Nap-GFFpYK-etoposide conjugate showed a 20 -fold inhibitory activity on these cells with artificially overexpressed MDR1. The phosphorylation of P-gp significantly enhanced the MDR phenotype of the breast cells, and protein kinase C (PKC), an isozyme family, could phosphorylate the linker region of P-gp (Orr et al., 1993). PKC-pseudosubstrate peptides 1–7 were synthesized and their sequences were P1 (NmFARKGALRQ), P2 (FARKGALRQ), P3 (NmRFARKGALRQKNV), P4 (RFARKGALRQKNV), P5 (NmRKRTLRLRL), P6 (RKRTLRLRL), and P7 (NmNDSRSSLRKR), respectively. In these PKC-pseudosubstrate peptides, P1 revealed the most likely reversing MDR mechanism of inhibition of P-gp

phosphorylation (Gupta et al., 1996). Zhi et al. designed a novel compound, LAX, composed of tetrapeptide (GFLG), DOX and lipid acid (Zhi et al., 2019), in which tetrapeptide was a trigger of lysosomal protease cathepsin B existing inside most tumor cells (Li et al., 2014). They selected gold nanorods (AuNRs) as a vector to deliver LAX to form an enzyme-responsive nanomedicine AuNRs-LAX. In addition, AuNRs-LAX could bypass the P-gp efflux due to their size, which was much larger than the active binding site of P-gp (Browning et al., 2018). The results revealed that the AuNRs-LAX treatment reduced the drug resistance index from greatly high 955.0 to 1.7 in MCF-7/ADR cell resisting DOX (Zhi et al., 2019).

In addition to efflux mechanism, apoptotic dysregulation is also an important factor of drug resistance. One important contributor of apoptotic dysregulation was mitogen-activated protein kinase (MAPK) signaling cascade. Extracellular signal regulated kinases (ERK), a principal protein molecule in MAPK cascade, stimulates cell survival and growth by initiating the transcription of specific genes (Choi et al., 2008). Within this context, Sheng et al. prepared peptide T10 (HAIYPRH) connected with peptide MPKKKPTPIQLNP, a ERK peptide inhibitor, by a thiol spacer (GGCG) to form peptide T10-ERK(HAIYPRHGGCGMPKKKPTPIQLNP) and conjugated DOX with peptide T10-ERK for the reversal study in drug resistant breast cancer (Sheng et al., 2016). The results revealed that the additive effect of ERK peptide inhibitor together with DOX-T10 led to less susceptibility and greater efficacy to drug resistance. To reverse apoptotic dysregulation, initiating the lysosomal apoptosis pathway was also efficient. Tetrapeptide GFLG, sensitive to cathepsin B, was also used to link mPEGylated dendron with DOX to self-assemble conjugate DOX-GFLG-mPEGylated dendron and this conjugate could enhance cell death mediated by lysosomal according to inducing cathepsin B in the cytoplasm (Wang et al., 2020). Proliferating cell nuclear antigen (PCNA) plays a central function including protein degradation, cell cycle regulation, chromatin remodeling, DNA methylation, translesion DNA synthesis, DNA repair and DNA replication (Strzalka and Ziemienowicz, 2011). Cancer-associated PCNA (caPCNA) has an 8 amino acid peptide caPeptide (CLGIPEQEY) on a binding domain. Lingeman et al. improved the endogenous expression of caPeptide by a tetracycline responsive promoter in MDA-MB-231 cells (Lingeman et al., 2014). The results showed that caPeptide combined with cisplatin generated a noticeable increase in the apoptosis of MDA-MB-231 cell line resisting cisplatin. Ras-related nuclear protein (Ran) controlled the cellular responses to DNA damage and cell cycle rate by regulating nuclear import and export pathways. When the Ran concentration reached a threshold, DNA damage in tumor cells was successfully repaired. Haggag et al. have reported a specific Ran guanine nucleotide exchange factor inhibitory peptide (RAN-IP, its sequence is CAQPEGQVQFK) which could block the interaction between Ran and Ran guanine nucleotide exchange factor in MDA-MB-231 breast cancer cells to inhibit RanGTP formation (Haggag et al., 2019). Ran-IP and DOX were co-delivered by a liposomal delivery system using a thin-film rehydration technique. Ran showed good reversing of the Ran-expression-mediated MDR activity and obviously enhanced the sensibility of tumor-bearing mice to DOX (Haggag et al., 2020).

One efficient strategy of overcoming resistance is bypassing resistance mechanisms by specific binding to new targets. Accordingly, tetra-branched peptides could bind to membrane heparan sulfate proteoglycans or the low density lipoprotein

receptor family at sulfated glycosaminoglycan chains or different endocytic receptors respectively though their branched structure which contained human neurotensin (NT4, the sequence is (ELYENKPRRPYIL)₄) (Brunetti et al., 2016), were used to conjugate with methotrexate (MTX) for MTX-resistant human breast cancer therapy. The results showed that MTX-conjugated NT4 bypassed drug resistance and was efficiently internalized by MTX-resistant human breast cancer cells (Depau et al., 2017). Neuropeptide Y (NPY) analogue [F7,P34]-NPY (YPSKPDFPGEDAPAEDLARYYSALRHYINLITRPRY) was toxic on breast cancer by the human Y1-receptor (hY1R) mediated pathway. Böhme et al. introduced two MTX at positions 4 and 22 of [F7,P34]-NPY and this conjugate was more effective than MTX on MTX-resistant cells (Böhme et al., 2016). Endocrine resistance was a common obstacle in therapy for ERa-positive breast cancer and prohibitin 2 (PHB2) could interact with ERa to inhibit ERa transcriptional activity. Guanine nucleotide-exchange protein 3 (BIG3) inhibited by brefeldin A could activate the ERa signaling pathways by capturing PHB2 in most breast cancer (Kim et al., 2009). Yoshimaru et al. synthesized a negative peptide ERAP (11R-GGG-QMLSDLTLQLRQR) which could release PHB2 from BIG3 and peptide ERAP treatment enhanced tamoxifen responsiveness in ERa-positive breast cancer cells (Yoshimaru et al., 2013). Annexin 1 (Anxa 1) was an apparently expressed biomarker on the surfaces of tumor vasculature ECs (Hatakeyama et al., 2011). In mice of null Anxa 1, the lack of angiogenesis significantly suppressed tumor growth (Chen et al., 2013). A peptide designated IF7 (IFLLWQR) could bind to Anxa 1 with high affinity and specificity so Yu et al. synthesized a nano-DDS of IF7-PTX-NP by conjugating peptide IF7 with paclitaxel. The results showed that IF7-PTX-NP could significantly induce necrosis of the tumor tissues and apoptosis of the tumor vascular endothelial cells with no obvious toxicity to the mice (Yu et al., 2015).

4.4 Other anticancer peptides

Long non-coding RNAs (lncRNAs) which were longer than 200 nucleotides were non-protein coding transcripts and regulated cell proliferation as well as invasion (Li et al., 2017). An lncRNA LINC00908 which specially translated in TNBC cell line MDA-MB-231 encoded a 60-aa peptide ASRPS (MTTKMRRLRPSAPSLGQEQEAEVVE GCFPAVTETFPAYIKRGGRIWSSDPRSDGEH). Peptide ASRPS reduced the expression of vascular endothelial growth factor (VEGF) by down-regulating STAT3 phosphorylation so the ASRPS expression reduced angiogenesis of TNBC (Wang et al., 2020). Peptide AFPeq (cyclo(EKTOVNOGN), O is hydroxyproline), a head-to-tail cyclized peptide developed by Jacobson et al. mimics the anti-breast cancer site of α -fetoprotein (Jacobson et al., 2014). AFPeq initially inhibited (days 0–7) and then stopped MCF-7 breast cancer xenografts growth (days 7–14) while it had no effect on liver and hepatocellular carcinoma cell line growth. In addition, AFPeq had good tolerance in mice, rats, dogs, and monkeys (Mansouri et al., 2018). There are two peptides specifically used to treat breast cancer now and they are pasireotide and goserelin. Pasireotide (Figure 4A, cyclo(Hyp(Unk)-Phg-WKY(Bn)F)) can specifically binding to somatostatin receptor subtypes sst5 and sst1,2,3 and suppress the adrenocorticotrophic hormone, IGF-1 and growth hormone secretion

potently (Schmid, 2008). Goserelin (Figure 4B, XHWSYSLRP) showed different mechanism of action. It can bind to gonadotrophin-releasing hormone (GnRH) receptor on anterior pituitary cells as an GnRH analogue and stimulate the anterior pituitary secreting luteinizing hormone and follicle-stimulating hormone with low proteolytic susceptibility (Parker and Schimmer, 2001).

Peptide drugs used to treat tumors have been limited by some factors such as serial design, structural modification and pharmonic screening. There are 118 types of peptide drugs successfully applied to global clinic as of May 2022 and these peptide drugs include 7 types of diagnostic reagents. However, to put this in perspective, the number of peptide drugs is only 2% of that of all new drugs. The research of peptide drugs is currently at the forefront of medical development now due to the constant improvement of genetic technology, information technology and genomics technology. Some novel peptides showed in Table 5 were designed and synthesized to inhibit tumor growth by different mechanisms (Figure 5). Some researchers selected nanocarriers to deliver melittin and other anticancer drugs such as peptides, chemotherapeutic drugs or siRNA for breast cancer therapy. The results showed the obvious anticancer activity of melittin. Another anticancer mechanism of peptides is suppressing the activity of transcription factors. Mutational transcription factor versions iPeps could inhibit the transcriptional program by tight sequestering their binding partners. In some studies, different sequences of iPeps were developed for anticancer activity detection and many peptide sequences showed good inhibition of cancer cell growth activity. The MDR of tumors seriously affected the extended use of chemotherapy drugs in breast cancer therapy due to its difficult prediction and simultaneous resistance to many different chemotherapy drugs. The American Cancer Society estimated that over 90% cancer deaths were related to MDR in different degrees. There are many mechanisms of MDR including changes in overexpression of ABC transporters, drug inactivation, drug targets, apoptotic dysregulation, cancer stem cells and epithelial-to-mesenchymal transitions. Among these mechanisms, P-gp efflux and apoptotic dysregulation are concerned with the peptides treating MDR. Some peptides rich in arginine and tryptophan were designed to reverse or bypass P-gp efflux. These peptides were conjugated with anticancer drugs for treating corresponding resistance in breast tumors. The corresponding results showed that drugs conjugated with peptides had noticeably higher efficiency compared to free drugs. In addition, some peptides initiated a lysosomal apoptosis pathway or inhibited cell growth and survival peptide ERK were designed and synthesized. These peptides could notably improve the resistance to breast tumor deaths and reverse the MDR. In addition, other peptides were designed to treat MDR by the method of specific binding to new targets and then bypassing resistance mechanisms. There also some new peptides used for breast cancer therapy through other mechanisms such as reducing the expression of VEGF or by mimicking the anti-breast cancer site of α -fetoprotein.

5 Summary and future perspectives

Peptides participate in and regulate the functional activities of various systems, organs, tissues and cells in organisms. They play important roles in vital activities. Research on peptide-based anticancer drugs has attracted wide interest due to its functionalities of scalable production, good safety and adaptive nature. In clinical medication of breast cancer, peptides have been

applied as promising targeting vectors, anticancer vaccines and anticancer drugs. Previous studies showed that peptides could specifically bind to different targets of breast tumor cells. In this review, we summarized nine targets of breast tumor cells including HSP gp96, integrins, gC1q receptor, neuropilin-1 receptor, keratin 1 receptor, galectin-3 receptor, ERs, HER2, and EGFR. Different peptides that were reported as delivering anticancer drugs to corresponding targets were itemized. In addition, CPPs which could penetrate cytomembranes by electrostatic and hydrophobic interactions were also used to deliver anticancer drugs into breast cancer cells. While CPPs are not able to distinguish tumor cells from normal cells, so that it is necessary to conjugate CPPs conjugated with a targeted portion. Peptide-based vaccines are one of medicines at the forefront of therapeutic cancer vaccine development. Some peptide-based vaccines for breast cancer have now been studied on phase III, phase II, phase I/II, and phase I clinical trials, including peptides E75, GP2, AE37, P3, P4, P5, P7, P13, P14, P15, MUC1-KLH conjugate plus QS-21, MFP, and L-BLP25. Some peptide-based vaccines in combination with vectors or adjuvants were designed due to the poor immunogenicity of single-peptide vaccines. Many cytotoxic peptides were also able to induce apoptosis of tumor cells with different mechanisms; for example, melittin disrupted cytomembrane and iPePs suppressed transcription to inhibit tumor growth. More importantly, peptides were reported that could suppress MDR breast cancer by reversing efflux, apoptotic dysregulation or bypassing resistance mechanisms because MDR breast cancer has obviously increased the mortality of breast cancer patients.

After 2000, a variety of peptides were discovered or designed for treating breast cancer. However, new peptides are few in clinical treatment of breast cancer. Only two anticancer peptides, pasireotide and goserelin, were approved to treat breast cancer as of May 2022. The clinical application of peptides is limited by several factors including target selection, design of sequences, structural modification, high proteolytic susceptibility and preclinical study. Firstly, anticancer peptides have exhibited weak targeted treatment for breast cancer. This is mainly because the targets of cancer cells are influenced by some genes and various signal pathways, so that anticancer peptides could not safely and effectively treat breast cancer by binding to a single target of cancer cells. Therefore, multifunctional peptides with synergistic mechanisms or targeting multiple points that will become more efficient should be developed and studied. Secondly, the design of sequences has limited the development of new peptide-based drugs. The sequences of peptides needed to be ameliorated continuously to obtain peptides suitable for efficient breast cancer therapy. For example, unstable amino acid residues needed to be replaced to avoid the isomerization, glycosylation and oxidation of peptides *in vivo*. Meanwhile, the physicochemical properties of peptides such as distribution, isoionic point and pH are required to be optimized. It is insufficient to simply design the sequences of peptide-based drugs only by computer-aided drug design technology without consideration of factors involving their use. Therefore, the sequences of new anticancer peptides have commonly originated from those of natural peptides with anticancer activities; for example, from snake venom or bee venom and bioactive peptides in the body. Thirdly, the structural modification of peptides is often

necessary due to the high proteolytic susceptibility, high non-target tissue uptakes and low internalization of peptides *in vivo*. Many strategies have been carried out to overcome these intrinsic disadvantages. The catenulated structure of peptides generally shows high elasticity; accordingly, stable cyclic peptides with one loop or two loops were designed. Peptides have also been conjugated with drugs, antibodies or oligonucleotides for targeted therapy with low side effects. In addition, oral peptides modified with PEG, glycosyl, liposomes or adjuvants were also prepared to avoid proteolytic degradation *in vivo* for better bioavailability. Finally, the preclinical studies such as pharmacological, toxicological and metabolic studies which are the prerequisite of clinical trials must be considered. These preclinical studies require considerable time and effort to ensure the safety and effectiveness of anticancer peptide-based drugs.

The successful preparation of new peptide-based drugs ultimately requires investment in numerous researches, time and money, but in return, the payoffs of new peptide-based drugs are expected to be enormous. Peptide-based drugs or vaccines for breast cancer therapy hold considerable promise for future use and could become a major player in the future pharmaceutical market.

Author contributions

LL: Conceptualization, Funding Acquisition, Investigation, Resources, Writing—Original Draft; GD: Resources, Writing—Review and Editing; WD: Supervision; ZC: Resources; XJ: Conceptualization, Supervision, Writing—Review and Editing; XL: Funding Acquisition, Project Administration, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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