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overview

The polymorphisms in Toll-like receptor genes and cancer risk

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Abstract

Toll-like receptors (TLRs) are a family of pattern recognition receptors and have important role in pathogen recognition including activation of innate and acquired immune responses. They are mainly expressed in epithelium but have also been found in cancer cells, where they can have pro-tumorigenic and anti-tumorigenic effect. Single nucleotide polymorphisms (SNPs) may change protein structure and influence receptor function. Polymorphisms in TLR *genes have been linked with various cancer types and reports were often contradictory. The strongest association with increased cancer risk was found for* TLR2 *polymorphism –196 to –174 del (Δ22) (gastric, gallbladder and cervical cancer) and* TLR4 *polymorphisms rs4986790 (gastrointestinal cancers and lymphoma) and rs4986791 (gastrointestinal cancers, nasopharyngeal and gallbladder cancer). Other polymorphisms associated with cancer risk include* TLR10-TLR1-TLR6 *gene cluster polymorphisms rs10008492 (non-Hodgkin's lymphoma) and rs7696175 (breast cancer),* TLR6 *rs5743815 (non-Hodgkin's lymphoma),* TLR10 *rs11466657 (meningioma),* TLR2 *GT microsatellite repeat number polymorphism (colorectal cancer) and rs3804100 (MALT lymphoma),* TLR3 *829A>C (nasopharyngeal cancer),* TLR4 *11350G>C (nasopharyngeal cancer), rs1927911 and rs10759931 (prostate cancer),* TLR5 *rs5744174 (gastric cancer) and* TLR9 *rs5743836 (Hodgkin's lymphoma) and rs352140 (Hodgkin's lymphoma and cervical cancer). Discrepancies in results of different studies regarding* TLR *polymorphisms and cancer risk may have arissen due to insufficient sample size, differences in ethnicity or age, undetected infections or other environmental factors.*

1. INTRODUCTION

Toll-like receptors (TLRs) are a family of innate immune receptors known as pattern recognition receptors (PRRs) and they recognize molecular motifs related to pathogens or pathogen associated molecular patterns (PAMPs) *(1)*. TLRs have a crucial role in recognition of many different pathogens, including viruses, bacteria, protozoa and fungi, and due to their important function, they are evolutionary conserved *(2)*. They were first described in *Drosophila* in 1984, and were later discovered in vertebrates, including humans *(1, 3)*. To date, 13 TLRs were discovered in mammals, and 10 are functional in humans *(2)*. Human genes encoding TLRs reside on chromosomes 1 (*TLR5*), 3 (*TLR9*), 4 (*TLR1*, *TLR2*, *TLR3*, *TLR6* and *TLR10*), 9 (*TLR4*) and X (*TLR7* and *TLR8*) *(1, 4)*. TLR signaling begins with binding of specific ligand, continues with dimerization and signal transduction into the cell followed by

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activation of three main transcription factors: interferon--regulatory factor (IRF3, IRF5 and IRF7), NF-κB and AP1. They then promote the transcription of inflammation mediators: cytokines, chemokines and interferons *(2, 5)*. TLRs are also important in activation of adaptive immunity: downstream signaling and expression of cytokines leads to maturation of dendritic cells and activation of B and T cells *(5)*.

2. TOLL-LIKE RECEPTORS: STRUCTURE, LOCALIZATION AND FUNCTION

TLRs are type I transmembrane glycoproteins consisting of three domains: leucine rich ligand binding ectodomain, transmembrane region, and cytoplasmic TIR-domain (the Toll/interleukin-1 receptor domain). Ectodomain contains multiple leucine rich repeats (LRRs) which are crucial in recognition and binding of pathogen motifs and also in forming characteristic horseshoe shape of TLRs, a structure important in ligand binding and downstream signaling *(6)*. TIR-domain dimerizes after the ligand binding in the ectodomain enabling the recruitment of TIR domain containing adaptor molecules which transduce the signal downstream: MyD88 (myeloid differentiation factor 88), MAL (MyD88 adaptor--like), TRIF (Toll receptor-associated activator of interferon) and TRAM (Toll receptor-associated molecule) *(2, 6)*. All TLRs except TLR3 use MyD88 for signal transduction, and TLR3 depends on TRIF. TLR4 can activate both MyD88 and TRIF. TLRs can form homodimers (like TLR3-TLR3) or heterodimers (such as TLR1-TLR2 and TLR2-TLR6) *(2)*. Due to differences in ectodomain, different TLRs bind different PAMPS, such as lipids and lipoproteins (TLR1, TLR2, TLR4 and TLR6), proteins (TLR5 and mouse TLR11), and microbial nucleic acids (TLR3, TLR7, TLR8 and TLR9), while ligands of TLR10 and mouse TLR12 and TLR13 have not yet been identified *(7)*. Nature of ligands they bind determines the location of TLRs in the cell: TLR1, TLR2, TLR4, TLR5 and TLR6 bind components of pathogen envelope or cell wall and are expressed on the surface of the cell (as well as TLR10), while TLR3, TLR7, TLR8 and TLR9 bind nucleic acids and are mainly located in the endoplasmic reticulum membrane or endosomal membrane *(2)*. TLRs are mainly expressed in lymphoid tissues, innate immune cells (dendritic cells, macrophages, monocytes, polymorphonuclear leukocytes, NK cells) and lymphocytes T and B. However, they can also be expressed in different cell types, including cancer cells and cancer cell lines *(5, 8)*. In normal tissues, TLRs are highly expressed in many epithelial cells *(9)*.

3. TOLL-LIKE RECEPTORS IN CANCER

TLRs participate in many important cellular processes: cell proliferation, survival, apoptosis, cell migration, metastasis and angiogenesis. Due to their important role in inflammation, it is considered that they can have a pro-tumorigenic and anti-tumorigenic function, an effect known as a „double edged sword" *(10, 11)*. In some cases enhanced TLR activation can lead to apoptosis of cancer cells and more efficient elimination of tumor cells by immune system, while in others it may support tumorigenesis by promoting chronic inflammation *(8, 12, 13)*. TLR signaling has been implicated in various autoimmune and inflammatory diseases and chronic inflammation is known to create a microenvironment rich in growth and survival factors and has been linked with development of many types of cancer *(13)*. TLR expression was reported in several cancer types and cancer cell lines. It was found that TLR4 and TLR5 are expressed in gastric epithelium infected with *Helicobacter pylori* as well as in precursor lesions and in gastric cancer cells *(14)*. It is considered that TLRs enable cells to interact with *H. pylori* which can induce tumorigenic factors and may promote cancer development. TLR expression has also been found in colon cancer, hepatocellular carcinoma, ovarian and cervical cancers, breast and prostate cancers, lung cancer, melanoma and neuroblastoma *(9)*. TLR expression in cancer cells has been linked with tumor progression, evasion of immune system surveillance, apoptosis and survival. TLR4 expression in lung cancer cells is linked with production of immunosuppressive cytokines (TGFb), angiogenic factors VEGF and IL-8, and with increased resistance to apoptosis *(15)*. Silencing of TLR4 expression in breast cancer cell line MDA--MB-231 significantly decreased cell proliferation and production of proinflammatory cytokines IL-6 and IL-8 *(16)*. In ovarian cancer cells and cell lines TLR4 activation by lipopolysaccharide or Paclitaxel activated NF-kB, promoted production of IL-8, IL-6, VEGF and MCP-1, and inhibited Paclitaxel mediated apoptosis, while TLR4 silencing lead to loss of resistance to Paclitaxel *(17)*. TLR2 mRNA expression was significantly higher in sporadic colorectal cancer cells than in noncancerous cells which could implicate its role in cancerogenesis *(18)*.

4. THE POLYMORPHISMS OF *TLR* GENES

Single nucleotide polymorphisms (SNPs) may often cause no change in protein function and pass unnoticed, but can also lead to amino acid substitutions and changes in protein function and stability, splicing, mRNA stability, post-translational modifications or regulation of expression (Figure 1A and 1B) *(19)*. SNPs in TLR ectodomain (in LRRs) can affect binding of ligands and SNPs in transmembrane domain may alter receptor localization and trafficking in the cell. SNPs in the cytoplasmic domain may lead to defects in recruitment of adapter proteins, receptor dimerization and internalization after ligand binding *(20, 21)*. TLR polymorphisms have been linked with susceptibility or protective effect in various diseases, mainly infective and inflammatory, but also in cancer (Table 1) *(20)*.

4.1. *TLR1*, *TLR6* and *TLR10* polymorphisms

Receptors TLR1, TLR6 and TLR10 have similar structures and genes *TLR1*, *TLR6* and *TLR10* form a single

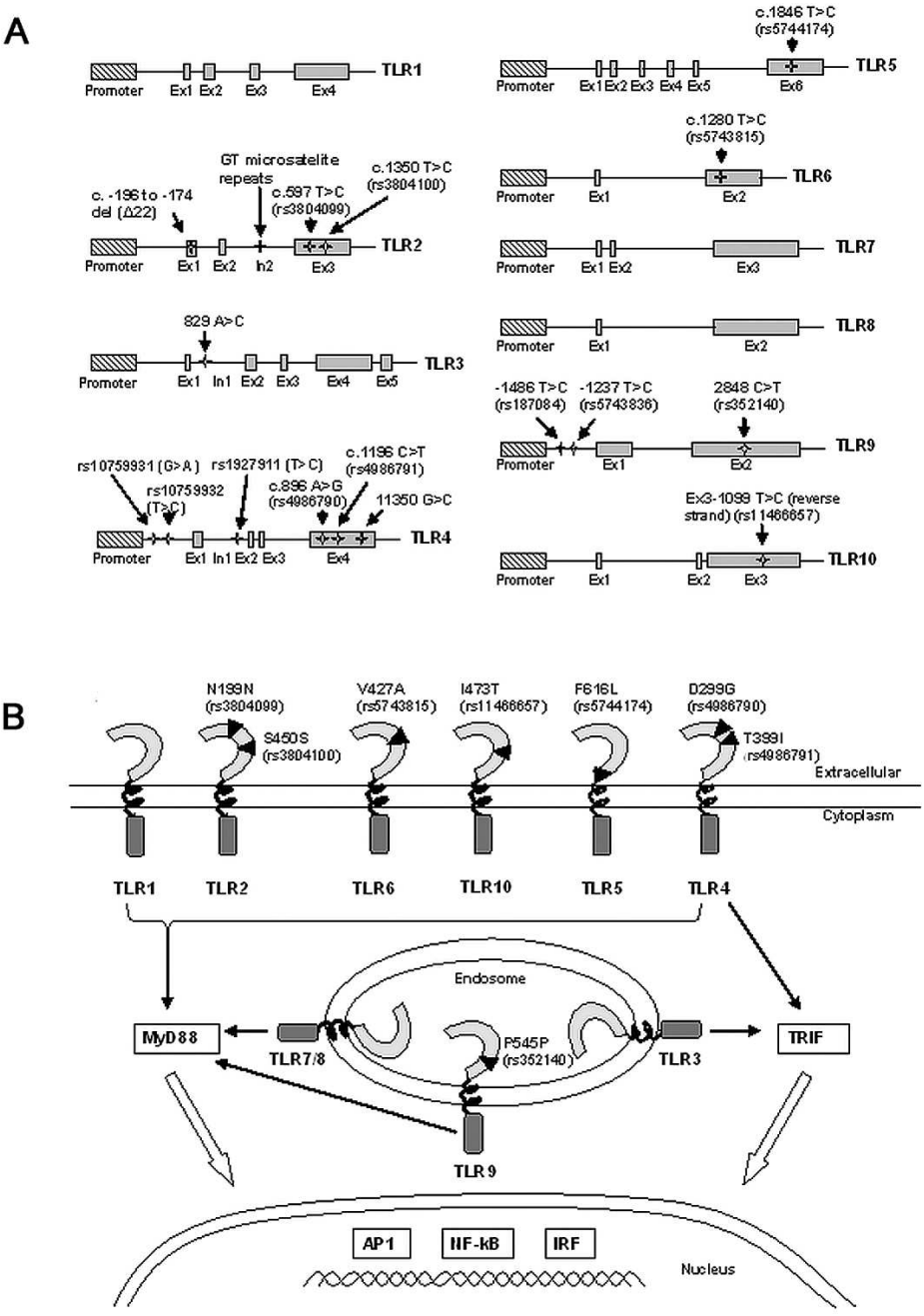

Figure 1. *Position of cancer risk associated TLR polymorphisms within genes (A) and proteins (B). A) Polymorphisms (four-angled star) in* TLR *genes. B) Location of polymorphisms (black triangle) in TLR proteins: ectodomain leucine rich repeats (light grey), transmembrane region (black wavy line) or Toll/interleukin-1 receptor (TIR) domain (dark grey box). After ligand binding all TLRs interact with myeloid differentiation factor 88 (MyD88) except TLR3 who interacts with Toll receptor-associated activator of interferon (TRIF). TLR4 can interact with MyD88 and TRIF. Downstream signaling leads to the activation of transcription factors: activator protein 1 (AP1), nuclear factor kB (NF-kB) and interferon--regulatory factors (IRFs).*

gene cluster on the chromosome 4p14 *(22)*. Receptor TLR1 recognizes triacylated lipoprotein, TLR6 binds diacylated lipoprotein and so far no specific ligand has been linked with TLR10 *(7)*. To bind ligands TLR1 and TLR6 must form dimers with TLR2, while TLR10 homodimerizes or heterodimerizes with TLR1 or TLR2. There have been several association studies between SNPs in *TLR10-TLR1-TLR6* gene cluster and prostate cancer risk, but with highly contradictory results regarding even the same investigated polymorphisms *(23, 24, 25)*. Finally, pooled analysis on genotype data from three case control studies with more than 3,000 prostate cancer patients and more than 2,500 controls of European ancestry found no overall association between polymorphisms in *TLR10--TLR1-TLR6* gene cluster or *TLR4* gene with prostate cancer risk *(26)*. However, polymorphisms in *TLR10-*

TABLE 1

The association of polymorphisms in *TLR* genes with cancer risk.

Polymorphism	Gene (protein) region	Cancer type	Association*	Sample size, population	References
TLR10-TLR1-TLR6					
rs4833103 (C>A)	In proximity of *TLR1*	Non-Hodgkin's lymphoma	Negative for allele A	1,946 patients, 1,808 controls, Caucasian	*(28)*
rs7696175 (C>T)	In proximity of *TLR1* and *TLR6*	Breast cancer	Positive for allele T	742 patients, 658 controls, African American; 1,230 patients, 1,118 controls Caucasian	*(30)*
rs10008492 (C>T)	In proximity of *TLR10*	Non-Hodgkin's lymphoma	Positive for allele T	1,946 patients, 1,808 controls, Caucasian	*(28)*
TLR6					
rs5743815 (c.1280 T>C, Val427Ala)	Exon 2 (LRR)	Non-Hodgkin's lymphoma	Positive for allele C	458 patients, 484 controls, Caucasian	*(27)*
TLR10					
rs11466657 (Ex3-1099 T>C (reverse strand), Ile473Thr)	Exon 3 (LRR)	Meningioma	Negative for heterozygous genotype AG	101 patients, 330 controls, Caucasian (U.S.)	*(29)*
TLR2					
c. -196 to -174 del (Δ22nt)	Exon 1 (5'UTR of *TLR2*)	Gastric cancer	Positive for 'del' allele	174 gastric cancer patients, 208 chronic gastritis patients, 225 controls, Brazilian Caucasian	*(34)*
		HCV associated hepatocellular carcinoma	Positive for 'del' allele	189 HCV associated hepatocellular carcinoma patients, 192 HCV infected patients, 347 controls, Germany	*(35)*
		Breast cancer	Positive for 'del' allele	261 patient, 480 controls, Greece	*(36)*
		Prostate cancer	Positive for 'del' allele	195 patients, 250 controls, North India	*(37)*
		Gallbladder cancer	Positive for 'del' allele	230 patients, 230 controls, North India	*(38)*
		Cervical cancer	Positive for 'del' allele	150 patients, 150 controls, North India	*(39)*
Number of GT microsatellite repeats	Intron 2	Colorectal cancer	Negative for 'M' allele, positive for 'S' allele and 'L' allele	89 patients, 88 controls, Croatia	*(40)*
rs3804099 (c.597 T>C, Asn199Asn)	Exon 3 (LRR)	Hepatocellular carcinoma	Negative for genotype CT	211 patients, 232 controls, China	*(41)*
rs3804100 (c.1350 T>C, Ser450Ser)	Exon 3 (LRR)	MALT lymphoma	Positive for allele C	1,946 patients, 1,808 controls, Caucasian	*(28)*
		Hepatocellular carcinoma	Negative for genotype CT	211 patients, 232 controls, China	*(41)*
TLR3					
829 A>C	Intron 1	Nasopharyngeal carcinoma	Positive for allele C	434 patients, 512 controls, Southern China	*(43)*

TLR4					
rs4986790 (c.896 A>G, Asp299Gly)	Exon 4 (LRR)	Colorectal cancer	Positive for allele G	89 patients, 88 controls, Croatia	*(40)*
		Non-cardia gastric cancer	Positive for allele G	45 hypochlorhydria patients, 149 controls; 312 non-cardia gastric cancer patients, 419 controls; 184 non-cardia gastric cancer patients, 123 cardia cancer patients, 211 esophageal cancer, Caucasian population	*(45)*
		Gastric cancer	Positive for genotype AG	174 gastric cancer patients, 208 chronic gastritis patients, 225 controls, Brazilian Caucasian	*(34)*
		Gastrointestinal cancer	Positive for allele G	9,463 patients, 10,825 controls	*(46)*
		Prostate cancer	Negative for genotype GG	9,463 patients, 10,825 controls	*(46)*
		Breast cancer	Positive for allele Gly	261 patient, 480 controls, Greece	*(36)*
		MALT lymphoma, Hodgkin's lymphoma	Positive for allele G	710 patients, 710 controls, Germany	*(47)*
rs4986791 (c.1196 C>T, Thr399Ile)	Exon 4 (LRR)	Gastrointestinal cancer	Positive for allele T	9,463 patients, 10,825 controls	*(46)*
		Nasopharyngeal carcinoma	Positive for allele T	236 patients, 287 controls, China	*(49)*
		Gallbladder cancer	Positive for allele T	230 patients, 230 controls, North India	*(48)*
11350 G>C	Exon 4 (3'UTR of *TLR4*)	Nasopharyngeal carcinoma	Positive for genotype GC	486 patients, 529 controls, China	*(50)*
rs1927911 (T>C)	Intron 1	Prostate cancer	Positive for allele C	157 patients, 143 controls, Korea	*(51)*
rs10759931 (G>A)	5' UTR	Prostate cancer	Positive for genotype GG	157 patients, 143 controls, Korea	*(51)*
rs10759932 (T>C)	5' UTR	Gastric cancer	Negative for allele C	1,053 patients, 1,100 controls, China	*(52)*
TLR5					
rs5744174 (c.1846 T>C, Phe616Leu)	Exon 6 (LRRCT)	Gastric cancer	Positive for allele C	248 gastric cancer patients, 846 gastric dysplasia and metaplasia patients, 496 controls with gastritis, China	*(33)*
TLR9					
rs5743836 (-1237 T>C)	5'UTR	Hodgkin's lymphoma	Positive for allele C	90 patients, 92 controls, Greece	*(54)*
rs187084 (-1486 T>C)	5'UTR	Cervical cancer	Positive for allele C	426 patients, 460 controls, Poland	*(55)*
rs352140 (2848 A>G, Pro545Pro)	Exon 2 (LRR)	Hodgkin's lymphoma	Positive for allele A	90 patients, 92 controls, Greece	*(54)*
rs352140 (2848 C>T, Pro545Pro)	Exon 2 (LRR)	Cervical cancer	Positive for genotypes CT and TT	426 patients, 460 controls, Poland	*(55)*

*Negative association: polymorphism is linked with decreased cancer risk (odds ratio (OR) < 1)
*Positive association: polymorphism is linked with increased cancer risk (OR > 1)
5'UTR: 5' untranslated region
3'UTR: 3' untranslated region
LRR: leucine rich repeats
LRRCT: leucine rich repeats C-terminal domain
HCV: hepatitis C virus
MALT: mucosa associated lymphoid tissue
'L' allele: 26 – 43 GT repeats in intron 2 of TLR2 (40)
'M' allele: 19 – 25 GT repeats (40)
'S' allele: < 18 GT repeats (40)

-TLR1-TLR6 gene cluster have been associated with lymphoma, meningioma and breast cancer risk. *TLR6* polymorphism rs5743815 (c.1280T>C, Val427Ala) was found to be associated with significantly increased non--Hodgkin's lymphoma risk *(27)*. A polymorphism close to *TLR10* gene, rs10008492 (C>T), was associated with significantly increased risk of non-Hodgkin's lymphoma, while polymorphism close to *TLR1* gene, rs4833103 (C>A), was associated with decreased risk of this tumor type development *(28)*. Both SNPs are in linkage disequilibrium with a *TLR1* polymorphism rs5743618 (c.1805G>T, Ser602Ile) which is known to affect ligand binding *(28)*. *TLR10* polymorphism rs11466657 (Ex3-1099T>C, reverse strand, Ile473Thr) was associated with decreased meningioma risk *(29)* and polymorphism between genes *TLR1* and *TLR6,* rs7696175 (C>T), with increased breast cancer risk in African American population *(30)*.

4.2. *TLR2* gene polymorphisms

4.2.1. *TLR2* -196 to -174 del polymorphism

TLR2 gene maps to 4q32 and TLR2 receptor binds lipoproteins, peptidoglycans and glycoproteins *(22)*. Special attention has been focused on *TLR2* -196 to -174 del (Δ22) functional polymorphism in 5' untranslated region known to reduce *TLR2* transcriptional activity. There have been several studies regarding impact of Δ22 polymorphism on gastric cancer development, but with contradictory results, especially in Japanese and Chinese populations *(31, 32, 33)*. Recently, Δ22 polymorphism was associated with increased gastric cancer risk in Brazilian population *(34)* and with higher hepatitis C viral load and was more frequent in hepatitis C associated hepatocellular carcinoma patients than controls in Germany *(35)*. Also, Δ22 polymorphism was found to be more frequent in breast cancer patients than in healthy controls in Greece *(36)*. It was also associated with increased prostate *(37)*, gallbladder *(38)* and cervical cancer risk *(39)* in India.

4.2.2. Other *TLR2* polymorphisms

Microsatellite GT number repeat polymorphism is located in intron 2 of *TLR2* gene. Middle (M) size 'allele' with 20 and 21 GT repeats is found to be associated with decreased colorectal cancer risk in Croatian population when compared with shorter (S) and larger (L) number of repeats *(40)*, suggesting possible impact of polymorphism on receptor transcriptional activity. Also, *TLR2* polymorphism rs3804100 (c.1350T>C, Ser450Ser) was associated with increased mucosa associated lymphoid tissue (MALT) lymphoma risk *(28)*, and together with rs3804099 (c.597T>C, Asn199Asn) with decreased hepatocellular carcinoma risk *(41)*, but not with breast cancer risk *(42)*.

4.3. *TLR3* gene polymorphisms

TLR3 maps to 4q35 and binds double stranded RNA *(22)*. There have been few reports of *TLR3* polymorphisms in cancer and mainly with no cancer risk association. Those which were proven to be associated include: (1) *TLR3* polymorphism 829A>C, associated with increased nasopharyngeal carcinoma risk in Chinese population *(43)*, and (2) *TLR3* polymorphism rs3775291 (c.1234 C>T, Leu412Phe) which was implicated as a negative prognostic factor for survival of stage II colorectal cancer patients *(44)*.

4.4. *TLR4* gene polymorphisms

TLR4 gene maps to 9q32-33 and TLR4 receptor binds lipopolysaccharide *(22)*. *TLR4* polymorphisms have been investigated in numerous studies and in various cancer types, with main focus on polymorphisms rs4986790 (c.896A>G, Asp299Gly) and rs4986791 (c.1196 C>T, Thr399Ile). Both polymorphisms lead to amino acid substitution in extracellular domain of the TLR4 receptor and are known to diminish response to lipopolysaccharide. Polymorphism Asp299Gly was found to be more frequent in colorectal cancer patients than healthy controls *(40)*. It was also later associated with increased non--cardia gastric cancer risk, but not with gastric cardia carcinoma or esophageal cancer *(45)*. Recently, association with increased gastric cancer risk was confirmed in Brazilian population *(34)* and meta analysis based on data from 22 studies confirmed association with increased gastrointestinal cancer risk, but with decreased prostate cancer risk *(46)*. Also, Asp299Gly was more frequent in breast cancer patients than healthy controls in Greece *(36)*. On the contrary, no such association was found in breast cancer patients from Croatian population *(42)*. Therefore it is still under the question whether this polymorphism could be used as a marker for breast cancer susceptibility. Polymorphism Asp299Gly was also associated with increased MALT lymphoma and Hodgkin's lymphoma risk *(47)*, but not with non-Hodgkin's lymphoma risk *(28)*. Interestingly, Asp299Gly was associated with improved survival in melanoma patients *(48)*. Polymorphism Thr399Ile was found to be associated with increased gastrointestinal cancer risk and increased overall cancer risk in recent meta analysis *(46)*, but there have also been reports of no association with gastric cancer *(34)*, possibly due to small sample size. Also, polymorphism Thr399Ile was associated with increased nasopharyngeal carcinoma risk in China *(49)* and increased gallbladder cancer risk in India *(38)*.

4.4.1. Other *TLR4* polymorphisms

There have been reports regarding several *TLR4* polymorphisms and cancer risk in China. *TLR4* polymorphism 11350G>C was associated with increased nasopharyngeal carcinoma risk *(50)*. rs1927911 (T>C) and rs10759931 (G>A) were associated with increased prostate cancer risk *(51)* and rs10759932 (T>C) with reduced gastric cancer risk *(52)*.

4.5. *TLR5* gene polymorphisms

TLR5 gene maps to 1q33.3 and TLR5 receptor binds flagellin *(22)*. TLR5 polymorphisms have mainly not been associated with cancer risk. However, *TLR5* polymorphism rs5744174 (c.1846T>C, Phe616Leu), which

affects ligand binding, was recently associated with increased gastric cancer risk in China, with especially high risk in patients infected with *H. pylori (33)*.

4.6. *TLR7* and *TLR8* gene polymorphisms

TLR7 and *TLR8* share a common locus on chromosome Xp22 and their receptors bind single stranded RNA *(22)*. So far polymorphisms in *TLR7* and *TLR8* have not been firmly associated with cancer risk.

4.7. *TLR9* gene polymorphisms

TLR9 gene maps to 3p21.3, and TLR9 receptor binds CpG rich bacterial DNA *(22)*. Recently, it was reported that TLR9 polymorphism Arg892Trp causes hyporesponsiveness to CpG oligodeoxynucleotides *(53)*. *TLR9* polymorphism rs5743836 (-1237T>C) was associated with significantly increased Hodgkin's lymphoma risk, as well as A allele of rs352140 (2848A>G, Pro545Pro) *(54)*. Recently, TLR9 rs187084 (-1486T>C) and rs352140 (2848C>T, Pro545Pro) polymorphisms were found to be associated with increased cervical cancer risk in Poland *(55)*.

5. CONCLUSION

Toll-like receptors have numerous important roles in innate and acquired immunity. Wide spectrum of their signaling pathways and downstream effectors makes them crucial in development of infective diseases, chronic inflammation and cancer. Polymorphisms in *TLR* genes can reduce receptor function, cause over excessive signaling or change the level of transcription, and therefore influence disease development and progression. Although there have been numerous studies regarding impact of polymorphisms on TLR function and disease development, there is a lot of controversial and yet uncertain data. Contradictory results in different studies may reflect insufficient sample size, ethnicity or age differences, infection with undetected pathogens or other environmental factors. The role of *TLR10-TLR1-TLR6* polymorphisms in prostate cancer is controversial and so far those polymorphisms cannot be firmly associated with prostate cancer risk.

Epstein-Bar virus (EBV) infection plays important role in development of non-Hodgkin's lymphoma as well as nasopharyngeal carcinoma. The association of polymorphisms in *TLR* genes with increased cancer risk has been shown in lymphoma (*TLR6* rs5743815) and nasopharyngeal carcinoma (*TLR3* 829A>C and *TLR4* rs4986791). This may affect virus recognition and immune response to pathogens leading to increased disease susceptibility.

Discrepancies regarding *TLR2* -196 to -174 del polymorphism and gastric cancer risk are similar to those in *TLR4* (rs4986790 and rs4986791). Both receptors are important in *H. pylori* infection, which has been implicated in gastric cancer development, and it is possible that they influence cancer development only in presence of *H. pylori* infection. Conflicting outcome may also result from different types of cancer investigated, only noncardia gastric cancer or all gastric cancer types. Despite somewhat contradictory results, *TLR2* -196 to -174 del polymorphism and *TLR4* rs4986790 and rs4986791 have been linked with various cancer types (gastric, hepatocellular, breast and prostate cancer) in various populations (Japanese, European, Indian) and their role in carcinogenesis and modulation of immune response to pathogens should be further investigated.

Little and less is known about effects of polymorphisms in *TLR3, TLR5, TLR7* and *TLR8* genes on cancer risk and development. *TLR3* polymorphism 829A>C has been implicated in nasopharyngeal carcinoma risk and *TLR5* polymorphism rs5744174 in gastric cancer risk, but possible impact of *TLR7* and *TLR8* polymorphisms on cancer risk still remains a mystery.

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