Published in final edited form as:

Cancer Lett. 2012 August 28; 321(2): 110–119. doi:10.1016/j.canlet.2012.01.040.

MUCINS AND TOLL-LIKE RECEPTORS: KITH AND KIN IN INFECTION AND CANCER

Shikha Tarang[†], Sushil Kumar[†], and Surinder K. Batra^{†,§}

[†]Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE U.S.A

[§]Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE U.S.A

Abstract

Inflammation is underlying biological phenomenon common in infection and cancer. Mucins are glycoproteins which establish a physical barrier for undesirable entry of foreign materials through epithelial surfaces. A deregulated expression and an anomalous glycosylation pattern of mucins are known in large number of cancers. TLRs are class of receptors which recognize the molecular patterns of invading pathogens and activate complex inflammatory pathways to clear them. Aberrant expression of TLRs is observed in many cancers. A highly orchestrated action of mucins and TLRs is well evolved host defence mechanism; however, a link between the two in other non-infectious conditions has received less attention. Here we present an overview as to how mucins and TLRs give protection to the host and are deregulated during carcinogenesis. Further, we propose the possible mechanisms of cross-regulation between them in pathogenesis of cancer. As both mucins and TLRs are therapeutically important class of molecules, an understanding of the underlying molecular mechanisms connecting the two will open new avenues for the therapeutic targeting of cancer.

Keywords

Mucins; Toll-like receptors; Infection; Inflammation; Cancer

1.0 Introduction

Mucins (MUCs) and Toll-like receptors (TLRs) are essential in giving protection to the host and maintaining cellular homeostasis [1]. MUCs are high molecular weight glycoproteins produced and mostly distributed between epithelial tissues lining ducts and lumens where they provide protection and lubrication [2]. Akin to their role under physiological conditions, cancer cells exploit MUCs in protecting themselves under adverse conditions [3]. An aberrant expression and glycosylation pattern of MUCs are thus observed in many

© 2012 Elsevier Ireland Ltd. All rights reserved.

[§]To whom correspondence should be addressed: Surinder K. Batra, Ph.D., Department of Biochemistry and Molecular Biology, Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 985870 Nebraska Medical Center, Omaha, NE 68198-5870, U.S.A., Phone: 402-559-5455; Fax: 402-559-6650, sbatra@unmc.edu.

Conflict of Interest Statement

None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

carcinomas [3]. Though the precise molecular mechanisms regulating the expression of MUCs are areas of investigation nonetheless many inflammatory cytokines and transcription factors are known to regulate their expression [4–7]. In the present article we focus on the interrelationship between MUCs and TLRs, as TLRs initiate inflammatory cascade on recognition of specific pathogen-associated molecular patterns (PAMPs) and consequently they may be important regulators of MUC expression.

TLRs are type 1 membrane anchored receptors, which recognize and regulate immune responsive genes [8, 9]. Deregulated TLR activation is observed in a number of pathological processes [10]. TLRs also recognize a large number of '*danger signals*' which are often host-derived molecules [11] and heterogeneous tumour microenvironment is a rich source of such endogenous molecules which are recognized by TLRs. Hence there is consistently higher TLR expression in several cancers [12, 13].

The present review article provides an overview to the biology of MUCs and TLRs and discusses how they are regulated during microbial infections. We propose the possible molecular mechanisms of cross-regulation between MUCs and TLRs in cancer. Several members of MUC family are in clinics as important diagnostic and prognostic markers [3]. Identification of novel approaches to modulate the expression of MUCs has promising therapeutic implications. As TLRs have gained remarkable clinical significance [14, 15] in only two decades of their discovery, an understanding of the molecular mechanisms of cross-regulation of MUCs and TLRs will help us with new opportunities to fight against cancer.

2.0 Biology of MUCs

MUCs are a family of large glycoproteins which represent the major structural components of the mucus [2, 16]. The basic structure of a MUC molecule consists of a protein backbone, known as 'apomucin,' which is attached with a large number of O-linked and a few N-linked oligosaccharides. A striking feature of MUCs is the presence of VNTR (variable number tandem repeats) [2, 17, 18]. There are 20 mucin genes identified which have wide tissue distribution and specificity [19, 20]. MUCs can be grouped into two different categories based on their sub-cellular localization - secreted and membrane-bound. The distinctive feature of membrane-bound MUCs is the presence of a transmembrane domain which attaches them to the plasma membrane [2, 17]. Secreted MUCs are produced from the surface epithelium by specialized 'goblet cells' and 'mucous cells' from sub-mucous glands [2] and include MUC2, MUC5AC, MUC5B, MUC6–8 and MUC19. They have characteristic cysteine-rich regions termed as 'CK' (Cysteine Knot; site for mucin dimerization) and 'D' (site for oligomerization) domains [21, 22]. The membrane-bound MUCs include MUC1, MUC3, MUC4, MUC12–17 and MUC20. They are type I membrane-anchored proteins with trans-membrane domain an NH₂-terminal extra-cellular region and a COOH-terminal intracellular cytoplasmic tail [2, 23]. Membrane-bound MUCs can also be released from the plasma membrane by enzymatic cleavage and alternative splicing [2]. Some MUCs such as MUC1 and MUC4 have more wide tissue distribution as compared to MUC2 which is primarily localized in the intestines [23]. The characteristic extensive post-translational modifications in MUCs such as glycosylation, sialylation and sulfation in a cell-type specific manner gives them specialized structure and facilitates their interaction with the extracellular and membrane bound proteins [24].

2.1 Physiological functions of MUCs

MUCs form a gelatinous layer on the apical surface of the epithelial cells by serving as a physical barrier between the lumen and epithelium which is continually exposed to microbial pathogens [2, 25]. Further any pathogenic bacteria which might have escaped is

entrapped and eliminated by the dense mucin matrix [25]. The extensive glycosylation of MUCs confers them the property of hydration and lubrication by providing a hydrophilic environment [3]. The TR region of MUCs is particularly rich in neutral and charged oligosaccharide structures which regulate the movement of molecules. MUCs gels hold biologically active molecules such as trefoil factors (TFFs) [26] which aid them in providing protection to the epithelial surfaces and promote wound healing [3, 26, 27]. Further MUCs play critical roles in cellular events influencing key functions of proliferation, differentiation, transformation and adhesion [2].

3.0 Biology of TLRs

TLRs are membrane receptors which upon recognition of pathogen-associated molecular patterns (PAMPs) initiate and activate the immune response against invading pathogens [9, 28] and till date 10 TLRs have been identified in humans. TLRs1–9 are well characterized and conserved between mice and humans. TLR10 is present in humans but not in mice whereas murine TLRs11–13 remains ambiguous. [29]

TLRs are homologous to *Drosophila* Toll protein (and thus named ‘*Toll-like receptors*’) and human interleukin-1 receptor (IL-1R) family [30]. In *Drosophila*, TLRs are involved in the embryonic development and defence against microbial infections [31–33] whereas in mice the only defects of TLR knock out are related to immune dysfunction [34]. Upon infection *Drosophila* Toll protein recognizes the endogenous protein Spatzle which is produced as a result of self-proteolytic cleavage of pro-Spatzle [35] while mammalian TLRs directly bind to PAMPs. The evolution of mammalian TLRs to recognize the molecular patterns gives multiple advantages to the host as PAMPs are differentially expressed molecules generally essential for the survival of the microbe and also enable the host to recognize and mount an immune response tailored against a specific class of microbe [36–38]. As TLRs recognize unique patterns in microbes they are known as pattern recognition receptors (PRRs). Other classes of PRRs are receptor kinases, mannose receptors, NOD-like receptors and RNA helicases, C-type lectin receptors [29, 39, 40].

Structurally TLRs may be divided into extracellular and cytoplasmic domains. The extracellular domain consists of 19–25 tandem leucine rich repeat (LRR) which is 24–29 amino acids in length and is believed to interact directly with the ligands [41]. The cytoplasmic domain of TLRs is similar to IL-1R and is known as the Toll/IL-1 receptor (TIR) domain [42]. TLRs are broadly expressed on immune cells and epithelial lining of cells at sites which are continually exposed to invading pathogens [43]. As the primary function of TLRs in mammals is defence, TLRs are also expressed in several types of cells which form the first protective barrier to invading pathogens such as cells of the skin, respiratory, intestinal and genitourinary tracts that form the first protective barrier to invading pathogens [44].

Quite remarkably, the sub-cellular localization pattern of TLRs in the cells has also evolved to facilitate the microbial ligand recognized by them. TLRs which recognize outer cell wall components of bacteria and fungi are expressed on the cell surface (TLR1, -2, -4, -5, -6, -10) whereas TLRs involved in the recognition of nucleic acid components are distributed in the intracellular compartments (TLR3, -7, -8, -9) [37, 45]. Recently a number of chaperones such as gp96, PRAT4A and Unc93B1 have been identified to play critical role in TLR localisation [46]. The salient feature of TLR ligands are their enormous molecular diversity which continues to grow but the most studied ligands for TLRs remain those from the microbial origin. The principle ligands for TLR2 in combination with TLR1 or TLR6 are bacterial cell wall components such as lipoproteins, lipotechoic acid and fungal zymosan. TLR4 is activated by lipopolysaccharide from gram-negative bacteria and TLR5 by bacterial

flagellin. The intracellular TLRs such as TLR3 is activated by the double-stranded RNA, TLR7 and TLR8 by single-stranded RNA and TLR9 by unmethylated CpG DNA motifs [9, 28]. In addition to the microbial ligands, there are host-derived endogenous molecules which signal the presence of 'danger', aptly called as danger-associated molecular patterns or DAMPs [11]. A large number of endogenous ligands have been identified as shown in the table 1. Very recently, the mitochondrial DNA which shows resembles to bacterial DNA due to the presence of non-methylated CpG motifs has been shown as endogenous TLR9 ligand [47]. However the theory of endogenous ligand recognition is challenged suggesting that endogenous ligands only facilitate the presentation of microbe-derived products to the TLRs [48]. The endogenous ligands act as PAMP sensitizing molecules by binding to the PAMPs released from commensal intestinal microbes and lower the cellular threshold for responsiveness to PAMPs [48–50]. Further studies are warranted to dissect the ability of putative TLR ligands in mediating the biological response. In table 1 we summarize the exogenous microbial ligands, host-derived endogenous ligands, sub-cellular localization and cell type expression pattern for TLRs1–11.

3.1 Physiological functions of TLRs

In mammals TLRs are the integral to the functioning of innate immune system, their primary role being to encounter and eliminate invading pathogens [36–38]. Upon binding with the respective ligands, the cytoplasmic TIR domain of TLRs associates with the TIR domain of the adaptor proteins MyD88, TIRAP, TRIF and TRAM. All TLRs except TLR3 signal through MyD88-dependent pathway. TLR3 signals only through MyD88-independent TRIF-dependent pathway while TLR4 is unique as it can signal through both MyD88-dependent as well as MyD88-independent pathways. Upon binding with the TIR domains of the TLRs MyD88 undergoes dimerization which allows for the recruitment of downstream kinases IRAK-1 (IL-1R-associated kinase-1) and IRAK-4 through death domain (DD) homophilic interactions. MyD88 binds to IRAK-4 thereby promotes phosphorylation of critical residues in IRAK-1 by IRAK-4. The downstream events include IRAK-1 phosphorylation and its interaction with TRAF6 (tumor necrosis factor (TNF) receptor-associated factor 6), leading to the activation of NF- κ B (nuclear factor κ B), JUN N-terminal kinases (JNKs), p38 and ERKs (Extracellular signal-regulated kinases) and interferon regulatory factor (IRF3, IRF5 and IRF7) signaling pathways. The activation of TRIF-dependent pathway by TLR3 and TLR4 leads to the activation of IKK complex consisting of TBK1, IKK ϵ /IKK ι further leading to the activation of NF- κ B and IRF3 [62]. These molecules further lead to the production of pro-inflammatory cytokines and chemokines which activate adaptive immunity and together mount an effective immune response against invading pathogens [63]. Even though the signaling by TLRs operate through a common pathway, the various TLR agonists induce a unique cytokine/chemokine profiles that is best tailored against a particular microbial class [64]. The detailed signaling pathways are indicated in the Figure 1.

4.0 MUCs and TLRs in infection

Several microbial products up regulate the expression of MUCs and TLRs [65]. Upon recognition of PAMPs the principle receptors of innate immune system TLRs direct the immune response against pathogens [9, 28]. In fact, it has been suggested that TLRs serve as a bridge between innate and adaptive forms of the immunity [38, 66]. A basal low-level expression of MUCs is up regulated on encounter with microbial pathogens. This is particularly evident in the case of intestinal MUCs, which provide several advantages to the commensal bacteria in terms of nutrition and protection [1].

It was observed that *Gymnophalloides seoi* adult antigen enhances the expression of TLR2 and MUC2 in HT29 cells [65] and treatment with monoclonal antibody to TLR2 abrogates the expression of MUC2 [65]. *Mycoplasma pneumoniae* has also been shown to induce

MUC5AC expression via TLR2 and inhibition of TLR2 and NF- κ B reduced the expression of MUC5AC, indicating the role of TLR2 in MUC5AC expression [67]. The outer cell wall component lipoprotein p6 from *Haemophilus influenzae* (NTHi) induces the expression of MUC5AC via TLR2 signaling pathway [68]. Another study by Kyoung et al. shows LPS induced up regulation of MUC5AC with concurrent increase in TLR4 expression and the knock down of TLR4 with siRNA leads to the decrease in MUC5AC suggests the involvement of TLR4 in LPS-induced MUC5AC gene expression [69, 70]. *Streptococcus pneumoniae* pneumolysin induce TLR4 dependent MUC5AC mucin transcription in airway epithelial cells which is important to maintain effective mucosal protection against *S. pneumoniae* infection [71]. Thus it is evident that MUCs and TLRs co-operate to strengthen the mucosal immune response. [72]. Several signaling molecules such as MAP kinases and NF- κ B directly regulate MUC expression. Also various cytokines and chemokines via activation of EGF-tyrosine kinase and MAP kinase pathways regulate MUC expression [73]. MUCs also regulate TLR signaling as MUC1 has been shown to negatively regulate TLR5 signaling [74]. The cytoplasmic tail of mucin MUC1 serves as a receptor for *P. aeruginosa* flagellin which competes with TLR5 binding to its ligand thereby negatively regulating its signaling in airway epithelial cells [74, 75]. Although, there are few studies on the regulation of TLRs by MUCs, in table 2 we have summarized the known interactions between MUCs and TLRs in infection. Given the cross-regulation between MUCs and TLRs in infection we speculate that cancer cells might use the TLR signaling pathways much in the same way to up regulate the expression of MUCs which in turn may also regulate TLR signaling. In the preceding sections we discuss the significance of MUCs and TLRs in cancer and propose the molecular mechanisms of their interaction.

5.0 MUCs and TLRs in cancer

MUCs are a class of major differentially expressed proteins between normal and cancer cells which makes them a potential target for anti-cancer therapies. As reviewed by Hollingsworth and Swanson [3] the up regulation of MUC expression is advantageous to cancer cells in several ways. In addition to giving physical protection MUCs provide additional advantages by sequestering the growth factors and cytokines. MUCs also promote the invasive and metastatic potential by influencing the adhesive and anti-adhesive cell-surface properties of tumour cells. Thus an altered MUC expression and/or glycosylation help in cancer progression by imparting specific growth advantage to the cancer cells [3]. In several carcinoma and haematological malignancies the abnormal expression of several MUCs are observed. As a class of glycoproteins MUCs are increasingly recognized as potential markers of disease progression and metastasis and are currently investigated as therapeutic targets for cancer [76]. MUC1 is over expressed in many leukaemia and solid cancers. CA15-3 assay, which measures the circulating MUC1-N subunit, is approved by the FDA as a prognostic marker in breast cancer [77, 78]. MUC4 is a prognostic marker for ovarian and pancreatic cancer. CA125 which is derived from a small subunit of MUC16 is in clinical use as diagnostic marker for ovarian cancer [3, 79]. The association between normal physiological expression and aberrant MUC expression in various cancers is summarized in table 3.

In recent years functionally active TLRs have been identified in several cancers (table 4) [133, 134]. While several endogenous TLR ligands are proposed but, the molecular mechanisms of their action are currently a subject of debate [48]. It will be of interest to identify the detailed mechanisms of TLR activation in tumor cells, nevertheless the implications of constitutive TLR signaling are far reaching. Activation of pro-survival NF- κ B pathway leads to an increased proliferation and chemoresistance [135, 136]. Several pro-inflammatory cytokines and chemokines such as TNF α , G-CSF, IL-1, IL-6, IL-8, COX-2, MCP-1 makes the microenvironment more conducive for the progression of cancer [137].

Immunosuppressive cytokines such as IL-10 and TGF- β dampen the immune response against growing tumor [137]. VEGF helps in angiogenesis nourishing the growing tumor. TLR signaling also helps in propagating tumor cells to distant sites by regulating cytoskeletal proteins and MMPs [134]. Interestingly, in some circumstances TLR signaling may inhibit the progression of cancer [137]. It is shown that polyI:C triggers cell death in several cancers [138–143] acting via TLR3 which might be due to its unique signaling by TRIF dependent pathway. Thus it is extremely important to carry out a systemic characterization of TLR signaling pathways to ensure that the therapeutic targeting is safe. The detrimental stimulation of TLRs on tumor cells can be avoided by selecting ligands which are recognized by immune cells present in the tumor microenvironment and not by cancer cell thereby preventing activation of the pro-survival TLR signaling pathways in cancer cells. Many TLR agonists and antagonists are in clinical trials for cancer as immunotherapeutic or chemotherapeutic agents [137, 144, 145]. Given the clinical relevance of TLRs, an elucidation of the role of TLR signaling in probable regulation of expression of MUCs will be highly useful. In the following sections we attempt to identify the probable mechanisms of regulation of MUC and TLR genes as illustrated in Figure 2. Identification of molecular mechanisms of interaction between MUCs and TLRs may identify new drug targets and strengthen our understanding on the mode of action of existing drugs.

5.1 Cross-regulation of MUC and TLRs in cancer

5.1.1 TLRs regulating MUCs expression—Inflammation is increasingly being recognized as the driving element for carcinogenesis [170, 171]. In addition to infection, inflammation links MUCs and TLRs in conditions such as inflammatory bowel disease [172, 173], colitis [174] and pancreatitis [173, 175] which are recognized as important risk factor for the development of cancer. Constitutively active TLR signaling in cancer cells leads to a state of ‘sterile’ inflammation [176]. Binding of ligands to TLRs initiate a complex signaling cascade leading to the activation of several pro-inflammatory cytokines, which via autocrine and paracrine effect initiate a cascade of intracellular signaling, altering number of cellular functions [9, 28]. Therefore, it is important to study the effect of cytokines from TLR signaling on MUC expression. Several pro-inflammatory cytokines are known to regulate the expression of different MUCs in cancer. The effect of IFN- γ , IL-1 α and TNF- α was studied on the expression and glycosylation of MUC1, MUC5AC, MUC4 and MUC16 in multiple pancreatic cancer cell lines [7]. In bronchial epithelial cells IL-1 β and IL-17A are potent inducers of MUC5AC synthesis [5]. MUC5AC induction by these cytokines was observed to be both time- and dose-dependent [5]. TNF- α , IL-1 β and IL-6 induce MUC2 and MUC4 intestinal MUCs, which are detected in gastric tumor [177]. TNF- α and IFN- γ induce MUC1 expression in ocular surface epithelial cells [4]. TLRs signaling activate NF- κ B and MAP kinases which are known to regulate the expression of different MUCs [6]. Thus activation of various signaling molecules, such as IRF3, NF- κ B, ERK, p38 and JNK pathways by TLRs either directly or via inflammatory molecules might regulate MUC expression. Although not much is known it will be of further interest to see the role of chemokines, redox molecules and others mediators of inflammation on MUC expression.

5.2 MUCs regulating TLR signaling

MUCs interacting proteins—A series of studies have demonstrated a surprisingly diverse role for the small, highly conserved cytoplasmic domain of MUC1 in intracellular signaling. The cytoplasmic domain of MUC1 mucin is shown to interact with a large number of intracellular signaling molecules [178]. The cytoplasmic tail of MUC1 is 72-amino acid and has multiple phosphorylation sites which are responsible for interaction with several oncogenic proteins and their signaling [179]. For instance MUC1 contains multiple binding motifs for the proteins GSK3 β , Src, β -Catenin and members of ErbB family [178] which may further interact and/or activate TRAF-6, NF- κ B and MAP kinases and may

participate in the expression of TLRs [180–187]. Thus, the cytoplasmic domain of MUCs can modulate TLR signaling and expression with one or more of these common signaling molecules. Unfortunately, limited information exists on the role of cytoplasmic domains of other MUCs. In addition to regulation of expression; MUCs can modulate TLR signaling pathways by multiple ways.

MUCs masking TLRs and ligand sequestration—The presence of large mucin molecules interfere with the ability of ligands to bind to the cell surface receptors principally by two methods [3]. It has been shown that the mucous layer captures and holds the biologically active molecules as a part of the matrix. In normal epithelia, large mucin glycoprotein molecules act as a molecular shield preventing the binding and attachment of ligands to the receptors. The extracellular domain of MUCs forms a matrix which masks the receptors and makes it inaccessible for binding with the ligands. As several tumors exhibit consistently higher expression of TLRs their masking by large mucin glycoproteins may actually affect the signaling pathways activated by them. The presence of large number of endogenous TLR ligands in the tumor microenvironment and their sequestration by MUCs might ultimately affect the fate of the tumor cells. As discussed previously MUC1 acts as a negative regulator of TLR5 signaling by binding with *Pseudomonas aeruginosa* flagellin [74]. In cancer, several molecules in the tumor microenvironment might get sequestered in the mucin matrix and may be unable to bind to the receptors on the cell surface. Alternatively, due to an increase in local concentration ligands may bind more efficiently and consistently to activate signaling through TLRs [3].

Altered glycosylation on MUCs acting as an intramembrane ligand for TLRs—TLRs sense an extremely diverse repertoire of ligands which range from exogenous microbial derived products to several host-derived endogenous molecules. In light of this diversity of ligand recognition by TLRs, there exists a possibility that altered glycosylated moiety of MUC molecules on tumor cells might act directly as TLR ligand thereby modulating the expression and signaling of these receptors. C-type lectin, a type of PRR, recognizes altered glycosylation on tumor cells and cross-talk with the TLRs pathway [188]. However, there is no report of TLR activation by altered glycosylation of self-molecules on tumor cells.

6.0 Conclusion and future directions

It is clear from the above account that MUCs and TLRs coordinate to mount an effective immune response against pathogens. Individually, MUCs and TLRs have both been found to be well associated with cancer. It will be important to study the interaction between the two in various disease conditions. Remarkably as MUCs generally appears since the initiation of cancer, a therapeutic intervention by TLR agonist/antagonists will be highly significant for early therapeutic intervention. An understanding of the molecular mechanisms of cross-regulation between MUCs and TLRs will be helpful in understanding the molecular mechanisms of TLR directed therapies. The proposition of altering MUCs expression by TLRs therefore holds great promise for translation from bench to bedside. Even after several decades of exhaustive research in the field, the current treatment strategy for cancer still remains inadequate. An understanding of the molecular mechanisms leading to disease development will certainly help in improving the efficacy of anti-cancer therapies.

Acknowledgments

The authors on this work are supported, in part, by grants from the Department of Defence (BC074639, BC083295, and BC09742) and the National Institutes of Health (RO1 CA78590, EDNRN U01 CA111294, RO1 CA133774, RO1 CA131944, and SPORE P50 CA127297 and TMEN U54 CA163160).

Abbreviations used

TLRs	Toll-like receptors
MUC	Mucin
PAMP	Pathogen associated molecular pattern
VNTR	Variable number tandem repeat
TIR	Toll/IL-1 receptor
PRR	Pathogen recognition receptor
TFF	trefoil factor
LRR	Leucin rich repeat
NOD	Nucleotide oligomerization domain
LPS	Lipopolysaccharides
TRIF	TIR-domain-containing adapter-inducing interferon- β
MyD88	Myeloid differentiation primary response gene (88)
HMG	High-mobility group
HSP	Heat shock protein
IRAK	Interleukin-1 receptor-associated kinase
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
TNF-α	Tumor necrosis factor-alpha
IL	Interleukin
VEGF	Vascular endothelial growth factor
G-CSF	Granulocyte colony-stimulating factor
CCL	CC chemokine ligand
CXCL	CXC chemokine ligand
COX-2	Cyclooxygenase-2
TGF-β	Transforming growth factor beta
CXCR	CXC chemokine receptor
ICAM-1	Inter-cellular adhesion molecule-1
MAPK	Mitogen-activated protein kinase
JNK	c-Jun N-terminal kinases
ERK	Extracellular-signal-regulated kinase
IRF	Interferon regulatory factor
TRAF	TNF receptor associated factor
TAK-1	TGF-beta activated kinase 1
EGF	Epidermal growth factor
CA 15-3	Carcinoma Antigen 15-3
CA125	Cancer antigen 125 or Carbohydrate antigen 125

MCP-1	Monocyte chemoattractant protein 1
MMP	Matrix metalloproteinase
IFN-γ	Interferon-gamma
GSK 3	Glycogen synthase kinase 3
Src	Sacroma

Reference List

1. Moncada DM, Kammanadiminti SJ, Chadee K. Mucin and Toll-like receptors in host defense against intestinal parasites. *Trends Parasitol.* 2003; 19:305–311. [PubMed: 12855381]
2. Andrianifahanana M, Moniaux N, Batra SK. Regulation of mucin expression: mechanistic aspects and implications for cancer and inflammatory diseases. *Biochim Biophys Acta.* 2006; 1765:189–222. [PubMed: 16487661]
3. Hollingsworth MA, Swanson BJ. Mucins in cancer: protection and control of the cell surface. *Nat Rev Cancer.* 2004; 4:45–60. [PubMed: 14681689]
4. Albertsmeyer AC, Kakkassery V, Spurr-Michaud S, Beeks O, Gipson IK. Effect of pro-inflammatory mediators on membrane-associated mucins expressed by human ocular surface epithelial cells. *Exp Eye Res.* 2010; 90:444–451. [PubMed: 20036239]
5. Fujisawa T, Velichko S, Thai P, Hung LY, Huang F, Wu R. Regulation of airway MUC5AC expression by IL-1 β and IL-17A; the NF-kappaB paradigm. *J Immunol.* 2009; 183:6236–6243. [PubMed: 19841186]
6. Theodoropoulos G, Carraway KL. Molecular signaling in the regulation of mucins. *J Cell Biochem.* 2007; 102:1103–1116. [PubMed: 17957706]
7. Wu YM, Nowack DD, Omenn GS, Haab BB. Mucin glycosylation is altered by pro-inflammatory signaling in pancreatic-cancer cells. *J Proteome Res.* 2009; 8:1876–1886. [PubMed: 19714813]
8. Janssens S, Beyaert R. Role of Toll-like receptors in pathogen recognition. *Clin Microbiol Rev.* 2003; 16:637–646. [PubMed: 14557290]
9. Takeda K, Akira S. Toll-like receptors in innate immunity. *Int Immunol.* 2005; 17:1–14. [PubMed: 15585605]
10. Garantziotis S, Hollingsworth JW, Zaas AK, Schwartz DA. The effect of toll-like receptors and toll-like receptor genetics in human disease. *Annu Rev Med.* 2008; 59:343–359. [PubMed: 17845139]
11. Lotze MT, Deisseroth A, Rubartelli A. Damage associated molecular pattern molecules. *Clin Immunol.* 2007; 124:1–4. [PubMed: 17468050]
12. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. *Nat Rev Cancer.* 2009; 9:57–63. [PubMed: 19052556]
13. Schmidt C. Immune system's Toll-like receptors have good opportunity for cancer treatment. *J Natl Cancer Inst.* 2006; 98:574–575. [PubMed: 16670380]
14. Dunne A, Marshall NA, Mills KH. TLR based therapeutics. *Curr Opin Pharmacol.* 2011
15. So EY, Ouchi T. The application of Toll like receptors for cancer therapy. *Int J Biol Sci.* 2010; 6:675–681. [PubMed: 21060729]
16. Andrianifahanana M, Moniaux N, Schmied BM, Ringel J, Friess H, Hollingsworth MA, Buchler MW, Aubert JP, Batra SK. Mucin (MUC) gene expression in human pancreatic adenocarcinoma and chronic pancreatitis: a potential role of MUC4 as a tumor marker of diagnostic significance. *Clin Cancer Res.* 2001; 7:4033–4040. [PubMed: 11751498]
17. Gendler SJ, Spicer AP. Epithelial mucin genes. *Annu Rev Physiol.* 1995; 57:607–634. [PubMed: 7778880]
18. Moniaux N, Escande F, Porchet N, Aubert JP, Batra SK. Structural organization and classification of the human mucin genes. *Front Biosci.* 2001; 6:D1192–D1206. [PubMed: 11578969]

19. Ali MS, Pearson JP. Upper airway mucin gene expression: a review. *Laryngoscope*. 2007; 117:932–938. [PubMed: 17473699]
20. Thai P, Loukoianov A, Wachi S, Wu R. Regulation of airway mucin gene expression. *Annu Rev Physiol*. 2008; 70:405–429. [PubMed: 17961085]
21. Asker N, Axelsson MA, Olofsson SO, Hansson GC. Dimerization of the human MUC2 mucin in the endoplasmic reticulum is followed by a N-glycosylation-dependent transfer of the mono- and dimers to the Golgi apparatus. *J Biol Chem*. 1998; 273:18857–18863. [PubMed: 9668061]
22. Offner GD, Nunes DP, Keates AC, Afdhal NH, Troxler RF. The amino-terminal sequence of MUC5B contains conserved multifunctional D domains: implications for tissue-specific mucin functions. *Biochem Biophys Res Commun*. 1998; 251:350–355. [PubMed: 9790959]
23. Verma M, Davidson EA. Mucin genes: structure, expression and regulation. *Glycoconj J*. 1994; 11:172–179. [PubMed: 7841791]
24. Senapati S, Das S, Batra SK. Mucin-interacting proteins: from function to therapeutics. *Trends Biochem Sci*. 2010; 35:236–245. [PubMed: 19913432]
25. Artis D. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. *Nat Rev Immunol*. 2008; 8:411–420. [PubMed: 18469830]
26. Sommer P, Blin N, Gott P. Tracing the evolutionary origin of the TFF-domain, an ancient motif at mucous surfaces. *Gene*. 1999; 236:133–136. [PubMed: 10433974]
27. Sands BE, Podolsky DK. The trefoil peptide family. *Annu Rev Physiol*. 1996; 58:253–273. [PubMed: 8815795]
28. Janssens S, Beyaert R. Role of Toll-like receptors in pathogen recognition. *Clin Microbiol Rev*. 2003; 16:637–646. [PubMed: 14557290]
29. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. *Int Rev Immunol*. 2011; 30:16–34. [PubMed: 21235323]
30. Rock FL, Hardiman G, Timans JC, Kastelein RA, Bazan JF. A family of human receptors structurally related to *Drosophila* Toll. *Proc Natl Acad Sci U S A*. 1998; 95:588–593. [PubMed: 9435236]
31. Hashimoto C, Hudson KL, Anderson KV. The Toll gene of *Drosophila*, required for dorsal-ventral embryonic polarity, appears to encode a transmembrane protein. *Cell*. 1988; 52:269–279. [PubMed: 2449285]
32. Schneider DS, Hudson KL, Lin TY, Anderson KV. Dominant and recessive mutations define functional domains of Toll, a transmembrane protein required for dorsal-ventral polarity in the *Drosophila* embryo. *Genes Dev*. 1991; 5:797–807. [PubMed: 1827421]
33. Hoffmann JA. The immune response of *Drosophila*. *Nature*. 2003; 426:33–38. [PubMed: 14603309]
34. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, Takeda K, Akira S. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. *J Immunol*. 1999; 162:3749–3752. [PubMed: 10201887]
35. Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. The dorsoventral regulatory gene cassette *spatzle/Toll/cactus* controls the potent antifungal response in *Drosophila* adults. *Cell*. 1996; 86:973–983. [PubMed: 8808632]
36. Aderem A, Ulevitch RJ. Toll-like receptors in the induction of the innate immune response. *Nature*. 2000; 406:782–787. [PubMed: 10963608]
37. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol*. 2001; 2:675–680. [PubMed: 11477402]
38. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006; 124:783–801. [PubMed: 16497588]
39. Fukata M, Abreu MT. Pathogen recognition receptors, cancer and inflammation in the gut. *Curr Opin Pharmacol*. 2009; 9:680–687. [PubMed: 19828376]
40. Kawai T, Akira S. Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity. *Immunity*. 2011; 34:637–650. [PubMed: 21616434]

41. Bell JK, Mullen GE, Leifer CA, Mazzoni A, Davies DR, Segal DM. Leucine-rich repeats and pathogen recognition in Toll-like receptors. *Trends Immunol.* 2003; 24:528–533. [PubMed: 14552836]
42. Bowie A, O'Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: signal generators for pro-inflammatory interleukins and microbial products. *J Leukoc Biol.* 2000; 67:508–514. [PubMed: 10770283]
43. Berche P. [Bacterial aggression]. *Ann Pharm Fr.* 2003; 61:270–275. [PubMed: 12843961]
44. Sandor F, Buc M. Toll-like receptors. II. Distribution and pathways involved in TLR signalling. *Folia Biol (Praha).* 2005; 51:188–197. [PubMed: 16419614]
45. Wagner H. The immunobiology of the TLR9 subfamily. *Trends Immunol.* 2004; 25:381–386. [PubMed: 15207506]
46. McGettrick AF, O'Neill LA. Localisation and trafficking of Toll-like receptors: an important mode of regulation. *Curr Opin Immunol.* 2010; 22:20–27. [PubMed: 20060278]
47. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010; 464:104–107. [PubMed: 20203610]
48. Erridge C. Endogenous ligands of TLR2 and TLR4: agonists or assistants? *J Leukoc Biol.* 2010; 87:989–999. [PubMed: 20179153]
49. Hreggvidsdottir HS, Ostberg T, Wahamoa H, Schierbeck H, Aveberger AC, Klevenvall L, Palmblad K, Ottosson L, Andersson U, Harris HE. The alarmin HMGB1 acts in synergy with endogenous and exogenous danger signals to promote inflammation. *J Leukoc Biol.* 2009; 86:655–662. [PubMed: 19564572]
50. Youn JH, Oh YJ, Kim ES, Choi JE, Shin JS. High mobility group box 1 protein binding to lipopolysaccharide facilitates transfer of lipopolysaccharide to CD14 and enhances lipopolysaccharide-mediated TNF-alpha production in human monocytes. *J Immunol.* 2008; 180:5067–5074. [PubMed: 18354232]
51. Kang SS, Kauls LS, Gaspari AA. Toll-like receptors: applications to dermatologic disease. *J Am Acad Dermatol.* 2006; 54:951–983. [PubMed: 16713451]
52. Takeuchi O, Sato S, Horiuchi T, Hoshino K, Takeda K, Dong Z, Modlin RL, Akira S. Cutting edge: role of Toll-like receptor 1 in mediating immune response to microbial lipoproteins. *J Immunol.* 2002; 169:10–14. [PubMed: 12077222]
53. Netea MG, Suttmuller R, Hermann C, Van der Graaf CA, Van der Meer JW, van Krieken JH, Hartung T, Adema G, Kullberg BJ. Toll-like receptor 2 suppresses immunity against *Candida albicans* through induction of IL-10 and regulatory T cells. *J Immunol.* 2004; 172:3712–3718. [PubMed: 15004175]
54. Kasakura K, Takahashi K, Aizawa T, Hosono A, Kaminogawa S. A TLR2 ligand suppresses allergic inflammatory reactions by acting directly on mast cells. *Int Arch Allergy Immunol.* 2009; 150:359–369. [PubMed: 19571568]
55. Liu H, Komai-Koma M, Xu D, Liew FY. Toll-like receptor 2 signaling modulates the functions of CD4⁺ CD25⁺ regulatory T cells. *Proc Natl Acad Sci U S A.* 2006; 103:7048–7053. [PubMed: 16632602]
56. Akdis CA, Kussebi F, Pulendran B, Akdis M, Lauener RP, Schmidt-Weber CB, Klunker S, Isitmangil G, Hansjee N, Wynn TA, Dillon S, Erb P, Baschang G, Blaser K, Alkan SS. Inhibition of T helper 2-type responses, IgE production and eosinophilia by synthetic lipopeptides. *Eur J Immunol.* 2003; 33:2717–2726. [PubMed: 14515255]
57. Ehrentauf H, Meyer R, Schwederski M, Ehrentauf S, Velten M, Grohe C, Knuefermann P, Baumgarten G, Boehm O. Systemically administered ligands of toll-like receptor 2, -4, and -9 induce distinct inflammatory responses in the murine lung. *Mediators Inflamm.* 2011; (2011): 746532. [PubMed: 21547259]
58. Huang B, Zhao J, Unkeless JC, Feng ZH, Xiong H. TLR signaling by tumor and immune cells: a double-edged sword. *Oncogene.* 2008; 27:218–224. [PubMed: 18176603]
59. Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. *Annu Rev Immunol.* 2010; 28:367–388. [PubMed: 20192808]

60. Park HD, Lee Y, Oh YK, Jung JG, Park YW, Myung K, Kim KH, Koh SS, Lim DS. Pancreatic adenocarcinoma upregulated factor promotes metastasis by regulating TLR/CXCR4 activation. *Oncogene*. 2011; 30:201–211. [PubMed: 20802527]
61. Kariko K, Ni H, Capodici J, Lamphier M, Weissman D. mRNA is an endogenous ligand for Toll-like receptor 3. *J Biol Chem*. 2004; 279:12542–12550. [PubMed: 14729660]
62. Takeda K, Akira S. TLR signaling pathways. *Semin Immunol*. 2004; 16:3–9. [PubMed: 14751757]
63. Miggin SM, O'Neill LA. New insights into the regulation of TLR signaling. *J Leukoc Biol*. 2006; 80:220–226. [PubMed: 16698941]
64. Ghosh TK, Mickelson DJ, Fink J, Solberg JC, Inglefield JR, Hook D, Gupta SK, Gibson S, Alkan SS. Toll-like receptor (TLR) 2–9 agonists-induced cytokines and chemokines: I. Comparison with T cell receptor-induced responses. *Cell Immunol*. 2006; 243:48–57. [PubMed: 17250816]
65. Lee KD, Guk SM, Chai JY. Toll-like receptor 2 and Muc2 expression on human intestinal epithelial cells by *Gymnophalloides seoi* adult antigen. *J Parasitol*. 2010; 96:58–66. [PubMed: 19737027]
66. Barton GM, Medzhitov R. Control of adaptive immune responses by Toll-like receptors. *Curr Opin Immunol*. 2002; 14:380–383. [PubMed: 11973138]
67. Chu HW, Jeyaseelan S, Rino JG, Voelker DR, Wexler RB, Campbell K, Harbeck RJ, Martin RJ. TLR2 signaling is critical for *Mycoplasma pneumoniae*-induced airway mucin expression. *J Immunol*. 2005; 174:5713–5719. [PubMed: 15843573]
68. Chen R, Lim JH, Jono H, Gu XX, Kim YS, Basbaum CB, Murphy TF, Li JD. Nontypeable *Haemophilus influenzae* lipoprotein P6 induces MUC5AC mucin transcription via TLR2-TAK1-dependent p38 MAPK-AP1 and IKK β -I κ B α -NF- κ B signaling pathways. *Biochem Biophys Res Commun*. 2004; 324:1087–1094. [PubMed: 15485666]
69. Binker MG, Binker-Cosen AA, Richards D, Oliver B, Cosen-Binker LI. LPS-stimulated MUC5AC production involves Rac1-dependent MMP-9 secretion and activation in NCI-H292 cells. *Biochem Biophys Res Commun*. 2009; 386:124–129. [PubMed: 19501047]
70. Chen L, Wang T, Zhang JY, Zhang SF, Liu DS, Xu D, Wang X, Chen YJ, Wen FQ. Toll-like receptor 4 relates to lipopolysaccharide-induced mucus hypersecretion in rat airway. *Arch Med Res*. 2009; 40:10–17. [PubMed: 19064121]
71. Ha UH, Lim JH, Kim HJ, Wu W, Jin S, Xu H, Li JD. MKP1 regulates the induction of MUC5AC mucin by *Streptococcus pneumoniae* pneumolysin by inhibiting the PAK4-JNK signaling pathway. *J Biol Chem*. 2008; 283:30624–30631. [PubMed: 18782768]
72. McGuckin MA, Linden SK, Sutton P, Florin TH. Mucin dynamics and enteric pathogens. *Nat Rev Microbiol*. 2011; 9:265–278. [PubMed: 21407243]
73. Rogers DF. Physiology of airway mucus secretion and pathophysiology of hypersecretion. *Respir Care*. 2007; 52:1134–1146. [PubMed: 17716382]
74. Ueno K, Koga T, Kato K, Golenbock DT, Gendler SJ, Kai H, Kim KC. MUC1 mucin is a negative regulator of toll-like receptor signaling. *Am J Respir Cell Mol Biol*. 2008; 38:263–268. [PubMed: 18079492]
75. Kato K, Lu W, Kai H, Kim KC. Phosphoinositide 3-kinase is activated by MUC1 but not responsible for MUC1-induced suppression of Toll-like receptor 5 signaling. *Am J Physiol Lung Cell Mol Physiol*. 2007; 293:L686–L692. [PubMed: 17586693]
76. Rachagani S, Torres MP, Moniaux N, Batra SK. Current status of mucins in the diagnosis and therapy of cancer. *Biofactors*. 2009; 35:509–527. [PubMed: 19904814]
77. Kufe DW. Mucins in cancer: function, prognosis and therapy. *Nat Rev Cancer*. 2009; 9:874–885. [PubMed: 19935676]
78. Kufe D, Inghirami G, Abe M, Hayes D, Justi-Wheeler H, Schlom J. Differential reactivity of a novel monoclonal antibody (DF3) with human malignant versus benign breast tumors. *Hybridoma*. 1984; 3:223–232. [PubMed: 6094338]
79. Bast RC Jr, Badgwell D, Lu Z, Marquez R, Rosen D, Liu J, Baggerly KA, Atkinson EN, Skates S, Zhang Z, Lokshin A, Menon U, Jacobs I, Lu K. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer*. 2005; 15(Suppl 3):274–281. [PubMed: 16343244]

80. Copin MC, Buisine MP, Devisme L, Leroy X, Escande F, Gosselin B, Aubert JP, Porchet N. Normal respiratory mucosa, precursor lesions and lung carcinomas: differential expression of human mucin genes. *Front Biosci.* 2001; 6:D1264–D1275. [PubMed: 11578957]
81. Arul GS, Moorghen M, Myerscough N, Alderson DA, Spicer RD, Corfield AP. Mucin gene expression in Barrett's oesophagus: an in situ hybridisation and immunohistochemical study. *Gut.* 2000; 47:753–761. [PubMed: 11076872]
82. Guillem P, Billeret V, Buisine MP, Flejou JF, Lecomte-Houcke M, Degand P, Aubert JP, Triboulet JP, Porchet N. Mucin gene expression and cell differentiation in human normal, premalignant and malignant esophagus. *Int J Cancer.* 2000; 88:856–861. [PubMed: 11093805]
83. Ho SB, Shekels LL, Toribara NW, Kim YS, Lyftogt C, Cherwitz DL, Niehans GA. Mucin gene expression in normal, preneoplastic, and neoplastic human gastric epithelium. *Cancer Res.* 1995; 55:2681–2690. [PubMed: 7780985]
84. Buisine MP, Devisme L, Degand P, Dieu MC, Gosselin B, Copin MC, Aubert JP, Porchet N. Developmental mucin gene expression in the gastroduodenal tract and accessory digestive glands. II. Duodenum and liver, gallbladder, and pancreas. *J Histochem Cytochem.* 2000; 48:1667–1676. [PubMed: 11101635]
85. Liu B, Lague JR, Nunes DP, Toselli P, Oppenheim FG, Soares RV, Troxler RF, Offner GD. Expression of membrane-associated mucins MUC1 and MUC4 in major human salivary glands. *J Histochem Cytochem.* 2002; 50:811–820. [PubMed: 12019297]
86. Brayman M, Thathiah A, Carson DD. MUC1: a multifunctional cell surface component of reproductive tissue epithelia. *Reprod Biol Endocrinol.* 2004; 2:4. [PubMed: 14711375]
87. Chauhan SC, Singh AP, Ruiz F, Johansson SL, Jain M, Smith LM, Moniaux N, Batra SK. Aberrant expression of MUC4 in ovarian carcinoma: diagnostic significance alone and in combination with MUC1 and MUC16 (CA125). *Mod Pathol.* 2006; 19:1386–1394. [PubMed: 16880776]
88. DeNardo SJ, Richman CM, Albrecht H, Burke PA, Natarajan A, Yuan A, Gregg JP, O'Donnell RT, DeNardo GL. Enhancement of the therapeutic index: from nonmyeloablative and myeloablative toward pretargeted radioimmunotherapy for metastatic prostate cancer. *Clin Cancer Res.* 2005; 11:7187s–7194s. [PubMed: 16203820]
89. Guddo F, Giatromanolaki A, Koukourakis MI, Reina C, Vignola AM, Chlouverakis G, Hilken J, Gatter KC, Harris AL, Bonsignore G. MUC1 (episialin) expression in non-small cell lung cancer is independent of EGFR and c-erbB-2 expression and correlates with poor survival in node positive patients. *J Clin Pathol.* 1998; 51:667–671. [PubMed: 9930070]
90. Kotera Y, Fontenot JD, Pecher G, Metzgar RS, Finn OJ. Humoral immunity against a tandem repeat epitope of human mucin MUC-1 in sera from breast, pancreatic, and colon cancer patients. *Cancer Res.* 1994; 54:2856–2860. [PubMed: 7514493]
91. Wang RQ, Fang DC. Alterations of MUC1 and MUC3 expression in gastric carcinoma: relevance to patient clinicopathological features. *J Clin Pathol.* 2003; 56:378–384. [PubMed: 12719460]
92. Wierecky J, Muller MR, Wirths S, Halder-Oehler E, Dorfel D, Schmidt SM, Hantschel M, Brugger W, Schroder S, Horger MS, Kanz L, Brossart P. Immunologic and clinical responses after vaccinations with peptide-pulsed dendritic cells in metastatic renal cancer patients. *Cancer Res.* 2006; 66:5910–5918. [PubMed: 16740731]
93. Mukhopadhyay P, Chakraborty S, Ponnusamy MP, Lakshmanan I, Jain M, Batra SK. Mucins in the pathogenesis of breast cancer: implications in diagnosis, prognosis and therapy. *Biochim Biophys Acta.* 2011; 1815:224–240. [PubMed: 21277939]
94. Audie JP, Janin A, Porchet N, Copin MC, Gosselin B, Aubert JP. Expression of human mucin genes in respiratory, digestive, and reproductive tracts ascertained by in situ hybridization. *J Histochem Cytochem.* 1993; 41:1479–1485. [PubMed: 8245407]
95. Yonezawa S, Sato E. Expression of mucin antigens in human cancers and its relationship with malignancy potential. *Pathol Int.* 1997; 47:813–830. [PubMed: 9503463]
96. Yonezawa S, Goto M, Yamada N, Higashi M, Nomoto M. Expression profiles of MUC1, MUC2, and MUC4 mucins in human neoplasms and their relationship with biological behavior. *Proteomics.* 2008; 8:3329–3341. [PubMed: 18651706]

97. Apostolopoulos V, Xing PX, McKenzie IF. Anti-peptide monoclonal antibodies to intestinal mucin 3. *J Gastroenterol Hepatol.* 1995; 10:555–561. [PubMed: 8963031]
98. Duncan TJ, Watson NF, Al-Attar AH, Scholefield JH, Durrant LG. The role of MUC1 and MUC3 in the biology and prognosis of colorectal cancer. *World J Surg Oncol.* 2007; 5:31. [PubMed: 17349047]
99. Rakha EA, Boyce RW, Abd El-Rehim D, Kurien T, Green AR, Paish EC, Robertson JF, Ellis IO. Expression of mucins (MUC1, MUC2, MUC3, MUC4, MUC5AC and MUC6) and their prognostic significance in human breast cancer. *Mod Pathol.* 2005; 18:1295–1304. [PubMed: 15976813]
100. Gipson IK. Mucins of the human endocervix. *Front Biosci.* 2001; 6:D1245–D1255. [PubMed: 11578960]
101. Hanaoka J, Kontani K, Sawai S, Ichinose M, Tezuka N, Inoue S, Fujino S, Ohkubo I. Analysis of MUC4 mucin expression in lung carcinoma cells and its immunogenicity. *Cancer.* 2001; 92:2148–2157. [PubMed: 11596032]
102. Singh AP, Chauhan SC, Bafna S, Johansson SL, Smith LM, Moniaux N, Lin MF, Batra SK. Aberrant expression of transmembrane mucins, MUC1 and MUC4, in human prostate carcinomas. *Prostate.* 2006; 66:421–429. [PubMed: 16302265]
103. Miyahara N, Shoda J, Ishige K, Kawamoto T, Ueda T, Taki R, Ohkohchi N, Hyodo I, Thomas MB, Krishnamurthy S, Carraway KL, Irimura T. MUC4 interacts with ErbB2 in human gallbladder carcinoma: potential pathobiological implications. *Eur J Cancer.* 2008; 44:1048–1056. [PubMed: 18397823]
104. Ohuchida K, Mizumoto K, Yamada D, Fujii K, Ishikawa N, Konomi H, Nagai E, Yamaguchi K, Tsuneyoshi M, Tanaka M. Quantitative analysis of MUC1 and MUC5AC mRNA in pancreatic juice for preoperative diagnosis of pancreatic cancer. *Int J Cancer.* 2006; 118:405–411. [PubMed: 16052519]
105. Wickstrom C, Davies JR, Eriksen GV, Veerman EC, Carlstedt I. MUC5B is a major gel-forming, oligomeric mucin from human salivary gland, respiratory tract and endocervix: identification of glycoforms and C-terminal cleavage. *Biochem J.* 1998; 334(Pt 3):685–693. [PubMed: 9729478]
106. Sonora C, Mazal D, Berois N, Buisine MP, Ubillos L, Varangot M, Barrios E, Carzoglio J, Aubert JP, Osinaga E. Immunohistochemical analysis of MUC5B apomucin expression in breast cancer and non-malignant breast tissues. *J Histochem Cytochem.* 2006; 54:289–299. [PubMed: 16148312]
107. Owens SR, Chiosea SI, Kuan SF. Selective expression of gastric mucin MUC6 in colonic sessile serrated adenoma but not in hyperplastic polyp aids in morphological diagnosis of serrated polyps. *Mod Pathol.* 2008; 21:660–669. [PubMed: 18360351]
108. Zalewska A, Zwierz K, Zolkowski K, Gindziński A. Structure and biosynthesis of human salivary mucins. *Acta Biochim Pol.* 2000; 47:1067–1079. [PubMed: 11996097]
109. Copin MC, Buisine MP, Devisme L, Leroy X, Escande F, Gosselin B, Aubert JP, Porchet N. Normal respiratory mucosa, precursor lesions and lung carcinomas: differential expression of human mucin genes. *Front Biosci.* 2001; 6:D1264–D1275. [PubMed: 11578957]
110. Taylor KL, Mall AS, Barnard RA, Ho SB, Cruse JP. Immunohistochemical detection of gastric mucin in normal and disease states. *Oncol Res.* 1998; 10:465–473. [PubMed: 10223622]
111. Byrd JC, Bresalier RS. Mucins and mucin binding proteins in colorectal cancer. *Cancer Metastasis Rev.* 2004; 23:77–99. [PubMed: 15000151]
112. Seo JT, Lee JS, Jun JH, Yang MH. Expression of mucin genes in the human testis and its relationship to spermatogenesis. *Yonsei Med J.* 2005; 46:667–672. [PubMed: 16259065]
113. Hebbar V, Damera G, Sachdev GP. Differential expression of MUC genes in endometrial and cervical tissues and tumors. *BMC Cancer.* 2005; 5:124. [PubMed: 16188033]
114. Lapensee L, Paquette Y, Bleau G. Allelic polymorphism and chromosomal localization of the human oviductin gene (MUC9). *Fertil Steril.* 1997; 68:702–708. [PubMed: 9341614]
115. Maines-Bandiera S, Woo MM, Borugian M, Molday LL, Hii T, Gilks B, Leung PC, Molday RS, Auersperg N. Oviductal glycoprotein (OVGP1, MUC9): a differentiation-based mucin present in serum of women with ovarian cancer. *Int J Gynecol Cancer.* 2010; 20:16–22. [PubMed: 20130498]

116. Leikauf GD, Borchers MT, Prows DR, Simpson LG. Mucin apoprotein expression in COPD. *Chest*. 2002; 121:166S–182S. [PubMed: 12010847]
117. Williams SJ, McGuckin MA, Gotley DC, Eyre HJ, Sutherland GR, Antalis TM. Two novel mucin genes down-regulated in colorectal cancer identified by differential display. *Cancer Res*. 1999; 59:4083–4089. [PubMed: 10463611]
118. Walsh MD, Young JP, Leggett BA, Williams SH, Jass JR, McGuckin MA. The MUC13 cell surface mucin is highly expressed by human colorectal carcinomas. *Hum Pathol*. 2007; 38:883–892. [PubMed: 17360025]
119. Shyu MK, Lin MC, Shih JC, Lee CN, Huang J, Liao CH, Huang IF, Chen HY, Huang MC, Hsieh FJ. Mucin 15 is expressed in human placenta and suppresses invasion of trophoblast-like cells in vitro. *Hum Reprod*. 2007; 22:2723–2732. [PubMed: 17720698]
120. Huang J, Che MI, Huang YT, Shyu MK, Huang YM, Wu YM, Lin WC, Huang PH, Liang JT, Lee PH, Huang MC. Overexpression of MUC15 activates extracellular signal-regulated kinase 1/2 and promotes the oncogenic potential of human colon cancer cells. *Carcinogenesis*. 2009; 30:1452–1458. [PubMed: 19520792]
121. Blalock TD, Spurr-Michaud SJ, Tisdale AS, Heimer SR, Gilmore MS, Ramesh V, Gipson IK. Functions of MUC16 in corneal epithelial cells. *Invest Ophthalmol Vis Sci*. 2007; 48:4509–4518. [PubMed: 17898272]
122. Kerschner JE. Mucin gene expression in human middle ear epithelium. *Laryngoscope*. 2007; 117:1666–1676. [PubMed: 17667140]
123. Wang Y, Cheon DJ, Lu Z, Cunningham SL, Chen CM, Luo RZ, Xing D, Orsulic S, Bast RC Jr, Behringer RR. MUC16 expression during embryogenesis, in adult tissues, and ovarian cancer in the mouse. *Differentiation*. 2008; 76:1081–1092. [PubMed: 18637025]
124. Gum JR Jr, Crawley SC, Hicks JW, Szymkowski DE, Kim YS. MUC17, a novel membrane-tethered mucin. *Biochem Biophys Res Commun*. 2002; 291:466–475. [PubMed: 11855812]
125. Senapati S, Ho SB, Sharma P, Das S, Chakraborty S, Kaur S, Niehans G, Batra SK. Expression of intestinal MUC17 membrane-bound mucin in inflammatory and neoplastic diseases of the colon. *J Clin Pathol*. 2010; 63:702–707. [PubMed: 20702471]
126. Chen Y, Zhao YH, Kalasavadi TB, Hamati E, Nehrke K, Le AD, Ann DK, Wu R. Genome-wide search and identification of a novel gel-forming mucin MUC19/Muc19 in glandular tissues. *Am J Respir Cell Mol Biol*. 2004; 30:155–165. [PubMed: 12882755]
127. Shemirani N, Osipov V, Kolker A, Khampang P, Kerschner JE. Expression of mucin (MUC) genes in mucoepidermoid carcinoma. *Laryngoscope*. 2011; 121:167–170. [PubMed: 21072847]
128. Higuchi T, Orita T, Nakanishi S, Katsuya K, Watanabe H, Yamasaki Y, Waga I, Nanayama T, Yamamoto Y, Munger W, Sun HW, Falk RJ, Jennette JC, Alcorta DA, Li H, Yamamoto T, Saito Y, Nakamura M. Molecular cloning, genomic structure, and expression analysis of MUC20, a novel mucin protein, up-regulated in injured kidney. *J Biol Chem*. 2004; 279:1968–1979. [PubMed: 14565953]
129. Vekony H, Leemans CR, Ylstra B, Meijer GA, van dWI, Bloemena E. Salivary gland carcinosarcoma: oligonucleotide array CGH reveals similar genomic profiles in epithelial and mesenchymal components. *Oral Oncol*. 2009; 45:259–265. [PubMed: 18693132]
130. Itoh Y, Kamata-Sakurai M, Denda-Nagai K, Nagai S, Tsuiji M, Ishii-Schrade K, Okada K, Goto A, Fukayama M, Irimura T. Identification and expression of human epiglycanin/MUC21: a novel transmembrane mucin. *Glycobiology*. 2008; 18:74–83. [PubMed: 17977904]
131. Valladares-Ayerbes M, Iglesias-Diaz P, Diaz-Prado S, Ayude D, Medina V, Haz M, Reboredo M, Antolin S, Calvo L, Anton-Aparicio LM. Diagnostic accuracy of small breast epithelial mucin mRNA as a marker for bone marrow micrometastasis in breast cancer: a pilot study. *J Cancer Res Clin Oncol*. 2009; 135:1185–1195. [PubMed: 19221791]
132. Ayerbes MV, Diaz-Prado S, Ayude D, Campelo RG, Iglesias P, Haz M, Medina V, Gallegos I, Quindos M, Aparicio LA. In silico and in vitro analysis of small breast epithelial mucin as a marker for bone marrow micrometastasis in breast cancer. *Adv Exp Med Biol*. 2008; 617:331–339. [PubMed: 18497056]

133. Chen R, Alvero AB, Silasi DA, Steffensen KD, Mor G. Cancers take their Toll--the function and regulation of Toll-like receptors in cancer cells. *Oncogene*. 2008; 27:225–233. [PubMed: 18176604]
134. Sato Y, Goto Y, Narita N, Hoon DS. Cancer Cells Expressing Toll-like Receptors and the Tumor Microenvironment. *Cancer Microenviron*. 2009; 2(Suppl 1):205–214. [PubMed: 19685283]
135. Szajnik M, Szczepanski MJ, Czystowska M, Elishaev E, Mandapathil M, Nowak-Markwitz E, Spaczynski M, Whiteside TL. TLR4 signaling induced by lipopolysaccharide or paclitaxel regulates tumor survival and chemoresistance in ovarian cancer. *Oncogene*. 2009; 28:4353–4363. [PubMed: 19826413]
136. Chen R, Alvero AB, Silasi DA, Steffensen KD, Mor G. Cancers take their Toll--the function and regulation of Toll-like receptors in cancer cells. *Oncogene*. 2008; 27:225–233. [PubMed: 18176604]
137. Huang B, Zhao J, Unkeless JC, Feng ZH, Xiong H. TLR signaling by tumor and immune cells: a double-edged sword. *Oncogene*. 2008; 27:218–224. [PubMed: 18176603]
138. Matijevic T, Marjanovic M, Pavelic J. Functionally active toll-like receptor 3 on human primary and metastatic cancer cells. *Scand J Immunol*. 2009; 70:18–24. [PubMed: 19522763]
139. Nomi N, Kodama S, Suzuki M. Toll-like receptor 3 signaling induces apoptosis in human head and neck cancer via survivin associated pathway. *Oncol Rep*. 2010; 24:225–231. [PubMed: 20514466]
140. Paone A, Starace D, Galli R, Padula F, De CP, Filippini A, Ziparo E, Riccioli A. Toll-like receptor 3 triggers apoptosis of human prostate cancer cells through a PKC-alpha-dependent mechanism. *Carcinogenesis*. 2008; 29:1334–1342. [PubMed: 18566014]
141. Paone A, Galli R, Gabellini C, Lukashev D, Starace D, Gorlach A, De CP, Ziparo E, Del BD, Sitkovsky MV, Filippini A, Riccioli A. Toll-like receptor 3 regulates angiogenesis and apoptosis in prostate cancer cell lines through hypoxia-inducible factor 1 alpha. *Neoplasia*. 2010; 12:539–549. [PubMed: 20651983]
142. Salaun B, Coste I, Rissoan MC, Lebecque SJ, Renno T. TLR3 can directly trigger apoptosis in human cancer cells. *J Immunol*. 2006; 176:4894–4901. [PubMed: 16585585]
143. Shen P, Jiang TW, Lu HQ, Zhang LZ, Han HX, Luo RC. [Effects of Poly I:C in inducing growth inhibition and apoptosis of human hepatocellular carcinoma cells]. *Nan Fang Yi Ke Da Xue Xue Bao*. 2009; 29:525–527. [PubMed: 19304544]
144. Maruyama K, Selmani Z, Ishii H, Yamaguchi K. Innate immunity and cancer therapy. *Int Immunopharmacol*. 2010
145. Basith S, Manavalan B, Lee G, Kim SG, Choi S. Toll-like receptor modulators: a patent review (2. Expert Opin Ther Pat. 2011; 21:927–944. [PubMed: 21406035]
146. Furrie E, Macfarlane S, Thomson G, Macfarlane GT. Toll-like receptors-2, -3 and -4 expression patterns on human colon and their regulation by mucosal-associated bacteria. *Immunology*. 2005; 115:565–574. [PubMed: 16011525]
147. Yoshioka T, Morimoto Y, Iwagaki H, Itoh H, Saito S, Kobayashi N, Yagi T, Tanaka N. Bacterial lipopolysaccharide induces transforming growth factor beta and hepatocyte growth factor through toll-like receptor 2 in cultured human colon cancer cells. *J Int Med Res*. 2001; 29:409–420. [PubMed: 11725828]
148. Goto Y, Arigami T, Kitago M, Nguyen SL, Narita N, Ferrone S, Morton DL, Irie RF, Hoon DS. Activation of Toll-like receptors 2, 3, and 4 on human melanoma cells induces inflammatory factors. *Mol Cancer Ther*. 2008; 7:3642–3653. [PubMed: 19001446]
149. Xie W, Wang Y, Huang Y, Yang H, Wang J, Hu Z. Toll-like receptor 2 mediates invasion via activating NF-kappaB in MDA-MB-231 breast cancer cells. *Biochem Biophys Res Commun*. 2009; 379:1027–1032. [PubMed: 19141294]
150. Thompson AJ, Colledge D, Rodgers S, Wilson R, Revill P, Desmond P, Mansell A, Visvanathan K, Locarnini S. Stimulation of the interleukin-1 receptor and Toll-like receptor 2 inhibits hepatitis B virus replication in hepatoma cell lines in vitro. *Antivir Ther*. 2009; 14:797–808. [PubMed: 19812442]

151. Szczepanski M, Stelmachowska M, Stryczynski L, Golusinski W, Samara H, Mozer-Lisewska I, Zeromski J. Assessment of expression of toll-like receptors 2, 3 and 4 in laryngeal carcinoma. *Eur Arch Otorhinolaryngol.* 2007; 264:525–530. [PubMed: 17165086]
152. Zhou M, McFarland-Mancini MM, Funk HM, Husseinazadeh N, Mounajjed T, Drew AF. Toll-like receptor expression in normal ovary and ovarian tumors. *Cancer Immunol Immunother.* 2009; 58:1375–1385. [PubMed: 19184006]
153. Gonzalez-Reyes S, Marin L, Gonzalez L, Gonzalez LO, del Casar JM, Lamelas ML, Gonzalez-Quintana JM, Vizoso FJ. Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. *BMC Cancer.* 2010; 10:665. [PubMed: 21129170]
154. Salaun B, Coste I, Rissoan MC, Lebecque SJ, Renno T. TLR3 can directly trigger apoptosis in human cancer cells. *J Immunol.* 2006; 176:4894–4901. [PubMed: 16585585]
155. Sadik CD, Bachmann M, Pfeilschifter J, Muhl H. Activation of interferon regulatory factor-3 via toll-like receptor 3 and immunomodulatory functions detected in A549 lung epithelial cells exposed to misplaced U1-snRNA. *Nucleic Acids Res.* 2009; 37:5041–5056. [PubMed: 19541850]
156. Galli R, Starace D, Busa R, Angelini DF, Paone A, De CP, Filippini A, Sette C, Battistini L, Ziparo E, Riccioli A. TLR stimulation of prostate tumor cells induces chemokine-mediated recruitment of specific immune cell types. *J Immunol.* 2010; 184:6658–6669. [PubMed: 20483744]
157. Gonzalez-Reyes S, Fernandez JM, Gonzalez LO, Aguirre A, Suarez A, Gonzalez JM, Escaff S, Vizoso FJ. Study of TLR3, TLR4, and TLR9 in prostate carcinomas and their association with biochemical recurrence. *Cancer Immunol Immunother.* 2011; 60:217–226. [PubMed: 20978888]
158. Schmausser B, Andrusis M, Endrich S, Muller-Hermelink HK, Eck M. Toll-like receptors TLR4, TLR5 and TLR9 on gastric carcinoma cells: an implication for interaction with *Helicobacter pylori*. *Int J Med Microbiol.* 2005; 295:179–185. [PubMed: 16044857]
159. He W, Liu Q, Wang L, Chen W, Li N, Cao X. TLR4 signaling promotes immune escape of human lung cancer cells by inducing immunosuppressive cytokines and apoptosis resistance. *Mol Immunol.* 2007; 44:2850–2859. [PubMed: 17328955]
160. Hassan F, Islam S, Tumurkhuu G, Naiki Y, Koide N, Mori I, Yoshida T, Yokochi T. Intracellular expression of toll-like receptor 4 in neuroblastoma cells and their unresponsiveness to lipopolysaccharide. *BMC Cancer.* 2006; 6:281. [PubMed: 17156435]
161. Yang H, Zhou H, Feng P, Zhou X, Wen H, Xie X, Shen H, Zhu X. Reduced expression of Toll-like receptor 4 inhibits human breast cancer cells proliferation and inflammatory cytokines secretion. *J Exp Clin Cancer Res.* 2010; 29:92. [PubMed: 20618976]
162. Gatti G, Quintar AA, Andreani V, Nicola JP, Maldonado CA, Masini-Repiso AM, Rivero VE, Maccioni M. Expression of Toll-like receptor 4 in the prostate gland and its association with the severity of prostate cancer. *Prostate.* 2009; 69:1387–1397. [PubMed: 19496069]
163. Kim WY, Lee JW, Choi JJ, Choi CH, Kim TJ, Kim BG, Song SY, Bae DS. Increased expression of Toll-like receptor 5 during progression of cervical neoplasia. *Int J Gynecol Cancer.* 2008; 18:300–305. [PubMed: 17587322]
164. Rayburn ER, Wang W, Zhang R, Wang H. Experimental therapy for colon cancer: anti-cancer effects of TLR9 agonism, combination with other therapeutic modalities, and dependence upon p53. *Int J Oncol.* 2007; 30:1511–1519. [PubMed: 17487373]
165. Lee JW, Choi JJ, Seo ES, Kim MJ, Kim WY, Choi CH, Kim TJ, Kim BG, Song SY, Bae DS. Increased toll-like receptor 9 expression in cervical neoplasia. *Mol Carcinog.* 2007; 46:941–947. [PubMed: 17440926]
166. Droemann D, Albrecht D, Gerdes J, Ulmer AJ, Branscheid D, Vollmer E, Dalhoff K, Zabel P, Goldmann T. Human lung cancer cells express functionally active Toll-like receptor 9. *Respir Res.* 2005; 6:1. [PubMed: 15631627]
167. Ilvesaro JM, Merrell MA, Swain TM, Davidson J, Zayzafoon M, Harris KW, Selander KS. Toll like receptor-9 agonists stimulate prostate cancer invasion in vitro. *Prostate.* 2007; 67:774–781. [PubMed: 17373717]

168. Merrell MA, Ilvesaro JM, Lehtonen N, Sorsa T, Gehrs B, Rosenthal E, Chen D, Shackley B, Harris KW, Selander KS. Toll-like receptor 9 agonists promote cellular invasion by increasing matrix metalloproteinase activity. *Mol Cancer Res.* 2006; 4:437–447. [PubMed: 16849519]
169. Tanaka J, Sugimoto K, Shiraki K, Tameda M, Kusagawa S, Nojiri K, Beppu T, Yoneda K, Yamamoto N, Uchida K, Kojima T, Takei Y. Functional cell surface expression of toll-like receptor 9 promotes cell proliferation and survival in human hepatocellular carcinomas. *Int J Oncol.* 2010; 37:805–814. [PubMed: 20811701]
170. Kundu JK, Surh YJ. Inflammation: gearing the journey to cancer. *Mutat Res.* 2008; 659:15–30. [PubMed: 18485806]
171. Goswami B, Rajappa M, Sharma M, Sharma A. Inflammation: its role and interplay in the development of cancer, with special focus on gynecological malignancies. *Int J Gynecol Cancer.* 2008; 18:591–599. [PubMed: 17944921]
172. Cario E. Toll-like receptors in inflammatory bowel diseases: a decade later. *Inflamm Bowel Dis.* 2010; 16:1583–1597. [PubMed: 20803699]
173. Kadayakkara DK, Beatty PL, Turner MS, Janjic JM, Ahrens ET, Finn OJ. Inflammation driven by overexpression of the hypoglycosylated abnormal mucin 1 (MUC1) links inflammatory bowel disease and pancreatitis. *Pancreas.* 2010; 39:510–515. [PubMed: 20084048]
174. Saleh M, Trinchieri G. Innate immune mechanisms of colitis and colitis-associated colorectal cancer. *Nat Rev Immunol.* 2010; 11:9–20. [PubMed: 21151034]
175. Del Pozo JL. Primers on molecular pathways: lipopolysaccharide signaling - potential role in pancreatitis and pancreatic cancer. *Pancreatol.* 2010; 10:114–118. [PubMed: 20460943]
176. Yu L, Wang L, Chen S. Endogenous toll-like receptor ligands and their biological significance. *J Cell Mol Med.* 2010; 14:2592–2603. [PubMed: 20629986]
177. Mejias-Luque R, Linden SK, Garrido M, Tye H, Najdovska M, Jenkins BJ, Iglesias M, Ernst M, de BC. Inflammation modulates the expression of the intestinal mucins MUC2 and MUC4 in gastric tumors. *Oncogene.* 2010; 29:1753–1762. [PubMed: 20062084]
178. Carson DD. The cytoplasmic tail of MUC1: a very busy place. *Sci Signal.* 2008; 1:e35.
179. Thompson EJ, Shanmugam K, Hattrup CL, Kotlarczyk KL, Gutierrez A, Bradley JM, Mukherjee P, Gendler SJ. Tyrosines in the MUC1 cytoplasmic tail modulate transcription via the extracellular signal-regulated kinase 1/2 and nuclear factor-kappaB pathways. *Mol Cancer Res.* 2006; 4:489–497. [PubMed: 16849524]
180. Al MA, Gendler SJ. Muc1 affects c-Src signaling in PyV MT-induced mammary tumorigenesis. *Oncogene.* 2005; 24:5799–5808. [PubMed: 15897873]
181. Demarchi F, Verardo R, Varnum B, Brancolini C, Schneider C. Gas6 anti-apoptotic signaling requires NF-kappa B activation. *J Biol Chem.* 2001; 276:31738–31744. [PubMed: 11425860]
182. Kim JH, Kim B, Cai L, Choi HJ, Ohgi KA, Tran C, Chen C, Chung CH, Huber O, Rose DW, Sawyers CL, Rosenfeld MG, Baek SH. Transcriptional regulation of a metastasis suppressor gene by Tip60 and beta-catenin complexes. *Nature.* 2005; 434:921–926. [PubMed: 15829968]
183. McKay MM, Morrison DK. Integrating signals from RTKs to ERK/MAPK. *Oncogene.* 2007; 26:3113–3121. [PubMed: 17496910]
184. Pearson G, Robinson F, Beers GT, Xu BE, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocr Rev.* 2001; 22:153–183. [PubMed: 11294822]
185. Perkins ND. Integrating cell-signalling pathways with NF-kappaB and IKK function. *Nat Rev Mol Cell Biol.* 2007; 8:49–62. [PubMed: 17183360]
186. Funakoshi-Tago M, Tago K, Sonoda Y, Tominaga S, Kasahara T. TRAF6 and C-SRC induce synergistic AP-1 activation via PI3-kinase-AKT-JNK pathway. *Eur J Biochem.* 2003; 270:1257–1268. [PubMed: 12631284]
187. An H, Xu H, Yu Y, Zhang M, Qi R, Yan X, Liu S, Wang W, Guo Z, Qin Z, Cao X. Up-regulation of TLR9 gene expression by LPS in mouse macrophages via activation of NF-kappaB, ERK and p38 MAPK signal pathways. *Immunol Lett.* 2002; 81:165–169. [PubMed: 11947920]
188. van KY. C-type lectins on dendritic cells: key modulators for the induction of immune responses. *Biochem Soc Trans.* 2008; 36:1478–1481. [PubMed: 19021579]

Fig. 1.

Toll-like Receptors (TLRs) recognize specialized structural motifs on the microbes known as pathogen-associated molecular patterns (PAMPs). The cellular distribution of TLRs represents the site of their encounter with the pathogens – TLRs which recognize cell wall moieties (TLR-2, -4, -5) are present on the cell-membrane whereas TLRs which recognize nucleic-acids (TLR3, -7, -8, -9) are localized in the endosomal compartment. TLR1, -6 signal through heterodimerization with TLR2 and thereby localized on the cell membrane. Upon ligand binding, the cytoplasmic Toll/IL-1 receptor (TIR) domain of the TLRs associate with TIR domain of the adaptor proteins MyD88, TIRAP, TRIF and TRAM. MyD88 is required for signaling by all TLRs except TLR3 which together with TLR4 signal through TRIF dependent-MyD88 independent pathway. TLR4 is unique in that it utilizes all the four adaptor proteins for signaling. The use of alternative adaptors provides specificity to the TLR signaling pathway. Further MyD88 recruits IRAK4 and IRAK1 molecules to the TLR signaling complex through interaction with their death domains (DD). This leads to the activation of TRAF6 which further activates several effector molecules such as transcription factors NF- κ B, IRF3 and MAP kinases like p38, ERK1/2 and JNK. Downstream signaling events by these molecules regulate the expression of pro-inflammatory cytokines and chemokines.

Fig. 2.

The proposed mechanisms of interaction between TLRs and MUCs: I. Ligand-TLR interaction initiates signaling pathways leading to the induction of several pro-inflammatory cytokines MAPKs and NF-κB which are known to induce mucin gene expression. Alternatively these molecules can also induce TLR expression in turn regulating mucin expression thereby forming a self-perpetuating signaling loop. Constitutively active TLR pathways are commonly observed in several cancers. II. Mucins can also activate signaling pathways such as their interaction with receptor tyrosine kinase ErbB2 and other molecules activates signaling pathways which have common downstream signaling components and lead to a cross-talk with TLR signaling

pathway. III. Mucins are large glycoprotein molecules which exhibit the *receptor masking* and can provide a steric hindrance for endogenous ligand binding to TLRs thus inhibiting their signaling pathway. IV. The sequestration of TLR ligands in the dense mucin matrix can have two possible outcomes either activation or inhibition of TLR signaling pathway. V. Altered glycosylation of mucin molecules can act as a ligand for TLRs and activate TLR signaling pathway.

Table 1

TLR ligands, sub-cellular localization and cell type distribution

TLR	Exogenous ligands	Endogenous ligands	Cell types [51]
TLR1	Tri-acylated lipopeptide [52]	Not identified [51]	Basophils, B-lymphocytes, dendritic cells, fibroblasts, keratinocytes, macrophages
TLR2	Peptidoglycan [53] Pam3CSK4 [54], [55] lipopeptide [56] Lipoteichoic Acid [57]	HSP60, HSP70, HSP90 [51, 58] RAGE [59], PAUF [60]	Basophils, B-lymphocytes, dendritic cells, endothelial cells, fibroblasts, keratinocytes, Langerhans' cells, macrophages, mast cells, NK cells, neutrophils
TLR3	Viral Double stranded RNA, Poly I:C [9, 51]	Endogenous mRNA [61]	B-lymphocytes, dendritic cells, endothelial cells, fibroblasts, keratinocytes, macrophages, NK cells, neutrophils
TLR4	Lipopolysaccharide from gram negative bacteria, taxol [9]	HSP60, HSP70, HSP90 [58], extra domain A of fibronectin, β -defensin 2, Fibrinogen [51], heparan sulphate [9] RAGE [59] PAUF [60]	Basophils, B-lymphocytes, dendritic cells, endothelial cells, fibroblasts, keratinocytes, Langerhans' cells, macrophages, mast cells, NK cells, neutrophils, regulatory T cells
TLR5	Bacterial Flagellin [51]	Not identified [51]	B-lymphocytes, dendritic cells, endothelial cells, fibroblasts, keratinocytes, macrophages, NK cells, regulatory T cells
TLR6	Di-acylated lipopeptide [9]	Not identified [51]	Basophils, B-lymphocytes, dendritic cells, fibroblasts, keratinocytes, macrophages, NK cells, neutrophils
TLR7	Single-stranded RNA (HIV-1) [51]	Imidazoquinolines (Imiquimod, Resiquimod Loxoribine Bropiramine [51])	B-lymphocytes, dendritic cells, fibroblasts, macrophages, neutrophils,
TLR8	Single-stranded RNA (HIV-1) [51]	Imiquimod, Resiquimod[51]	dendritic cells, fibroblasts, macrophages, NK cells, regulatory T cells
TLR9	Unmethylated CpG DNA [9]	Herpes simplex virus-2 [51] Mitochondrial DNA [47]	Basophils, B-lymphocytes, dendritic cells, endothelial cells, fibroblasts, keratinocytes, Langerhans' cells, macrophages, NK cells, neutrophils
TLR10	Not identified [51]	Not identified [51]	dendritic cells, keratinocytes, B-lymphocytes
TLR11	Uropathogenic bacteria [9]	Not identified [51]	Endothelial cells

Table 2

MUC and TLR in infection

Microbe/microbe derived product	TLR	Mucin	Cell Type	Reference
<i>Gymnophalloides seoi</i>	TLR2	MUC2	HT29	[65]
<i>Mycoplasma pneumoniae</i>	TLR2	MUC5AC	A549	[67]
<i>Haemophilus influenza</i> (lipoprotein p6)	TLR2	MUC5AC	HMEEC-1	[68]
LPS	TLR4	MUC5AC	Airway epithelium	[69, 70]
<i>Streptococcus pneumoniae</i>	TLR4	MUC5AC	Airway epithelium	[71]

Table 3

MUCs in physiological conditions and aberrant expression in cancers

Mucin	Distribution in normal physiological conditions	References	Aberrant expression/Glycosylation in Cancer	References
MUC1	Salivary glands, airways, oesophagus, stomach, pancreas, duodenum, male and female reproductive tract	[16, 80–86]	Breast, colon, gastric, lung, ovarian, pancreatic, prostate cancer and haematological malignancies, renal	[77, 87–93]
MUC2	Airways, duodenum, colorectum	[80, 84, 94]	Breast, colon, gastric, pancreatic cancer	[91, 93, 95, 96]
MUC3	Salivary, airways, hepatobiliary, duodenum, colorectum	[80, 83, 84, 94, 97]	Breast, colon, gastric cancer	[91, 98, 99]
MUC4	Salivary glands, airways, oesophagus, colorectum, female reproductive tract,	[80–82, 85, 94, 100]	Lung, ovarian, pancreatic, prostate, breast, gall bladder cancer	[16, 87, 93, 101–103]
MUC5AC	Airways, stomach, pancreas	[16, 80, 83]	Breast, gastric, pancreatic cancer	[91, 93, 104]
MUC5B	Salivary glands, airways, oesophagus, pancreas, female reproductive tract	[16, 80–83, 100, 105]	Breast cancer	[93, 106]
MUC6	Stomach, pancreas, duodenum	[16, 83, 84]	Colon, gastric cancer	[91, 93, 107]
MUC7	Salivary glands, airways	[108, 109]	Gastric, colon cancer	[110] [111]
MUC8	Airways, male reproductive system	[109, 112]	Endometrial, cervical cancer	[113]
MUC9	Female reproductive system	[114]	Colon, ovarian cancer	[111, 115]
MUC11	Airways, colon	[80, 116, 117]	Colon	[111, 117]
MUC12	Pancreas	[16]	Colon	[117]
MUC13	Airways	[80]	Colon	[118]
MUC15	Placenta	[119]	Colon	[120]
MUC16	Ocular surface, Cornea, airways, female reproductive tract	[121–123]	Breast, Ovarian	[93, 123]
MUC17	Duodenum	[124]	Colon	[125]
MUC19	Airways, Salivary glands	[126]	Salivary gland cancer	[127]
MUC20	Airways, oesophagus, stomach, duodenum, colon	[109, 109, 128]	Salivary gland cancer	[109, 129]
MUC21	Airways, thymus, large intestine male reproductive system	[130]	Lung cancer	[130]
MUCL1	-		Breast	[131, 132]

Table 4

The expression of TLRs in various human tumor tissues/cell lines and the techniques to study them – Reverse transcriptase PCR (PCR), Functional tests (FT), Western blot (WB), Flow cytometry (FC), immunofluorescence (IF), in-situ hybridization (ISH)

TLR	Type of Cancer/cell-lines/tissues	Technique used for the study	References
TLR1	colon	PCR	[146]
TLR2	colon	PCR,FT	[146, 147]
	melanoma	PCR,FC	[148]
	breast	PCR,WB,FT,FC	[149]
	hepatocellular	PCR,FT	[150]
	laryngeal	IHC	[151]
	ovarian	IHC,FT	[152]
TLR3	colon	PCR	[146]
	breast	IHC,WB	[153, 154]
	ovarian	IHC,FT	[152]
	lung	PCR,IF,FT	[155]
	melanoma	WB	[148]
	laryngeal	IHC	[151]
	prostate	IHC,PCR,WB	[156, 157]
TLR4	gastric	IHC	[158]
	colon	PCR	[146]
	ovarian	IHC,FT	[152]
	lung	PCR,FT	[159]
	melanoma	PCR,WB	[148]
	brain	PCR,FT,FC	[160]
	breast	PCR,WB,FT,FC	[161]
	laryngeal	IHC	[151]
	prostate	IHC,FT	[157, 162]
TLR5	gastric	IHC	[158]
	ovarian	IHC,FT	[152]
	cervical	IHC,FT	[163]
<i>TLR9</i>	gastric	IHC	[158]
	colon	PCR,FT	[164]
	cervical	IHC,PCR	[165]
	lung	IHC, ISH, PCR,IF,FT	[166]
	prostate	IHC,WB, FT	[157, 167]
	breast	DNA arrays, WB, IHC, FT	[168]
	hepatocellular	IHC, WB,FT	[169]