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Toll-like receptor stimulation in cancer: A pro- and anti-tumor double-edged sword

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ABSTRACT

Toll-like receptors (TLRs) are a family of transmembrane receptors that recognize various pathogen- and damage-associated molecular pattern molecules playing an important role in inflammation by activating NF-κB. TLRs, mainly expressed by innate immune cells, are involved in inducing and regulating adaptive immune responses. However, the expression of TLRs has also been observed in many tumors, and their stimulation results in tumor progression or regression, depending on the TLR and tumor type. Here we review the role of TLRs in conferring anti- or pro-tumoral effects. The anti-tumoral effects can result from direct induction of tumor cell death and/or activation of efficient anti-tumoral immune responses, and the pro-tumoral effects may be due to inducing tumor cell survival and proliferation or by acting on suppressive or inflammatory immune cells in the tumor microenvironment.

Contents

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1. Introduction

The immune system contributes to fighting pathogen attack (Akira et al., 2006). The first line of defense involves the innate immune system, with the contribution of various cell types including monocytes and macrophages, dendritic cells (DCs), neutrophils, and natural killer (NK) cells (Janeway and Medzhitov, 2002). These innate immune cells use intracellular or membrane-associated pattern recognition receptors (PRRs) to recognize pathogen-associated molecular pattern (PAMP) or damaged-associated molecular pattern (DAMP) molecules released from dying cells (Newton and Dixit, 2012), then produce inflammatory cytokines and type I interferons (IFNs) to establish an effective defense system (Akira et al., 2006). The PRR family includes several types of recognition receptors: nucleotide-binding oligomerization domain-like receptors, C-type lectin receptors and Toll-like receptors (TLRs). The latter receptors are expressed by immune cells but also by epithelial cells, for defense against pathogens entering the body through the skin and mucous membranes.

The involvement of the immune system in controlling tumor development and progression has been well documented. It was demonstrated in immunodeficient mouse models lacking T, B and NK T cells, a grated numbers of tumors than in immunocompetent mice (Shankaran et al., 2001). The concept of immuno-editing, also called “3E” theory, for elimination, equilibrium and escape, implies the activation of the adaptive immune system and its ability to recognize and eliminate transformed cells (Dunn et al., 2004). The first step, elimination, consists of establishing effective anti-tumor immunity for the eradication of tumor cells. With equilibrium, genetic variants of tumor cells emerge and malignant cells survive and counteract the pressure induced by the immune system. Thus, immunity at this stage is still able to control tumor cells, thereby leading to a dynamic balance between tumor and immune cells. Finally, with escape, malignant cells escape from the immune system, for tumor progression and metastasis. The importance of immunity in the control of tumor progression is illustrated by the fact that in many solid tumors, a high density of intratumoral immune cells is associated with good overall survival of patients (Fridman et al., 2012; Pagès et al., 2010), which confirms the concept of immunosurveillance (Hanahan and Weinberg, 2011).

Despite this anti-tumoral role of the immune response, chronic inflammation can feature tumor-infiltrating immune cells secreting inflammatory cytokines and chemokines that can promote tumor progression (Fridman et al., 2012). Indeed, in 2011, new markers were added to the hallmarks of cancer – “avoiding immune destruction” and “tumor-promoting inflammation” (Hanahan and Weinberg, 2011) – in addition to those established in 2000 (Hanahan and Weinberg, 2000).

In many cancers, chronic inflammation, mainly caused by chemicals and physical agents and/or by some immune cells (Balkwill and Mantovani, 2001), is considered a cofactor of carcinogenesis and/or favoring tumor progression and metastasis. Further evidence of the link between inflammation and tumor development is illustrated by the reduced cancer rates in patients taking non-steroidal anti-inflammatory drugs and increased rates in obese patients with high inflammation in adipose tissue (Trinchieri, 2012). With chronic inflammation, some signaling pathways, such as NF-kB or mitogen-activated protein kinase (MAPK) pathways, are constitutively activated, with many studies demonstrating that their activation has a pro-tumoral effect (Balkwill and Coussens, 2004). In hepatocellular carcinoma (HCC) (Pikarsky et al., 2004) and colitis-associated cancer (Greten et al., 2004), the activation of NF-kB prevented tumor cell death and stimulated the production of pro-inflammatory cytokines in the tumor microenvironment, thereby enhancing tumor progression. Likewise, NF-kB activation is involved in both tumor initiation and progression in liver cancer (Pikarsky et al., 2004). Therefore, the inflammatory response can lead to carcinogenesis after NF-kB activation, by the induction of anti-apoptotic molecules (Coussens and Werb, 2002; Karin, 2006). TLR stimulation leads to NF-kB activation and subsequent production of pro-inflammatory cytokines and chemokines, growth factors and anti-apoptotic proteins involved in tumor progression and chemoresistance. Repeated TLR stimulation may result in strong inflammation, because it contributes to the recruitment of inflammatory cells in the tumor microenvironment (Chen et al., 2007).

Thus, TLR stimulation in cancers may be a double-edged sword having an anti- or pro-tumoral effect in the tumor microenvironment (Dajon et al., 2015; Dranoff, 2003). In this review we discuss the contrasting roles of TLRs in different tumor types.

2. Toll-like receptors

The Toll gene was initially discovered in 1979 and was implicated in the establishment of the dorsoventral axis in Drosophila (Lohs-Schardin et al., 1979). In 1996, the team of J. Hoffmann demonstrated that the Toll gene is also involved in immunity in adult Drosophila (Lemaitre et al., 1996), and in 1997, the team described TLR mammal proteins with high homology to Drosophila Toll (Medzhitov et al., 1997). Ten TLRs (and three pseudogenes, TLR11, TLR12 and TLR13) have been described in humans and mice. TLRs are type I transmembrane glycoproteins with (1) an ectodomain containing leucine-rich repeats to enable the recognition of the ligands (Rock et al., 1998), (2) a transmembrane domain and (3) an intracellular Toll-interleukin 1 (IL-1) receptor domain (TIR) required to induce signal transduction (Kawai and Akira,