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Review article

Controversial roles played by toll like receptor 4 in urinary bladder cancer; A systematic review

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ABSTRACT

Introduction: Urinary bladder cancer (UBC) is a prevalent human cancer. The main mechanisms which lead to eradication or progression the disease has yet to be clarified. Toll like receptor (TLR) 4 is a membrane receptor which is expressed either on immune cells or tumor cells. This review article was aimed to clear the main mechanisms played by TLR4 and its related intracellular pathways on outcome of UBC.
Method: PubMed, Scopus and Google scholar databases have been used for searching related research articles which have evaluated the roles played by TLR4 and its related intracellular pathways on outcome of UBC.
Results: Collected information from the related articles revealed that TLR4 either participates in induction of immune responses against UBC or development of the malignancy. There are limited investigations regarding the genetic variations of TLR4 in UBC.
Discussion: According to the results it seems that TLR4/ligands interaction outcome is dependent on several factors including TLR4 ligand doses, interaction of TLR4 with its ligands on immune cells or tumor cells, and other TLRs/ligand interaction simultaneously.

Contents

1. Introduction

Immune responses are the main arms of the body for fight against cancers which is named as immunesurveillance [16]. It has been established that innate immunity plays key roles in immunesurveillance and recent investigations approved the crucial roles of membrane sensors (receptors) as potential tumor antigen recognizers [13]. The membrane sensors are categorized as pathogen recognition receptors (PRRs) which induce immune responses against microbes and tumors following recognition of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs), respectively [4].

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Toll like receptors (TLRs) are a set of membrane sensors which activate intracellular signaling pathways and consequently transcription from pro-inflammatory molecules, in responses to PAMPs and DAMPs in TRIF and MYD88 dependent manner [39]. Cytokines and co-stimulatory molecules are the main targets of the intracellular pathways, hence, TLRs/ligands interaction may be considered as inducer/protectors of tumors [58]. TLR4 is a member of TLRs which has two distinct characterizations in comparison to other TLRs including; 1. It has been expressed either on the cytoplasmic membrane or on the vesicles' membrane, 2. It uses both adaptor proteins, TRIF and MYD88, for activation of intracellular signaling pathways (Fig. 1) [59]. Additionally, TLR4 can recognize intrinsic lipopolysaccharide (LPS) and also other DAMPs which are released in the patients suffering from cancers [29]. Thus, it may be hypothesized that TLR4 may play key roles in immunesurveillance against tumors. On the other hand, it has been reported that inflammation can be considered as a main cause of induction of tumors and help to tumor development [22]. Furthermore, it has been demonstrated that TLR4 expression is restricted to some immune cells in normal conditions but it is found on the human tumor cells, including urinary bladder cancer (UBC) cells, aberrantly [26,52]. Therefore, the participation of TLR4 in progression of tumors is plausible.

Urinary bladder cancer (UBC), as a heterogeneous disease, has diverse morphologic and clinical manifestations [6]. The disease is a prevalent malignancy and high number of patients died from this disease [17]. This situation justifies rummaging through the literature for all mechanisms lead to induction and development of UBC.

According to the introducy regarding the plausible roles played by TLR4 in fight, induction and development of cancers, it may be hypothesized that the molecules and related pathways may participate in the immune responses against UBC or in pathobiology of the disease. Therefore, this review article focuses on the relationship between TLR4 and UBC.

1.1. TLR4 and down-stream molecules

TLR4 is a transmemberane receptor which is also known as age-related macular degeneration 10 (ARMD10) and CD284. Its gene is located in 9q33.1 and consists of 4 exon and 3 intron and is highly conserved in mammalian [37,58]. TLR4 molecule has three domains including leucine-rich repeats (LRRs), transmembrane and toll/interleukin-1 receptor (TIR) domains (Fig. 1). TLR4 LRR is the responsible domain for recognition of ligands (PAMPs and DAMPs), specially LPS, to activate intracellular signaling pathways in dimmer format [55]. This is the unique TLR which activate intracellular signaling molecules via either TRIF or MYD88 adaptor proteins. TLR4/ligands interaction stimulates transcription from pro-inflammatory cytokines, chemokines, co-stimulatory molecules and so on [55]. Activation of intracellular signaling molecules through MYD88 mainly results in separation of NF-κB from Iκκ, the inhibitor of NF-κB, then translocation the transcription factor to nucleus [18]. While, in TLR4/TRIF dependent pathway, the TLR4/ligand complex is internalized into endosomes and then TRAM and TRIF is recruited to activate IRF3 [20]. The main involved signaling molecules in both pathways are illustrated in Fig. 1.

Today, several TLR4 ligands are described including hyaluronan, lipopolysaccharide (LPS), free fatty acids, monophosphoryl lipid A (MPLA), high-mobility group box-1 (HMGB-1), Bacillus Calmette–Guérin (BCG), heat shock protein 60 and allergenic nickel [2,8].

1.2. Urinary bladder cancer

Investigations demonstrated that UBC is a cancer with a significant morbidity and mortality and the fourth and ninth most common neoplasia in men and women, respectively [7,17]. The disease is a heterogeneous disorder covering diverse clinical manifestations [15]. Urothelial carcinoma is the most common form of UBC which consists

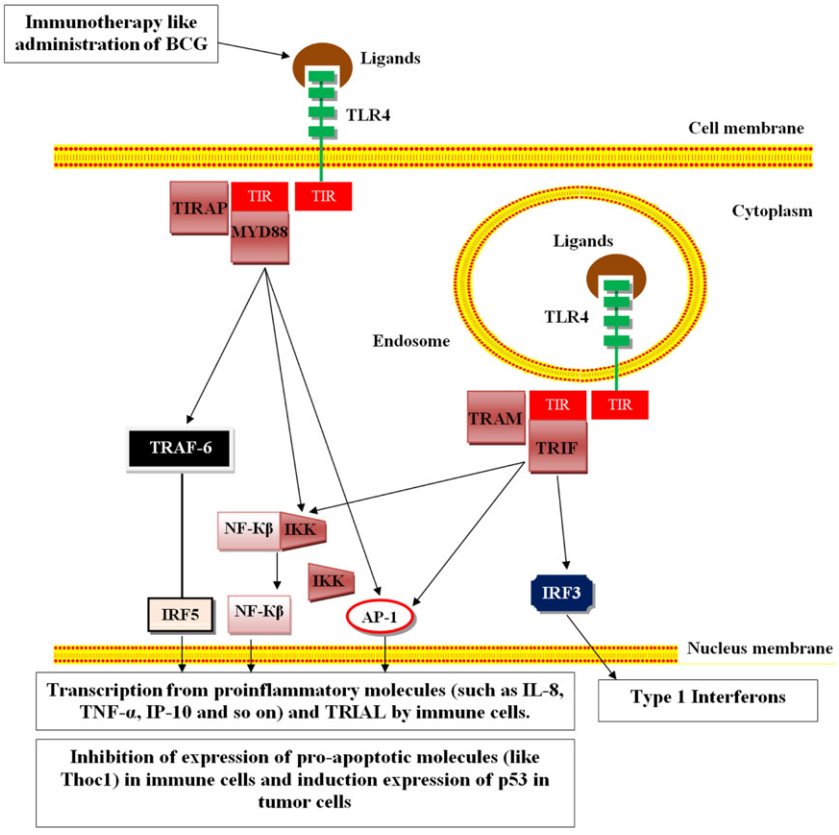

Fig. 1. Interaction of TLR4 and its ligands like BCG leads to activation of intracellular signaling pathways, TRIF and MYD88 dependent pathways, and inhibition of expression of pro-apoptotic molecules in immune cells in in vivo condition and also induction of pro-apoptotic molecules in tumor cells in in vitro condition.