

# Polymorphisms in Toll-like Receptor Genes – Implications for Prostate Cancer Development

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## ABSTRACT

*Toll-like receptors are key players in initiation of innate immune response of the host. In addition to innate immunity they can also induce adaptive immune responses. The concept that inflammation can promote chronic prostatic diseases, such as benign prostatic hyperplasia or prostate carcinoma is supported by several new findings. Epidemiological data have correlated prostatitis with an increased risk of prostate cancer; while PCR-based analyses of bacterial colonization in prostate cancer specimens and normal prostate tissue showed high correlation of bacterial colonization and chronic inflammation with a diagnosis of prostate carcinoma. Even evidence from genetic studies support the hypothesis that prostate inflammation may be a cause of prostate cancer. From these points of view identification of factors, such as SNPs in TLR genes, associated with risk for prostate carcinoma development seems reasonable. Consequently, there are many investigations showing the connection between SNPs in TLR genes and pronounced susceptibility to different diseases. In this article we review the key findings about the genetic variability of TLR genes and prostate cancer risk.*

**Key words:** toll-like receptors, polymorphisms, prostate cancer

## Introduction

The prostate is a composite exocrine gland divided into four zones: anterior fibromuscular stroma, peripheral zone (PZ), central zone, and preprostatic tissue. The preprostatic tissue is the smallest, but most complex, prostate zone. Its main component is a cylindrical, smooth, muscular sphincter. Inside this muscles are tiny periurethral glands. The group of glandular ducts that »escape« the limit of the muscular cylinder and develops beyond it is called the transitional zone (TZ). This zone accounts for about 5% of the mass of glandular tissue in the normal prostate and is the most common site of benign prostatic hyperplasia (BPH). The peripheral zone is the most frequent site of most prostate carcinomas. The central zone is relatively insensitive to the appearance of tumors, but they occur there with a frequency of about 8%. Tumors also occur in the TZ, with a frequency of about 24%<sup>1</sup>.

Peripheral zone prostate cancer is the third most common cause of death from cancer in men of all ages. It is the most common noncutaneous cancer among U.S. men<sup>2</sup>. One in six men will be diagnosed with prostate cancer; one in 30 will die from the disease. It is rare in men younger than 40. In the USA, 230.110 men per year

will be diagnosed with prostate cancer; that is one man diagnosed every 3 minutes. Prostate cancer deaths in USA are estimated at 29.900 per year; that is one death every 18 minutes. The risk increases with age, but 25% of diagnoses are made under age 65. Natural history of prostate cancer is unknown. Prostate cancer treatment often depends on the stage of the cancer: how fast the cancer grows and how different it is from surrounding tissue helps determine the stage. Treatment may include surgery, radiation therapy, chemotherapy or control of hormones that affect the cancer.

Indolent tumors are indistinguishable from aggressive tumors that progress to cancer. The established risk factors are age, family history, race, and chronic inflammation and infection<sup>3</sup>. However, there is increasing body of evidence that inherited genetic variant may predispose to aggressive but not indolent prostate cancer, which, when combined with already mentioned risk factors, ultimately leads to prostate cancer development<sup>4</sup>.

The prostate cancers are biologically heterogeneous diseases. Some are very difficult to destroy and often become androgen independent<sup>5</sup>. An important factor in

prostate cancer is the invasiveness. Androgen-independent tumors are more aggressive, more likely to be chemo-resistant and have a higher risk of metastasis.

## Toll-like Receptors

Toll-like receptors (TLRs) are a group of evolutionary conserved family of pattern recognition receptors (PPRs) which recognize molecular motifs of microbial origin, known as pattern associated molecular patterns (PAMPs)<sup>6,7</sup>.

TLRs are type I membrane proteins characterized by three domains. The first is the ectodomain which is responsible for ligand binding. The cytoplasmic domain, known as TIR-domain, is responsible for downstream signaling. These two domains are connected by the trans-membrane region. To date 11 TLRs have been identified in humans. TLR1, 2, 4 and 6 recognize lipids and lipoproteins, TLR5 and 11 bind protein ligands and TLR3, 7, 8 and 9, that are located intracellularly and bind nucleic acids derived from bacteria and viruses<sup>8</sup>.

After ligation by specific ligands, TLRs initiate innate immune response through activation of three main transcription factors: interferon-regulatory factor (IRF3, IRF5 and IRF7), NF- $\kappa$ B and AP-1<sup>9–11</sup>. These transcription factors stimulate the transcription of inflammatory cytokines, chemokines and interferons (IFNs).

Several adaptor proteins are required for signaling after TLR activation. These include: myeloid differentiation factor 88 (MyD88) (with the exception of TLR3), MyD88 adaptor-like (Mal), TIR-related adaptor protein inducing interferon (TRIF) and Trif-related adaptor molecule (TRAM)<sup>12</sup>. TLR3 activates TIR domain-containing adaptor protein inducing interferon- $\beta$  (TRIF)-dependent pathway.

In addition to innate immunity they can also induce adaptive immune responses through the stimulation of immature dendritic cells (DCs) which can then migrate from peripheral tissues to lymph nodes where they provide naive T-cells with signals required for T-cell activation. TLRs are mainly expressed on the cells of lymphoid tissues, but nonlymphoid tissues also express considerable amounts of different TLRs where they play an essential role in recognizing pathogens and mediating inflammatory responses<sup>13–17</sup>.

However, there is accumulating evidence that TLRs are also expressed on the cells of a variety of human tumors and tumor cell lines<sup>18–20</sup>. The first evidence for the presence of functionally active TLRs on human tumor cells and their role in preneoplastic to neoplastic tissue progression was observed in gastric cancer<sup>21</sup>.

Soon after this finding, functionally active TLRs were found on a variety of different cancer tissues: TLR3, -4 and -9 on prostate cancer cells<sup>22,23</sup>.

## Genetic Polymorphisms

DNA sequence of all human beings is 99.9% identical. It differs by 0.1%. Does it make a difference? Yes. 0.1%

difference translates into 3 million separate »spelling« differences in a genome of 3 billion bases. This is called genetic polymorphism. Genetic polymorphisms are naturally occurring markers that identify regions of the genome and vary among the individuals – genetic polymorphism is any variant gene that occurs with a frequency of more than 1% in the normal population. There are many types of DNA polymorphisms, including restriction fragment length polymorphisms (RFLPs), variable number of tandem repeats (VNTRs), and single nucleotide polymorphisms (SNPs). The latter are alterations in DNA involving a single base pair. SNP's are the most simple form and most common source of genetic polymorphism in the human genome and therefore are often used in population studies in search of the connection between pathological changes and certain SNP. Their incidence is 1 per 300–600 bp. It is estimated that up to 10 millions SNPs are probably present in the human genome. There are several sorts of SNPs: missense, nonsense, silent, frameshift and splice site. SNPs located in the coding region can (but may not) influence the amino acid sequence in the protein. If the SNP is located in the promotor region of the gene it may influence the level of its expression<sup>24</sup>. Now that the human genome is almost entirely sequenced, attention is turning to the evaluation of variation. It is estimated that ~60,000 SNPs occur within exons. The consequences of polymorphisms are: changes in drug metabolism, drug transport, disease susceptibility, receptor sensitivity, adverse drug reaction and different response of patients to certain therapy.

TLRs are principal mediators of rapid microbial recognition resulting in acute host responses. Therefore it is reasonable to assume that the genetic polymorphisms of TLR genes could influence toll-like receptor mediated anti-pathogen response, as well as their function in tissue regeneration and/or selective anti cancer activity<sup>25,26</sup>. Consequently, there are many studies showing the connection between SNPs in TLR genes and pronounced susceptibility to different diseases<sup>27,28</sup>. For instance, an A-G substitution resulting in Asp299Gly change in TLR4, has a positive correlation with susceptibility to gram negative bacterial infections and sepsis, atherosclerosis, asthma, malaria and *Helicobacter pylori* induced gastric cancer<sup>29,30</sup>. Polymorphic variant in TLR2, which changes the amino acid sequence (Arg753Gln), has been reported to alter the susceptibility to the development of staphylococcal infections and tuberculosis. The polymorphism of nucleotide at the position 392 in TLR5 gene creates artificial stop codon resulting in increased susceptibility to infection caused by bacteria *Legionella pneumophila*<sup>25</sup>. Pirie and coworkers have connected polymorphic markers 2593C/T, 2642C/A and 2690A/G in a TLR3 gene with increased risk of diabetes Type I development in blacks from South Africa<sup>31</sup>, while Ranjith-Kumar and coworkers noticed possible connection between polymorphic marker L412F and asthma<sup>32</sup>.

The importance of TLRs for tumor immunity is evident in an increasing body of evidence that TLR-variants are associated with cancer risk. For instance, SNPs in the

TLR4 and TLR10 genes are connected with the higher risk of nasopharyngeal cancer development<sup>33,34</sup>, while 896A>G polymorphism in TLR4 gene increases the risk of gastric carcinoma development<sup>33</sup>. The possible cause of some subtypes of lymphoma is connected to the SNPs in TLR1, -2, -4, -5 and -9 genes<sup>35</sup>.

## Genetic Polymorphisms and Prostate Cancer

The concept that inflammation can promote chronic prostatic diseases, such as benign prostatic hyperplasia or prostate carcinoma, is supported by several new findings. Epidemiological data have correlated prostatitis with an increased risk of prostate cancer, while PCR-based analyses of bacterial colonization in prostate cancer specimens and normal prostate tissue showed high correlation of bacterial colonization and chronic inflammation with a diagnosis of PC<sup>36,37</sup>. Even evidence from genetic studies support the hypothesis that prostate inflammation may be a cause of prostate cancer. From these points of view, it is necessary to identify the factors, such as SNPs in TLR genes, which are associated with risk for prostate carcinoma development is needed.

The first observation of the connection between TLR genes polymorphisms and susceptibility to prostate cancer development came in 2004<sup>38</sup>. The authors performed a systematic genetic analysis of TLR4 sequence variants by evaluating eight SNPs that span the entire gene, in a large population-based prostate cancer (1383 newly diagnosed prostate cancer patients) case-control (780 controls) study in Sweden. They found an association between a sequence variant 11381 G/C in the 3'-untranslated region and prostate cancer risk. Carriers of the genotype variant CG or CC had increased risk of prostate cancer and earlier onset of the disease (before the age of 65 years) when compared with the controls (wild type genotype GG), as well as. Obviously, sequence variants in the genes that regulate inflammation may modify individual susceptibility to prostate cancer. However, in one latter, more extended study considering both, the number of tested individuals as well as number of SNP genotyped, SNP 11381G/C was not associated with risk of prostate cancer development. On the other hand, 8 SNP variants showed an inverse association with prostate cancer risk<sup>39</sup>. However, the association between six common haplotypes and prostate cancer was observed. The authors also found that the age modified the association between TLR4 SNPs and prostate cancer. Among men aged <65, carriers of certain SNPs had a lower risk of prostate cancer, indicating that TLR4 polymorphism had a greater influence among younger men. Similarly, Cheng et al. have shown that inherited variation in TLR4, 5'-UTR polymorphism – rs 10759932, but not the polymorphism 11381G/C, influences prostate cancer risk<sup>40</sup>.

Apart from TLR4, SNP sequence variants in the TLR6-TLR1-TLR10 gene cluster have also been shown to be connected with prostate cancer risk in Swedish popu-

lation. The authors found that eight SNPs and six haplotypes in the same gene cluster were associated with prostate cancer risk<sup>40,41</sup>. Contrary to this are the results of Chen et al.<sup>42</sup>. The authors assessed if genetic polymorphisms of TLR6-TLR1-TLR10 gene cluster were associated with the risk of prostate cancer in US population. However, neither individual SNPs nor common haplotypes in this gene region were associated with altered risk of prostate cancer. Thus, these two studies yielded inconsistent results. In an attempt to clarify whether these opposite results reflect differences in ethnic homogeneity of tested populations (Swedish – more homogeneous than US population) Stevens et al. performed more expanded study in which they enrolled 1414 men diagnosed with prostate cancer and the same number of healthy matched control men. They genotyped 28 SNPs in the region of chromosome 4p14 that include the genes for TLR6-TLR1-TLR10. Two SNPs in TLR10 and four SNPs in TLR1 were associated with reduced risk of prostate cancer. Haplotype analysis and linkage disequilibrium findings revealed their mutual dependency which shows that they represent a single association with reduced prostate cancer risk<sup>43</sup>.

Of special interest is searching for the variants of the broader spectrum of genes involved in inflammation, including those connected to the Toll-like receptor signaling pathways. Namely, detection of such variants in different groups of patients, including cancer patients, might help to estimate the predisposition for the development of different diseases and for the estimation of the patient's response to immunotherapy. One such study was done by Sun et al.<sup>44</sup>. Interleukin – receptor-associated kinases (IRAK) 1 and 4 are critical components in the TLR signaling pathway. In a large case-control study the authors tested whether SNP sequence variants in IRAK1 and -4 genes are associated with prostate cancer risk, and whether there is a correlation between IRAK and TLR1-6-10 gene sequence variants. IRAK SNP polymorphisms did not correlate with prostate cancer risk. However, one SNP in IRAK4 when combined with the high risk genotype of TLR1-6-10, conferred a significant excess risk of prostate cancer, suggesting synergistic effect between these two gene variants. Additionally, the potential role of common SNPs of a gene cluster TLR4, TLR2, PTGS2 and 5-Lo, involved in innate and inflammatory response was investigated, in prostate cancer cases, age-matched controls and centenarians from Sicily. Statistical analysis evidenced a significant association of certain SNPs in pro-inflammatory genes with an increased risk of prostate cancer<sup>45</sup>.

It is also important to mention the enormous work done by Stark et al.<sup>46</sup>. The authors quantified the effects of 99 different SNPs and haplotypes in 20 genes involved in TLR signaling on specific prostate carcinoma mortality. This research was conducted on 1.252 prostate carcinoma patients. Ten TLR genes (TLR1, -2, -3, -4, -5, -6, -7, -8, -9 and -10) and 10 genes involved in TLR signal transduction or in final TLR physiological impact (COX-2, IL-1RN, IL-6, IL-10, IRAK1, IRAK4, MIC-1, MyD88,

TIRAP, TNF- $\alpha$ ) were analyzed. However, prostate carcinoma mortality was not significantly associated neither with haplotypes nor with specific SNP's.

The inconsistent results regarding both, genetic variants in Toll-like receptor genes as well as in the genes included in Toll-like receptor signaling pathway, clearly support the need for further investigations. Prostate cancer is a biologically heterogeneous disease, without reliable prognostic factors, such as relationship between

genetic and phenotypic profile. Therefore it is for the time being impossible to predict tumor behavior in a sense of their progression and spread.

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## **POLIMORFIZMI GENA ZA TOLL-LIKE RECEPTORE – UTJECAJ NA RAZVITAK KARCINOMA PROSTATE**

### **S A Ž E T A K**

Toll-like receptori su ključni za pokretanje prirođenog imunološkog odgovora domaćina. Pokreću i stečeni imunološki odgovor. Ideja da upala može uzrokovati kronične bolesti prostate, kao što je dobroćudna hiperplazija, ali i razvitak karcinoma, ima sve više potvrda. Tako su npr. rezultati epidemioloških studija pokazali povezanost prostatitisa i povećanog rizika razvitka karcinoma prostate; genske su analize pokazale povezanost kolonizacije bakterija u uzorcima normalnog tkiva prostate i tkiva karcinoma prostate i kronične upale. I analize gena čiji su proteinski produkti uključeni u pokretanje i provođenje imunološkog odgovora potkrepljuju hipotezu da i kronična upala, između ostalog, doprinosi razvitku karcinoma prostate. S obzirom na ove činjenice pronalazak čimbenik (kao što su npr. SNP-ovi u genima za TLR) povezanih s rizikom razvitka karcinoma prostate se čini opravdanom. Shodno tome već postoji niz istraživanja koja pokazuju povezanost između SNP-ova u genima za TLR i povećane podložnosti razvitka različitih bolesti. U ovom članku opisani su ključni nalazi o genskoj varijabilnosti gena za TLR i rizika razvitka tumora prostate.