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Review

Role of Toll-like receptors in cervical, endometrial and ovarian cancers: A review

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HIGHLIGHTS

- TLRs are immunomodulators that may play an important role in the development of cancer.
- The main function of the TLR is to recognize the molecular structure of foreign pathogens and promote immune response.

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ABSTRACT

Objective. The Toll-like receptors (TLRs) have been implicated in inflammation, innate immunity and cancer. The goal of this paper is to review the available published research about Toll-like receptors and their roles in gynecologic malignancies.

Methods. A Medline search was conducted and published articles from the late 1990s to the present (2014) were reviewed using search phrases, Toll-like receptors and cervical, endometrial and ovarian cancers.

Results. TLR4 and TLR5 are commonly absent in normal cervix, however TLR5 expression is strong in high grade cervical dysplasia as well as invasive cancer. The expression of TLR3 and TLR4 is low in endometrial cancer. TLR2, TLR3, TLR4 and TLR5 are highly expressed in normal and neoplastic ovarian epithelium. TLR3 has been shown to have a dual function: it can contribute to tumor elimination by upregulation of interferons α and β (INF) and natural killer cell (NK) activation or it can indirectly contribute to tumor progression.

Conclusions. Inflammation is an essential element in tumorigenesis. Toll-like receptors can trigger an inflammatory response and cell survival in the tumor micro-environment. TLRs are critical immunomodulators that may play an important role in the development of gynecologic cancers. Currently TLR agonists are being investigated for a potential role as an adjuvant in the treatment of gynecologic malignancies.

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Introduction

Scientists have long been searching to discover the mechanism of the immune response against invading microorganisms. The discoveries of three Nobel laureates; Bruce Beutler, Jules Hoffmann and Ralph

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Steinmann on the innate and adaptive immune response opened up new approaches for prevention and therapy against infections, inflammatory diseases and cancer.

There are two lines of defense in the immune system. The first one is innate immunity in which the components of microorganisms bind to Toll-like receptors. This will activate the inflammatory response leading to the destruction of invading microorganisms. The second one is adaptive immunity which comes into action when microorganisms break through the first line of defense. In adaptive immunity dendritic cells activate T and B cells, producing antibodies and killer cells that destroy cells that have been infected by invading pathogenic microorganism.

Toll-like receptors (TLRs) are members of the interleukin-1 receptor family [1]. The main function of the TLR is to trigger a signal transduction pathway to promote expression of genes. These gene products control the innate immune response and develop antigen-specific acquired immunity by recognizing the molecular structure of foreign pathogens [2,3]. There are 10 functional TLRs that have been described in humans. TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10 are expressed on the cell surface and migrate to phagosomes after activation. TLR3, TLR7, TLR8 and TLR9 are expressed intracellularly, mostly in the endosomes and the endoplasmic reticulum with ligand-binding domains. They differ in ligand binding specificities, expression patterns, and in their target genes. When a TLR binds to its cognate ligand, the result ultimately is the expression of a multitude of host defense genes. These include inflammatory cytokines and chemokines, antimicrobial peptides, co-stimulatory molecules, major histocompatibility (MHC) molecules, and other effectors necessary to arm the host cell against an invading pathogen [4].

Toll-like receptors are pattern recognition receptors (PRRs) which are capable of detecting a number of different molecular structures including: double stranded DNA (TLR3), lipopolysaccharides (TLR4), flagellin (TLR5), single stranded viral RNA (TLR7, TLR8) and unmethylated CpG (Cysteine–Phosphate–Guanine) sites of DNA (TLR9) in bacteria and viruses [5]. TLRs have also been described as transmembrane proteins that recognize specific pathogen associated molecular patterns (PAMPs) found in viruses and other invading pathogens. Different TLRs are able to identify different PAMPs. Upon activation of the TLR, a signal transduction is initiated, which involves several adaptor and activator proteins. The TLR and the nuclear factor kB (NF-kB) signaling pathways have been implicated in inflammation, autoimmune disease and cancer [6]. NF-kB is a light chain enhancer of activated B cells that binds to DNA, which in turn induces cytokine transcription and subsequent induction of an immune response. Alternatively, NF-kB can be activated through TNF, which exercises its function by binding to a member of the tumor necrosis factor (TNF) receptors which includes adaptor and activator proteins [7]. Whether common nucleotide variation in these pathways is associated with the risk of cancer has not been well established.

TLRs have a variety of functions in normal healthy cells, including tissue homeostasis, regulation of cell death and survival. These same roles in tissue homeostasis also mean that the TLR may have a critical role in tumorigenesis. TLRs can create an environment conducive for carcinogenesis through the inflammatory response, angiogenesis and cell death. By expanding immune cells and integrating inflammatory responses and tissue repair processes, TLR can regulate cell proliferation and survival and create the environment for tumor cells to evade the immune response [8]. There are at least three mechanisms that demonstrate the ways in which TLRs regulate the inflammatory response: the anti-apoptotic effect of nuclear factor kappa B (a transcription factor engaged in inflammatory conditions), induction of oxidative damage to DNA and the induction of the tissue repair response [9]. In addition, TLRs also appear to have important roles in tumor angiogenesis. Vascular endothelial growth factor (VEGF) is secreted by tumor cells, immune cells and cancer associated fibroblasts (CAFs) [10]. Their varied permeability leads to high interstitial pressure and hypoxia, which stimulates additional VEGF production. TLRs bind PAMPs and are a major component in the defense against invading organisms. In addition to PAMPs; they also recognize damage-associated molecular pattern (DAMP), which are proteins of nucleic acids released during necrosis and cell death. DAMP activation of TLRs expressed on tumor cells initiates signaling cascades that mediate the release of cytokines and chemokines from tumor cells [11,12]. These agents recruit immune cells that release additional cytokines, proangiogenic mediators and growth factors that can facilitate tumor growth.

NF-κB is a protein complex responsible for cytokine production that is used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. NF-κB is involved in cellular responses to stimuli and plays a key role in regulating the immune response to bacterial or viral infections. This inflammatory role has also implicated NF-κB in cancer and autoimmune diseases. When NF-κB activates, it turns on gene expression that maintain cell proliferation to protect the cell from apoptosis. Any defect in NF-κB results in increased cell death [13] (Fig. 1). In tumor cells, NF-κB is active either due to mutations in genes that encode it or in genes that regulate it [14]. Using immunohistochemical technique from hysterectomy specimens removed for benign gynecologic disease, Fazeli et al. reported the in vivo expression of TLRs in female reproductive tract. TLR1, TLR2, TLR3, TLR5 and TLR6 were present in the epithelia of many different regions of female reproductive tract, however TLR4 was only present in the endocervix, endometrium and fallopian tubes [15].

TLR and cervical neoplasia

It has been well established that human papillomavirus (HPV) plays a role in the development of CIN, however it is also widely observed that not all cases of HPV infection go on to result in clinically significant disease. The difference between HPV infections that subsequently resolves vs. HPV infection that progresses into invasive neoplasia may be coexisting with inflammation and/or infection. Multiple TLRs have been implicated in this process. Oncoproteins E6 and E7 have been noted to alter the expression of several components of the NF-kB signal pathway in cervical keratinocytes. Susceptibility to cervical and vulvar malignancy may be augmented by genetic variation in the TLR and NF-kB signaling pathways, including variants within the TNF region [16]. Werner et al. noted that TLR4 is normally absent in normal cervical keratinocytes, noting that infection results in the upregulation of TLR4 and beta 6 integrin and subsequent inflammation [17]. TLR-4 was found to be highly expressed TLRs in the HeLa cell line [18]. Lee et al. observed that the expression of TLR5 and TLR9 was absent or weak in normal cervical squamous cell epithelium but gradually increased during progression of low-grade cervical intraepithelial neoplasia (CIN) to high-grade CIN and then to invasive cervical squamous cell carcinoma [19]. Yu et al. observed a decrease in the expression of TLR4 during the progression of cervical neoplasia and this down regulation of TLR4 appeared to be associated with cyclin-dependent kinase inhibitor (P16-INK4a) which is a crucial marker for host cells [20]. Hasan et al. noted that TLR-9 expression was altered by HPV 16 because of the inhibition of TLR-9 transcription by HPV 16, E6 and E7 oncoproteins [21]. Kim et al. used immunohistochemical staining to show that TLR5 expression was undetectable (80%) or weak (20%) in normal cervical squamous epithelium. However, moderate expression was detected in 33.3% of low-grade CIN (3/9), 41.7% of high grade CIN (5/12), and 45.8% of invasive squamous cell carcinoma (11/24). Strong expression was detected in as much as 33.3% of high-grade CIN (4/12) and 50% of invasive cancer (12/24) [22]. They also stated although the relationship between TLR and HPV infection is unknown, activation of the TLR-5 in response to HPV infection could also be a consequence of the action on E6 and E7. These data further support that TLR signaling can be a useful marker in the progression of cervical cancer.

TLR and endometrial neoplasia

TLRs are expressed in human endometrium and may play an important role in pathogenesis of endometrial disease. Allhorn et al. investigated