Toll-Like Receptor Pathway and its Targeting in Treatment of Cancers

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17.1 Introduction

The innate immune system has been shown to be responsible for the diagnosis and reaction to pathogens, leading to inflammatory response and accumulation of professional phagocytes to the site of invasion [1]. Also, it has been reported that innate immune response is significantly associated with changes in cellular metabolic signaling pathways [2]. In addition, the innate immune response has been found to be crucial for stimulation of adaptive immune response against pathogens by formation and presentation of antigens and the production of mediators that are needed in combination to induce T cell- and B cell-mediated responses [3].

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Table 17.1 Expression of TLRs in several cancer cells

Cancer type	TLRs expressed
Basal cell carcinoma	TLR7
Breast cancer	TLR2, 3, 4, 5, 7, and 9
Brain cancer	TLR2 and 4
Colorectal cancer	TLR2, 3, 4, 5, 7, and 9
Cervical cancer	TLR3, 4, 5, and 9
Esophageal squamous cell carcinoma	TLR3, 4, 7, and 9
Gastric cancer	TLR2, 4, 5, and 9
Human head and neck squamous cell carcinoma	TLR4
Hepatocellular carcinoma	TLR2, 3, 4, 6, and 9
Laryngeal cancer	TLR2, 3, and 4
Lung cancer	TLR2, 3, 4, 7, 8, and 9
Melanoma	TLR2, 3, 4, and 7
Ovarian cancer	TLR2, 3, 4, and 5
Oral squamous cell carcinoma	TLR2 and 4
Pancreatic carcinoma	TLR4 and 7
Prostate cancer	TLR3, 4, and 9

Toll-like receptors (TLRs) are transmembrane pathogen recognition receptors (PRRs) that recognize various pathogen-associated molecular patterns (PAMPs), such as bacterial lipoproteins (TLR2), double-stranded RNA (dsRNA) (TLR3), lipopolysaccharide (LPS) (TLR4), flagellin (TLR5), single-stranded RNA (ssRNA) (TLR7 and 8), and cytosine-phosphorothioate-guanine (CpG) DNA (TLR9) [4]. In addition to TLRs, intracellular NOD-like receptors (NLRs) are also involved in human immunity. NLRs are intracellular innate immune detectors of microbial and other dangerous signals [5]. NLRs that contain NALP, NOD1, and NOD2 have been found to be involved in several signaling pathways, leading to regulation of production of proinflammatory cytokines, including interleukin-1β (IL-1β) and IL-18. Moreover, NLRs play important roles in the induction of cell death [6]. Additionally, NLRs can discriminate between pathogens which break cellular and mucosal barriers and nonpathogenic microorganisms, therefore providing a functional benefit over TLRs to work as sentinels of the innate immune system at mucosal levels [7]. It has been reported that NODs are also involved in immune response against tumors. Although simultaneous targeting of TLRs and NLRs has been found to be effective in the induction of $CD4^+$ and $CD8^+$ T cell function, leading to suppression of tumor growth [8], NOD's targeting/triggering effects on tumors are not adequately stated. Hence, we decided to review the role of TLRs in tumorigenesis and discuss the prospect of TLRs in the treatment of cancers.

Activation of various TLRs may lead to complete opposite results, such as anti- or protumor effects. TLR role is cell specific, and the varied outcome of TLR function originates from difference of TLR stimulators in combination with other microenvironmental factors. It has been found that TLR4 and TLR9 activation leads to tumor cell escape from immune system attack, promoting tumor growth. In contrast, triggering of TLR3 on breast cancer cell promotes antiproliferative signaling. Besides, TLR3 expression in head and neck cancer (HNC) induces tumor aggressive behaviors [9].

It has been found that chronic inflammation may lead to cancer initiation [10]. TLR has been recognized as not only being responsible for secretion of proinflammatory cytokines but also for the upregulation of metalloproteinase and integrins, thereby promoting tumor cell invasion and metastasis [11]. Among tumorigenesis cytokines, IL-6 has been shown to play a crucial role in the differentiation, angiogenesis, proliferation, and apoptosis of several cell types [10]. Initially, it has been thought that TLRs are present only on immune cells; however, recently, it has been understood that TLRs also have important functions in human cancers (Table 17.1). Later, it has been discovered that TLRs promote proinflammatory cytokines, leading to tumor growth and chemoresistance. However, various differential pro- and antitumor effects have been recognized for TLRs [12].

17.2 TLRs Play Important Roles in Human Carcinogenesis

In addition to bacterial and viral components, TLR expression increases in response to inflammation by-products and cellular injury, namely, damage-associated molecular patterns (DAMPs) [13]. Even though TLR7 activation shows antitumor responses in various tumors, including basal cell carcinoma (BCC), breast cancer, and