Opinion

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Toll-like Receptor: Breast Cancer Development and Immunotherapy

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Abstract

Breast cancer is well known leading causes of mortality in the females. Current studies have suggested that the imbalances in inflammatory and immune-associated proteins may also give rise to breast cancer and disease progression. Toll like receptors (TLRs) are essential components of innate immune system that protect the host against bacterial and viral infection. It not only express in innate immune cell, its expression also found in breast cancer cells. Activation of TLRs leads to the activation of inflammatory pathways. Recent reports provide such evidences, which suggest the important role of TLRs in breast cancer pathogenesis and recurrence. TLRs are not only involved in cancer development, but also involve in anticancer immunotherapy. There are some agonists and antagonist of TLRs, used in anticancer immunotherapy, is targeted in clinic successfully.

Keywords: Agonist; Antagonist; Toll like receptor; Breast cancer; Immunotherapy; Inflammation

Introduction

In innate immunity toll like receptors (TLRs) plays an important role [1]. In cancer cell the higher expression of TLRs leads to proliferation and metastasis, and sometime inhibition. In the pathophysiology of the different cancer it assists to the initiation and progression of cancer cells [2,3]. TLRs are activated through pathogen associated molecular patterns (PAMPs) as well as endogenous molecules, which cause the activation of inflammatory pathways. Previous evidences support that chronic inflammation can lead to cancerous condition [4]. This opinion article discussing briefly about the involvement of TLRs with the breast cancer development and immunotherapy.

TLRs Family and Breast Cancer

These are the type I transmembrane receptors, protects the host against the different pathogen infections [5]. It is a family of pattern-recognition receptors of innate immunity system. It has the extracellular leucine rich repeat (LRR) and cytoplasmic Toll/IL-1 receptor (TIR) domain. There are mainly 10 different TLRs in the human body. They are TRL1 to TLR10. They are classified into two sub groups **(Figure 1)**.

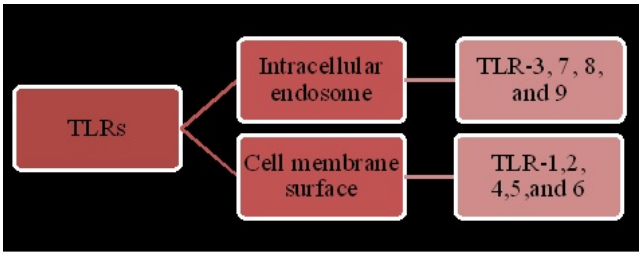

Figure 1 TLRs family.

TLRs play an important role in initiating and promoting of breast cancer. TLRs are mainly expressed in macrophages, dendritic cells and other innate immune cells. They are highly expressed in the breast cancer cells [6].

TLR3 have the tumour suppressive function. It inhibits the tumour development. Activated TLR3 induce the apoptosis of the breast cancer cell. Tumour cell with high expression of TLR3 have the high chance to metastasise [7].

TLR4 plays important roles in the migration of cancer cells [8]. It helps to introduce chemokinase gene. Previous studies showed that there is a significant association of high TLR4 expression with the metastasis of lymph node and local cancer proliferation [9].

TLR5 is highly expressed in breast carcinomas [10]. When TLR5 is activation by its ligand flagellin, exhibit potent antitumor activity and inhibits breast cancer cell proliferation [10].

TLR9 is expressed in epithelium breast cancer cells [11]. It assists in the progression of breast cancer [12]. Women with breast cancer have higher circulating levels of TLR9 compared to normal.

Each TLR have specific ligand like bacterial lipoprotein (TLR2), viral double stranded RNA (TLR3), CpG-DNA (TLR9) etc. TLRs are able to recognize the endogenous danger associated

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molecular pattern (DAMP) that might release to activate inflammatory pathways in the development of cancer [13].

As inflammation is a new hallmark of the cancer progression [14], recently it is found that increasing interest in this field of research. TLR signalling also plays a significant role in proliferation of tumour cell, local invasion and distant metastasis.

There is a link between breast cancer and inflammation [6]. Though TLRs are expressed in macrophage, dendridic cell, and other innate immune cell, it was also found the high expression of TLRs in breast cancer cell [15]. Knockdown of TLR4 impairs the proliferation and survival of breast cancer cells.

Treatment with TLRs

There are many options for the targeting of TLRs, because the key function of TLRs is to induce cytokines [16]. It is well validated in cancer, and successfully being targeted in the clinic. Several compounds that are able to stimulate TLRs 3, 4, 7, 8 and 9 have now been tested in clinical trials [17]. Several pharmaceutical companies and biotechnologies have different programmes to develop new drugs that act as either **(Table 1):**

1. Agonists of TLRs to enhance immune responses against tumours and infectious agents or to correct allergic responses or;
2. Antagonists designed to reduce inflammation due to infection or autoimmune disease.

Table 1 Compounds that affect toll-like receptor TLR2 and TLR4 activity or expression in breast cancer.

References	Year	Ligand	Role in normal cell	Effect in Breast cancer
Zhang G et al. [18]	2012	Serum amyloid A	chemo-attractant	depending on stage, it increases in breast cancer patients
Tang D et al. [19]	2010	HMGB1	Regulate apoptosis	More express in tumour cell than normal cell
Xie W et al. [20]	2010	Peptidoglycan	Forms cell wall of bacteria	Cause of invasive breast cancer

Conclusion

TLRs have a significant role in maintaining tissue homeostasis by regulating the inflammatory responses to injury in our body [21]. We can also say that TLRs also play an important role in cancer development and treatment. Therefore the activation of different TLRs plays opposite role in the breast cancer. Activation of TLR3, TLR5 inhibits cancer cell proliferation and metastasis. In the other hand the activation of other TLRs like TLR2 and TLR4 induces to promote cancer cell proliferation and metastasis. Hence it can be demonstrated that the role of TLRs in the development of cancer is complex. There is a growing interest in the targeting of Toll-like receptors (TLRs) for the prevention and treatment of cancer [22]. TLRs have opened up a productive area for the development of new drugs. It can be said hopefully that future studies of targeting multiple TLRs may give effective therapeutic targets for drug development and treatment of breast cancer.

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