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REVIEW ARTICLE

Toll-like receptor 4 and breast cancer: an updated systematic review

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Abstract
Toll-like receptors (TLRs) may play dual roles in human cancers. TLR4 is a key molecule which may participate in both friend and foe roles against breast cancer. This review article collected recent data regarding the mechanisms used by TLR4 in the eradication of breast cancer cells and induction of the tumor cells, and discussed the mechanisms involved in the various functions of TLR4. The literature searches revealed that TLR4 is a key molecule that participates in breast cancer cell eradication or induction of breast cancer development and also transformation of the normal cells. TLR4 eradicates breast cancer cells via recognition of their DAMPs and then induces immune responses. Over-expression of TLR4 and also alterations in its signaling, including association of some intrinsic pathways such as TGF-β signaling and TP53, are the crucial factors to alter TLR4 functions against breast cancer.

Keywords Breast cancer · TLR4 · Metastasis

Introduction

In humans, breast cancer is prevalent in women and its incidence is increasing world wide [1]. The malignancy is a complicated disorder which is associated with alterations in the expression and functions of several immune system-related/-non-related molecules [2]. It has been hypothesized that determination of the main molecules which play key roles in the induction or stimulation of breast cancer and also the causes of deterioration of its complications such as metastasis can provide insight on overcoming the diseases. Accordingly, the main molecules, which participate in the molecular pathology of the cancer or fight against it, can be considered as new targets for molecular therapies.

Toll-like receptors (TLRs) and their corresponded downstream molecules, which belong to pathogen recognition receptor (PRRs) family, play significant roles in activation/inhibition of immune and non-immune cells via recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [3–5].

It has been documented that the interaction of TLRs with PAMPs/DAMPs can be associated with various cell functions including inflammatory cytokine production [6, 7], migration [8], phagocytosis [9], induction of NADPH oxidase pathway [10] and also deterioration of malignancies [11]. TLR4 is a key PRR which is expressed on the cell surface of various numbers of immune cells. Interestingly, the molecule also is expressed by cancer cells. Thus, it has been hypothesized that TLR4 may play dual roles during cancers such as breast cancer. Therefore, this review article is aimed at addressing the main mechanisms played by TLR4 and its related signaling molecules in either defense or promoting breast cancer.

TLR4: the unique TLR which uses both MYD88 and TRIF as adaptor proteins

TLRs use two pathways to send their messages to the nucleolus to alter cell functions. Some of them such as TLR1, TLR2, TLR5, TLR6, TLR7, TLR8 and TLR9 use myeloid differentiation primary response (MYD88) to activate cell signaling, while TLR3 uses TIR domain-containing adapter-inducing interferon-β (TRIF). Interestingly, TLR4

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is a unique TLR which uses both MYD88 and TRIF adaptor proteins for transduction of its signaling [7, 12]. TLR4 has other synonyms including CD284 and age-related macular degeneration10 (ARMD10) [13]. It is capable of recognizing various microbial PAMPs and internal DAMPs [14, 15]. TLR4, like other TLRs, recognizes corresponded ligands by its extracellular leucine-rich repeat (LRR) domain, and interacts with MYD88 and TRIF via its cytoplasmic toll/interleukin-1 receptor (TIR) domain [13]. In the MYD88-dependent pathway, TLR4 generates a dimerization with myeloid differentiation 2 and then recruits TIR domain-containing adaptor protein (TIRAP) and MYD88, two adaptor proteins. Activation of MYD88 leads to phosphorylation of interleukin-1 receptor-associated kinase-4 (IRAK-4), IRAK-1 and tumor necrosis factor (TNF) receptor-associated factor-6 (TRAF-6), sequentially [13]. TRAF-6 is the molecule responsible for the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1 (AP-1) and interferon regulatory factor 5 (IRF5), the main TLR4-related transcription factors [16]. TLR4, in the TRIF-dependent pathway, recruits TRAM and then TRIF, and activates them [17]. Activated TRIF phosphorylates TRAF3, receptor-interacting protein 1 (RIP-1) and mitogen-activated protein kinase (MAPK) pathways simultaneously [18]. MAPK and RIP-1 lead to the activation of AP-1, while TRAF3 activates IRF3 [19].

Endogenous and exogenous lipopolysaccharides (LPS) are the main ligands for TLR4. Additionally, several internal molecules also are the activators of TLR4-dependent pathways [20]. Thus, TLR4 can be considered as a classical receptor for internal DAMPs, which are produced during human disorders such as cancers.

Breast cancer

Breast cancer is the most common cancer in women, and is the leading cause of cancer-related death, even more than lung cancer [21]. Each year 1.7 million women are diagnosed with breast cancer [22]. In Iran over the period of 2000–2010, 52,068 new cases were identified and the average annual crude incidence of breast cancer was 22.6 and 0.7 per 100,000 human females and males, respectively [23]. Although the main causes of breast cancer are not clearly understood, environmental factors and genetic variables are considered. Mutations in tumor suppressor genes and proto-oncogenes of epithelial cells lead to cancer. Also, environmental factors are suggested because of the variable incidence of breast cancer in a different geography [24].

Breast cancers are classified into in situ and invasive carcinoma: breast carcinomas that penetrate the basement membrane are invasive carcinoma and those that do not penetrate the basement membrane are called in situ carcinoma. According to the histologic pattern, there are two types of non-invasive breast carcinoma including ductal carcinoma in situ and lobular carcinoma in situ, and invasive carcinoma has several morphological patterns, the most common of which are invasive ductal carcinoma and invasive lobular carcinoma [25, 26].

The most common presenting sign of breast carcinoma is the palpable mass that is detected by the patient or her physician. When this mass is detected, the tumor has a large size and regional lymph node metastasis is present so mammographic screening can help us to detect nonpalpable masses [27].

Methods

Scopus, MEDLINE and Google Scholar were used to explore general research regarding the roles of TLR4 in the induction of appropriate immune responses against breast cancer and also pathogenesis of the disease using TLR4 and breast cancer as keywords. The original papers which have explored TLR4 roles in the breast cancer immunity and pathogenesis have been introduced to this project. The general search regarding TLR4 revealed 15,939 papers; however, the refined search by "breast cancer" resulted in 90 articles. After excluding the review articles and the papers which were published in invalid journals, 46 papers have remained.

Results

Investigations about the roles of TLR4 in the pathogenesis of breast cancer can be categorized into two main sections: the investigations which reported the defensive roles of TLR4 against breast cancer and the studies that reported TLR4 deteriorates breast cancer development and metastasis.

TLR4 can participate in immune responses against breast cancer

Some investigations revealed that TLR4 plays important roles against breast cancer progression and induction. For example, Park and Kim reported that activation of TLR4 by LPS can lead to the increased expression of intracellular adhesion molecule-1 (ICAM-1), an adhesion molecule which promotes adhesion of immune cells to breast tumor cells and then eradication of the tumor cells [28]. Ghochikyan and colleagues also reported that using Immunomax®, as a potential commercial ligand of TLR4, is associated with increased tumor cell killing by natural killer (NK) cells and consequently increased survival chances in metastatic breast cancer animal models [29]. Association of TLR4 silencing with increased breast cancer progression

and metastasis to the lung was reported by Ahmed and colleagues [30]. Several investigations also revealed that loss of function of TLR4 alleles is associated with reduced response to chemotherapy in the patients with breast cancer [31–34]. Tolerogenic macrophages which are increased during chronic inflammation of the developed breast cancer also suffer from dysfunction via TLR4 signaling pathway [35], which confirms the important roles played by TLR4 against breast cancer. Immunotherapy of breast cancer using TLR4 ligands was associated with tumor regression in an animal model [36]. A study by Lamrani et al., demonstrated that TLR4 activation when associated with interferon (IFN) γ pathway activation simultaneously leads to induction of a proper level of nitric oxide (NO) synthase (NOS) and subsequently increased cytoplasmic levels of NO and reactive oxygen species (ROS) in murine breast cancer models [37].

Based on the information presented by the investigators, TLR4 is an important molecule which can induce or stimulate immune responses against breast cancer. Additionally, previous review articles also proved the anti-cancer roles of TLR4 against other tumors such as hepatocellular carcinoma [38]. Based on the roles of TLR4 in induction of pro-inflammatory molecule expressions including pro-inflammatory cytokines [39], adhesion molecules [40], scavenger receptors [41], Fc γ receptor III (CD16) [42], etc., it can promote macrophages, NK cell and cytotoxic T lymphocytes to overcome breast cancer cells.

TLR4 promotes breast cancer development and metastasis

Although TLR4 is a part of the immune responses against breast cancer to eradicate the malignancy, its roles in the promotion of breast cancer development and also metastasis were documented in several studies. For instance, overexpression and important roles played by TLR4 and its signaling molecules during breast cancer and also their roles in invasiveness and metastasis were documented by Wang et al. [11], Volk-Draper et al. [43], Chen et al. [44], Yang et al. [45], Green et al. [46], Chalmers et al. [47], Ehsan et al., [48]. In parallel with the studies, Gonzalez-Reyes et al., demonstrated that expression of TLR4 has a positive correlation with breast cancer metastasis [49]. Interestingly, Yang et al., also revealed that inhibition of TLR4 signaling pathways results in the suppression of breast cancer proliferation in in vitro condition [50]. Another investigation proved the roles of TLR4–MYD88-dependent pathway in the deterioration of prognosis in breast cancer [51]. Additionally, investigations demonstrated that using Paclitaxel, a TLR4 ligand, promotes TLR4 activation and consequently increases breast cancer metastasis [52, 53]. Decreased chance of survival in breast cancer animal models was also associated with up-regulation of functional TLR4 [54]. Depletion of the TLR4 gene in breast cancer animal models was also associated with reduced metastasis and increased survival [55]. Wang et al., reported that serum levels of Resistin, which is an inflammatory obesity-related molecule, are increased during breast cancer [56]. They also using in vitro and in vivo experiments revealed that resistin via interaction by TLR4, as an agonist, and activation of signal transducer and activator of transcription 3 (STAT3) pathway and also activation of NF-κB enhances breast cancer-related epithelial–mesenchymal transition and stemness [56]. Another in vivo investigation showed that propolis ethanol extraction suppresses MDA-MB-231 cell proliferation, as a breast cancer cell line, through suppression of TLR4 in both MYD88 and TRIF signaling pathways [57]. A study by Edwardson and colleagues revealed that TLR4 is the molecule responsible for the production of pro-inflammatory cytokines by breast cancer cells, which is the main cause of pro-inflammatory microenvironment of tumors [58]. Previous investigation reported that cancer-associated fibroblast (CAFs) interactions with breast cancer cells may suppress the tumor progression [59]. Accordingly, autophagy in CAFs can be associated with breast cancer development [60]. Zhao et al., demonstrated that autophagic CAFs produce and release a TLR4 ligand, high-mobility group box 1 (HMGB1), which leads to breast cancer progression in TLR4-dependent manner [61]. It has been documented that microRNA-497 (miRNA-497) has a negative correlation with breast cancer progression, as its down-regulation is associated with proliferation, invasion and metastasis of breast cancer cells [62]. Interestingly, Xu et al., reported that up-regulation of miRNA-497 is associated with increased expression of TLR4 and its signaling molecules such as IRAK1 [63]. The effects of miRNA-10b on the increased expression of TLR4 and also the increased risk of metastasis of breast cancers were documented by Ibrahim and colleagues [64].

It appears that TLR4 functions and also phosphorylation of its related signaling molecules are significantly different in the breast tumor cells when compared to normal breast cells. Accordingly, Tosun et al., showed that stimulation of human breast cancer cells by TLR4 ligand, LPS, was not associated with anti-cancer functions, while interactions between LPS and TLR4 on the human breast epithelial cells, the normal cells, and also hybrid cells which were derived from the cancer and normal cells were associated with anti-cancer responses [65]. In parallel with the study, Fried et al., demonstrated that LPS in high doses can induce apoptosis in the hybrid cells but not in the cancer and normal cells [66]. Previous investigations revealed that macrophage migration inhibitory factor (MIF) is up-regulated during solid tumors including breast cancer [67]. Moreover, MIF induces ROS in the cytoplasm of breast cancer cells which is a main cause of ERK phosphorylation and consequently production of HMGB1 [68]. On the other hand, MIF induces expression of

TLR4 [68]. Thus, it seems that MIF stimulates breast cancer metastasis and progression in TLR4-dependent manner. Furthermore, Bergenfelz and colleague revealed that up-regulation of S100A9, a DAMP which is associated with increased inflammation, is associated with decreased survival of breast cancer animal models via up-regulation of TLR4 [69]. Interestingly, increased expression of S100A9 is associated with poor prognosis of breast cancer [70] and TLR4 may be a part of this puzzle. Furthermore, the roles played by TLR4 in the induction of drug resistance in breast cancer were also demonstrated by Xu et al. [71]. The roles of saturated fatty acids, which are released as a result of obesity-associated lipolysis, on activation of chronic inflammation in TLR4-dependent manner during breast cancer were documented by Howe and colleagues [72]. Zhou et al., reported that the interaction of TLR4 ligands/H_2O_2 with TLR4 leads to activation of TGF-β1 signaling non-invasive breast cancer cells [73]. Li and colleagues also demonstrated that TLR4 elevates metastasis of breast cancer through Akt/GSK3β/β-catenin-dependent pathway [74]. The key roles played by TLR4–MYD88 pathway in the expression of CC ligand chemokine 2 (CCL2) and CCL5, and consequently growth and metastasis of breast cancer in both human and mice were also reported by Egunsola and colleagues [75]. Stimulation of breast cancers with TLR4 ligands is also associated with increased metastatic and invasive migration of breast cancer cells through up-regulation of αvβ3 integrin molecule [76]. Up-regulation of β1 integrins, which are the key molecules involved in the metastasis of breast cancer cells, have also been reported by previous investigation [77].

Conclusion

Based on the information presented in the result section, it seems that TLR4 play dual roles during breast cancer development including eradication and stimulation of breast cancer. Based on the results, a question is raised, which parameters determine the roles of TLR4 in breast cancer? In other words, which parameters determine whether TLR4 is a friend or foe for breast cancer. Some investigations particularly answer this question. Accordingly, Harichaaran and Brown reported that TLR4 activation inhibits and induces growth of breast cancer in the presence or absence of TP53, respectively [78]. TP53 is a tumor suppressor whose down-regulation in tumor cells was documented by several investigators [79–81]. Additionally, Slattery and colleagues reported that lifestyle factors such as smoking may be considered as a risk factor for alteration in TLR4 function during breast cancer [82]. The effects of genetic factors on the functions of TLR4 have also been evaluated by investigators; it was shown that TLR4 rs4986790, rs4986791, Asp299Gly and + 3725GC polymorphisms were associated with increased risks of breast cancer. Interestingly, they proved that some of the polymorphisms alter interactions between TLR4 and its ligands [83–86]. Additionally, type of ligands may also be considered as an important factor to determine the outcome of TLR4 functions. For example, endogenous saturated fatty acids are the ligands which may be associated with the negative roles of TLR4 during breast cancer [72], or, as mentioned in the earlier section, TLR4 ligands, if associated with H_2O_2 can result in the activation of TGF-β1 signaling, which is a crucial pathway to induce metastasis [73]. Figure 1 describes the mechanisms which alter TLR4 functions to induce breast cancer development.

Collectively, TLR4 is either a friend or foe during breast cancer. In the friend roles, TLR4 fights against breast cancer cells via recognition of their DAMPs and subsequently induces immune responses to eradicate the tumor cells, which are seen in the normal human breasts. And in the foe roles, some factors including up-regulation of TLR4, smoking, genetic variations, alteration in some miRNAs expression, association of some intrinsic pathways such as TGF-β signaling and TP53 as well as over-expression of breast cancer-related DAMPs can alter TLR4 functions which helps the tumor to progress.

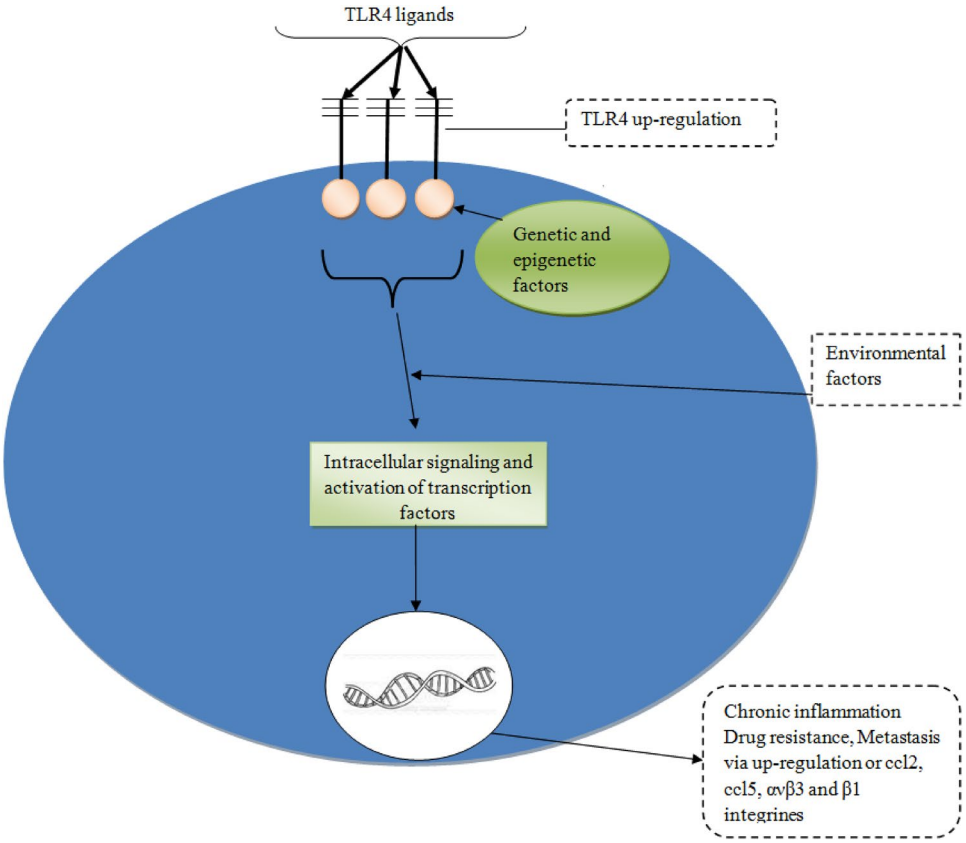

Fig. 1 TLR4 promotes breast cancer cells. Over-expression of TLR4, on the effects of microRNAs and genetic variations, as environmental factors, increased production of its ligands and also alteration in the components of its ligands lead to activation of intracellular signaling pathways which alter TLR4 main functions. Accordingly, it results in breast cancer cell development, drug resistance and also metastasis

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Compliance with ethical standards

Conflict of interest Authors have no conflict of interest.

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