

Role of Toll-like receptors in nonresolving inflammation-related cancer

¹Chun-lin Ou, ^{1,2}Zhen-qiang Sun, ¹Xiao-ling Li*

¹ Cancer Research Institute, Central South University, Changsha 410078, Hunan, China

² Department of Gastrointestinal Surgery, Affiliated Tumor Hospital, Xinjiang Medical University, Urumqi 830011, Xinjiang, China

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Abstract

To some degree, the relationship between nonresolving inflammation and cancer has been confirmed. Inflammatory cells and cytokines infiltrates tumor tissue in tumor microenvironment. Toll-like receptors, as an important pattern recognition receptors (PRRs) are closely associated with tumor microenvironment formation and play an important role in regulating tumorigenesis. Thus, deeper investigation into molecular effect mechanism of Toll-like receptors is highly worthwhile for tumor prevention, early diagnosis and treatment.

1. Introduction

The connection of tumor and inflammation is a host issue in recent years. Epidemiologic evidence supports that approximately 25% of all human cancer worldwide may be caused by nonresolving inflammation. In addition inflammatory cells and molecules in tumor microenvironment influence nearly every aspect of tumorigenesis. Mantovani [1] reported that nonresolving inflammation accelerate “inflammation-cancer

chain” in tumorigenesis, which may eventually evolve into “nonresolving inflammation-related cancer”. Consequently, the importance of biological malignant behavior of nonresolving inflammation is regarded as “the seventh characteristics of tumor” [1-4]. For nonresolving inflammation importance in the development of malignant tumors, many researchers have been paying more and more attention to those factors that lead to nonresolving inflammation happening in tumor microenvironment, such as TAM, TNF- α , CXC, especially Toll-like receptors. Recently, most researchers nearly reach a consensus that

* Corresponding author: medicine120@163.com

Toll-like receptors have close association with nonresolving inflammation-related cancer.

2. Toll-like receptors and Tumors

2.1 Biological characteristics of Toll-like receptors

Toll-like receptors (TLRs) is a type of protein in mammals, similarly to drosophila Toll proteins. TLRs is also a class of high homology of transmembrane protein. By far, 13 types of TLRs have been found in mammals, of which 11 kinds of human TLRs have been indicated some biological function[5, 6]. However, human TLR11 may be a pseudogene[7]. TLRs are widely expressed in professional immune cells as well as nonprofessional immune cells[8-10]. Furthermore, TLRs expression can be dynamically changed under the effect of endogenous and exogenous ligands[11].

The family of TLRs is an evolutionarily highly conserved protein molecule family. It is made up of three main parts: extracellular region, transmembrane region and intracellular region that all TLRs share their intracellular domain with the interleukin-1-receptor (IL-1R) family [12, 13]. TLRs is one of the components of innate immunity, which is able to recognize many kinds of pathogen-associated molecular patterns (PAMPs)[7, 14, 15]. Moreover, the activation of TLRs pathway leads to the induction of immune responses. Subsequently it increases the expression of inflammatory mediators through activating the antigen-presenting cells (APCs)[16, 17]. Therefore, TLRs act as a bridge between innate and adaptive immunity[11, 18-20].

2.2 TLRs and the tumorigenesis of nonresolving inflammation-related cancer

Tumor can be considered as a process of tissue repair dysregulation as well as "wounds that do not heal"[21]. TLRs as an important molecule of

innate immunity, on the one hand, TLRs can protect the organism through stimulating the innate immune and improving the adaptive immune; on the other hand, when the TLRs in the surface of tumor cells continuing to be stimulated, it will lead to the nonresolving inflammation response that can stimulate largely the process of tumorigenesis. In recent years, many evidences indicate that TLRs play an important role in the tumorigenesis of nonresolving inflammation related cancer, including tumor microenvironment, invasion and metastasis, immune escape, and so on.

2.2.1 TLRs and tumor microenvironment of nonresolving inflammation-related cancer

Tumor microenvironment is also called tumor inflammatory microenvironment, in other words, it's an advantageous environment to the formation and development of tumor, which can form a protective barrier to sustain the growth of tumor. Pienta[22] put forward the concept of "ecosystem cure", and emphasized that altering the tumor microenvironment is more meaningful than destroying cancer. Nevertheless, TLRs is widely expressed in many kinds of tumor tissues, such as throat cancer, lung cancer, breast cancer, gastric cancer, melanoma and so on[23]. When the TLRs in the surface of tumor cells was activated that can induce the expression of largely cytokines and chemokines, it will create the conditions for the formation of tumor inflammatory microenvironment.

Recently, largely studies take advantage of TLRs as the drug targets to regulate the tumor inflammatory microenvironment, which is a new research direction that cure and improve the inflammatory diseases and cancer. Woods[24] reported that it can cause the degradation of IK β and the activation of NF - KB and TNF- α when use LPS(LPS, a kind of ligand of the TLR4) to stimulate the human ovarian granulose tumor cell

lines, which can lead to the formation of tumor microenvironment and the occurrence and metastasis of tumor. Ben[25] found that the pro-inflammatory factors that tumor B lymphocyte is secreted were obviously decreased in the corresponding tumor microenvironment when used the TLR9 agonists (CpG-ODNs) to stimulate respectively the tumor tissue of subcutaneous, brain and eyes, which implies TLR9 may be a potential targets for cancer treatment.

2.2.2 TLRs and invasion/metastasis of nonresolving inflammation-related cancer

Invasion and metastasis is a very complex and multistep process, which is affected by many factors. According to the epidemiology and statistics, approximate 90% of mortality rate of cancer patients is attributable to tumor metastasis. However, only approximate 0.02% of cancer cells eventually form distant metastasis[1]. Fidler[26] believed that tumor metastasis depended on interaction between tumor cells and organism homeostasis. TLRs activation can cause the formation of tumor inflammatory microenvironment, which leads to change organism homeostasis. Hence, TLRs greatly increase risk of invasion and metastasis.

For a long time, invasion and metastasis of tumor cells is a difficult problem for tumor therapy. Because of TLRs importance in invasion and metastasis of nonresolving inflammation-related cancer, more and more researchers take TLRs as a critical factor in researches of malignant tumor. Liu[27] found that reducing miR-181a expression and two downstream of tumor suppressor genes of PTEN and MAP2K4, could promote tumor invasion and metastasis by stimulating pancreatic cancer cell lines with LPS for activating the TLR4 signaling pathways. It implies that LPS-TLR4-miR-181a signaling cascade pathway plays an essential role in invasion and metastasis of pancreatic cancer.

Hagstrom[28] detected 127 cases of follicular thyroid carcinoma by immunohistochemical staining, and found that TLR4 expression level in adenocarcinoma could prognostic occurrence of tumor metastasis. Amarante[29] found that the high TLR3 expression levels usually accompanied with high expression levels of CXCR4 and IFN in breast cancer tissue when studying the relationship between TLR3 and human breast cancer. Obviously, it implies that TLR3 has a potential connection with metastasis of human breast cancer. Sheyhidin[30] found that high expression level of TLR3 and TLR4 could significantly increase migration of lymph nodes as well as tumor invasiveness of in the process of esophageal squamous(ESCC). On the contrary, high TLR9 expression in fibroblast-like cells can greatly reduce invasion and metastasis of ESCC.

2.2.3 TLRs and the mechanism of immune escape of nonresolving inflammation-related cancer

Before tumor cells recognized immune escape, it will be appearing a balanceable condition between proliferation of tumor cells and immune damage. As a result, it usually leads to tumor cells in dormancy for years. At the same time, most researchers believe that nonresolving inflammation environment related to tumor can help initial tumor cells to obtain specific immune resistance[31,32]. Nevertheless, tumor micro-environment of non-resolving inflammation related cancer caused by activating of TLRs which would break the balanceable. It may increase the risk of immune escape and accelerate tumor occurrence and development.

In recent years, the strategy in treating tumor has been changed and the new treated strategy aims to break immune tolerance, activate anti-tumor immunity, enhance the immune surveillance, sustain the tumor dormancy, and so on[33-35]. TLRs play an important role in the immune escape so that large studies have revealed the mechanism of TLRs inducing tumor immune escape. Wlasiuk[36] found that all CLL cells can express TLR9. TLR9 expression was positively

correlated with that of HLA-G and CD85j in the research of immune escape mechanism of chronic lymphocytic leukemia (CLL). Expression level of HLA-G and CD85j can inhibit immune response and promote occurrence of immune escape. Demoulin[37] showed a new mechanism of tumor immune escape that tumor cells prevented tumor microenvironment of plasmacytoid DCs (pDCs) maturing in the TLRs mechanism to play a role in the immunosuppression and tolerance because the matured pDCs can activate the immune response of anti-tumor. Furthermore, Severa[38] found that it could impair pDCs maturation, combined with a concomitant EBV-mediated upregulation of T-cell inhibitory molecules B7-H1 and ICOS-L when EBV was infected pDCs by the mechanism of TLRs. EBV-infected pDCs are unable to mount a full T-cell response and consequently increase the risk of tumor immune escape.

2.3 TLRs and the immunotherapy of nonresolving inflammation related cancer

TLRs as the drug targets of antitumor can be traced back to last century, Coley[39] firstly discovered that it can achieve an effect for anti-tumor by repeating to inject LPS. Nowadays, more and more TLRs agonists have been used in tumor immunotherapy[40] and TLRs as a kind of drug potential targets have been widely applied by clinical trials, as shown in Table 1 (modified from[41, 42]).

In addition to using TLRs agonists directly for cancer treatment, TLRs agonists are more acted as immune adjuvant to treat cancer, especially the TLR9 agonist(CpGODN), which have been confirmed good effect in malignant glioma, lymphoma, an so on. In recent years, the combination of chemotherapy and TLRs agonists have applied in cancer treatment. For example, ferrous fumarate combined with TLR7 agonist(S28690) to treat chronic lymphocytic leukemia, which can enhance chemosensitivity[43, 44]. In addition, if TLR9 agonist(PF-3512676) are

added in the process of chemotherapy of non-small cell lung cancer patients, the curative effect can be remarkable improved[45-49]. These findings provide a new perspective for clinical treatment: when radiation therapy has not been widely carried out, the chemotherapy combined with immunotherapy may be a potentially effective way.

Table 1 The application of TLRs agonists in nonresolving inflammation-related

Cancer type	Nonresolving inflammation	Agent	Target
Melanoma	Nonresolving dermatitis	BCG	TLR2 TLR4
		Hiltonol	TLR3
		Resiquimod	TLR7, TLR8
Pancreatic cancer	Nonresolving pancreatitis	IPH 3102	TLR3
		852A	TLR7
		Hiltonol	TLR3
Bladder cancer	Nonresolving urocystitis	TMX-101	TLR7
		BCG	TLR2 TLR4 TLR9
Bile duct's sarcoma	Nonresolving cholangitis	SMP-105	TLR2
Non-Hodgkin's lymphoma	AIDS	Imiquimod	TLR7
		LPS	TLR4
Lung cancer	Nonresolving bronchitis	ISS1018+Rituxan	TLR9
		Stimuvax	TLR4
Colorectal cancer	Nonresolving ulcerative colitis	IMO-2055+Ava	TLR9
		stin and Tarceva	
Cervical cancer	Nonresolving cervicitis	MGN-1703	TLR9
		Stimuvax	TLR4
Prostate cancer	Nonresolving prostatitis	MPLA	+TLR4
		Cervarix	
		Stimuvax	TLR4
Breast cancer	Nonresolving mastitis	MGN-1706	TLR9
		Agatolimod+	TLR9
		Trastuzumab	
		CPG-7909+	TLR9
		Herceptin	
		Imiquimod	TLR7
		Stimuvax	TLR4

Since TLRs are widely expressed in surface of

many kinds of tumor cells, it suggests tumor immunotherapy have two sides. On the one hand, TLRs agonists, as a kind of therapeutic drug or immune adjuvant in tumor immunotherapy, can strengthen and accelerate immune response of immune cells, such as T cells and B cells. Therefore, it inhibits tumor development. On the other hand, when activating TLRs from tumor tissues, they will lead to large amounts of inflammatory cytokines secreted. Meanwhile, the formation of nonresolving inflammation microenvironment can lead to tumor occurrence and development of. Thus, the key problem of when to use TLRs agonists in process of tumorigenesis can make meaningful role in anti-tumor immunity.

3. Prospect

In recent years, studies of nonresolving inflammation-related cancer are hotspot in tumor immunity research. Meanwhile, a lot of evidence suggests that TLRs are able to affect the tumorigenesis of nonresolving inflammation-related cancer by multiple ways. As a consequence, the researches on TLRs that relate to nonresolving inflammation-related cancer have a great significance for treatment and prevention of tumors. However, TLRs is a double-edged sword in process of tumorigenesis. The main reason is that TLRs can be expressed both in normal immune cells and malignant cells at the same time, Consequently, it is able to do the dual function of TLRs in tissue protection as well as inflammation. Therefore, only some deeper studies are needed for potential target therapy of malignances.

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