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Pattern Recognition Receptors and Cancer: Is There Any Role of Inherited Variation?

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1. Introduction

1.1 What are pattern recognition receptors?

The group of the pattern recognition receptors (PRRs) includes families of Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs) and RIG-I-like receptors (RLRs). The summary of the most modern conceptual data about members of these families and about their structure and functions can be obtained from the recent comprehensive reviews (Elinav et al., 2011; Kawai and Akira, 2011; Osorio and Reis E Sousa, 2011; Loo and Gale, 2011), and the schemes of their signaling are presented in Figures 1-2.
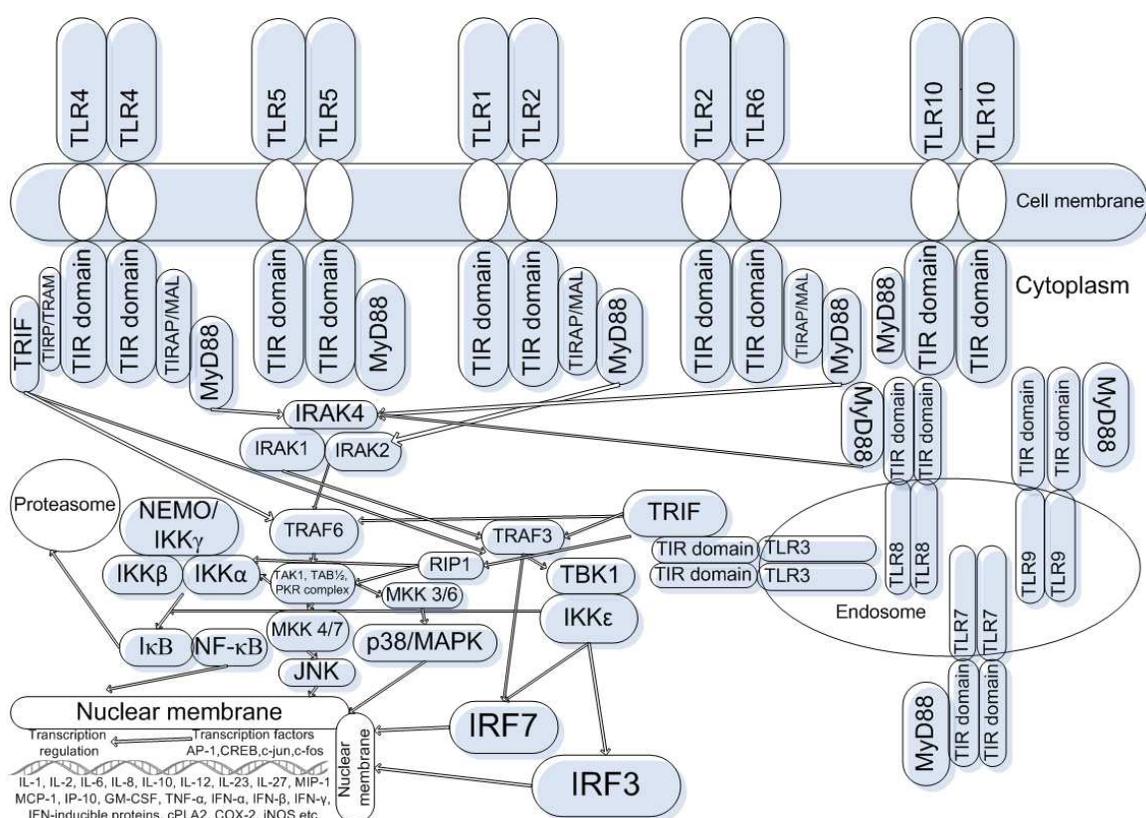

Fig. 1. The signaling of the Toll-like receptor pathway. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are usually located on the cell surface whilst TLR3, TLR7, TLR8 and TLR9 are settled

on the ER membrane (in the resting state) or on the endosomal/lysosomal membrane (after ligand stimulation and trafficking). According to the known data about their structure (Hashimoto et al., 1988), TLRs belong to type I transmembrane glycoproteins and contain three major domains (Matsushima et al., 2007). The ectodomain is oriented towards the extracellular space or cytoplasm (depending on receptor localization) and contains multiple (16-28) leucine-rich repeats (LRRs) that harbor 24–29 amino acids and may contain two types of motifs: typical (T) motifs (LxxLxLxxNxLxxLxxxxF/LxxLxx) and bacterial (S) motifs (LxxLxLxxNxLxxLPx(x)LPxx) (Bell et al., 2003; Matsushima et al., 2007). LRR modules fold into the parallel β-sheets that bend into a concave surface, forming one or two distinct horseshoe structures determining the unique horseshoe shape of TLRs (Matsushima et al., 2007). LRR hydrophobic residues are packed within the interior of ectodomain structure, forming a ligand-binding hydrophobic pocket (Bell et al., 2003, 2006; Kim et al., 2007; Liu et al., 2008). In addition, C-terminal LRRs may control the receptor dimerization and the signal transmission (Takada et al., 2008). The single-spanning transmembrane domain is homologous to IL-1R analog and anchors the receptor in the correct orientation on cell membrane (Huyton et al., 2007; Medzhitov et al., 1997). Third, the cytoplasmic TLR domain (toll/interleukin-1 receptor domain, TIR domain) is usually composed of approximately 150 amino acid residues (Jin and Lee, 2008) and dimerizes after the ligand-ectodomain interaction (TLR ligands are presented in Table 1) and respective alterations in the receptor conformation, triggering the recruitment of the adaptor proteins (MyD88, TIRAP/MAL, TRIF, TRAM, SARM) to initiate the specific signaling pathway of the immune response stimulation (Jin and Lee, 2008; O'Neill and Bowie, 2007). It is important that all TLRs form hetero- or homodimers, and this feature may facilitate the dimerization of the cytoplasmic domain. All adaptors indicated above contain TIR domains, and interactions between such domains of receptor and adaptor are key for the successful signaling (Palsson-McDermott and O'Neill, 2007). The process of TLR signaling is mediated by a number of other adaptor proteins and, finally, leads to activation of NF-κB (Yamamoto et al., 2004), MAPK (Yamamoto et al., 2004), JNK (Takeuchi and Akira, 2001), IRF1, IRF3, IRF5, IRF7 and IRF8 (Honda and Taniguchi, 2006) that move into the nucleus and directly or indirectly control the transcriptional activity of the genes encoding various proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-13, IL-23, IL-27, MIP-1, MCP-1, RANTES, SOCS, IP-10, GM-CSF, TNF-α, IFN-α, IFN-β, IFN-γ and IFN-inducible proteins (Chang, 2010; Wong et al., 2011; Zhu and Mohan, 2010).

Member of TLR family	Exogenous ligand	Endogenous ligand
TLR1 (form heterodimers with TLR2)	Triacylated lipopeptides	β-defensin 3
	Lipoarabinomannan	
	Soluble factors of *Neisseria meningitidis* cell wall	
	OspA protein of *Borrelia burgdorferi*	
TLR2	Lipoprotein	HSP22
	Peptidoglycan	HSP60
	Di- and triacylated lipopeptides	HSP70
	Lipoteichoic acid	HSP72
	Zymosan	gp96
	Lipoarabinomannan	HMGB1
	Outer-membrane porins of N.gonorrhoeae and S.dysenteriae	β-defensin 3

	OspA protein of *Borrelia burgdorferi*	Surfactant proteins A and D
	Phenol-soluble modulin of Staphylococcus epidermidis	Eosinophil-derived neurotoxin
	Cell membrane glycolipids of *Trypanosoma cruzi*	Antiphospholipid antibodies
	Hemagglutinin protein of wild-type measles virus	Serum amyloid A
	Envelope proteins of HSV-1 and CMV	Biglycan
	Atypical LPS of *L.interrogans* and *P.gingivalis*	Versican
		Hyaluronic acid fragments
TLR3	dsRNA	mRNA
	Polyinosine-polycytidylic acid	
TLR4	Lipopolysaccharide	HMGB1
	Glucuronoxylomannan	Tenascin-C
	RSV fusion protein	HSP60
	MMTV and MMLV	HSP70
	Taxol	gp96
		Mrp8 and Mrp14
		Neutrophil elastase
		Antiphospholipid antibodies
		Lactoferrin
		Surfactant proteins A and D
		β-defensin-2
		Biglycan
		Low-molecular-weight oligosaccharide fragments of hyaluronan
		Fibrinogen
		Fibronectin
		Heparansulfate
		Oxidized LDL
		Saturated fatty acids
TLR5	Flagellin	
TLR6 (form heterodimers with TLR2)	Diacylated lipoprotein	
	Peptidoglycan	
	Zymosan	
TLR7	Imidazoquinolines	Antiphospholipid antibodies
	ssRNA	ssRNA
TLR8	ssRNA	ssRNA
		Antiphospholipid antibodies
TLR9	Bacterial and viral CpG DNA	IgG-chromatin complexes
	Hemozoin	
TLR10 (may form heterodimers with TLR1 and TLR2)	Unknown	Unknown

Table 1. Ligands of TLRs. Abbreviations: TLR – Toll-like receptor, HSP – heat shock protein, gp – glycoprotein, HSV – herpes simplex virus, CMV – cytomegalovirus, LPS – lipopolysaccharide, dsRNA – double-stranded RNA, HMGB1 - high mobility group box 1, RSV – respiratory syncytial virus, MMTV – mouse mammary tumor virus, MMLV – Moloney murine leukemia virus, Mrp – myeloid related protein.
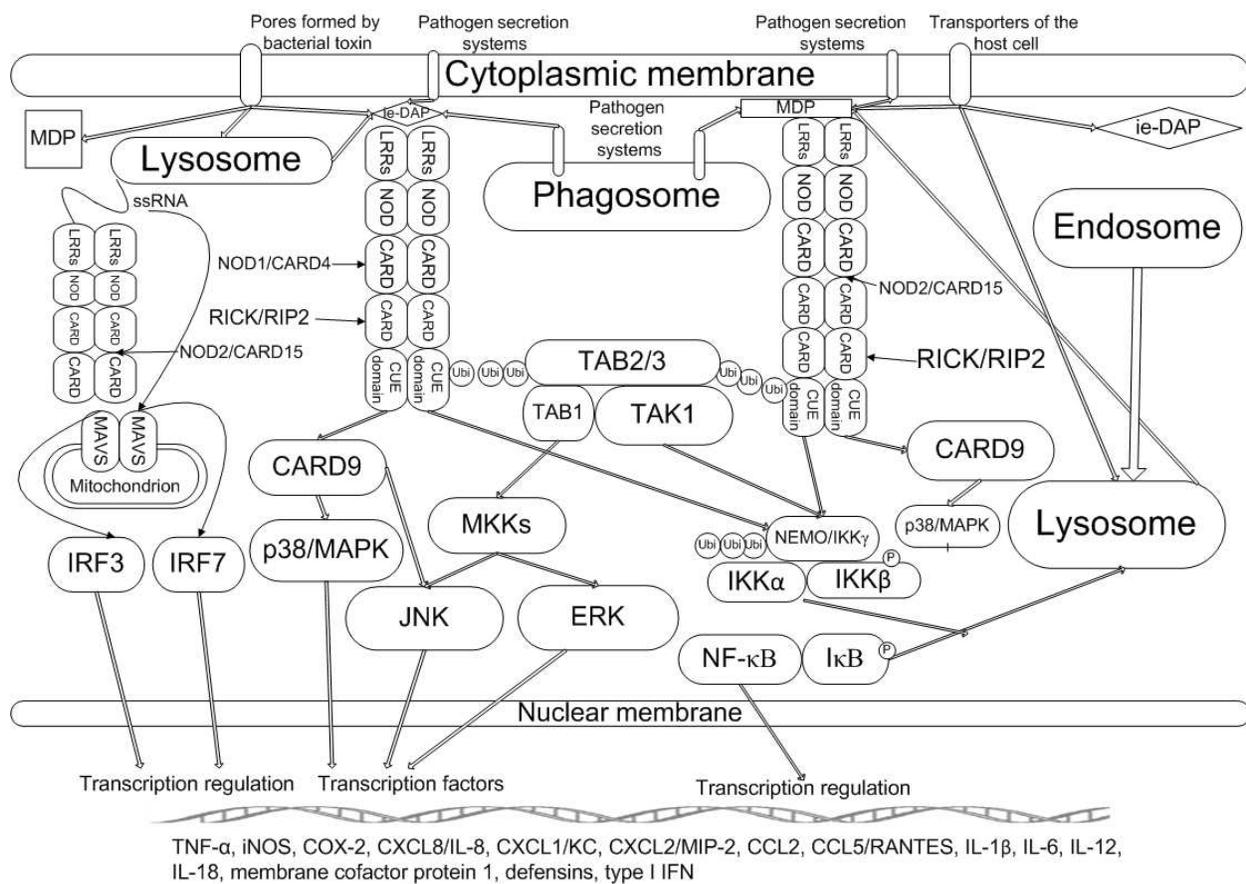
Fig. 2. The signaling of the NOD-like receptor pathway. NLRs usually have three-domain structure (Chen et al., 2009). First, the C-terminal domain, contains multiple leucine-rich repeats (LRRs), directly recognizing exogenous and endogenous ligands (Kumar et al., 2009). The second, central, nucleotide-binding oligomerization domain (NOD) has intrinsic ATPase activity and is responsible for the self-oligomerization and the formation of a complex after the ligand binding for the activation and recruitment of downstream signaling proteins (Kumar et al., 2009). These two domains are common for all known NLRs (Chen et al., 2009). Third, variable, the N-terminal protein-protein interaction domain, may represent a caspase recruitment domain (CARD), death effector domain (DED), pyrin domain (PYD), acidic transactivating domain, or baculovirus inhibitor of apoptosis protein repeat domain (BIR domain) (Kanneganti et al., 2007). The most investigated of NLRs are NOD1/CARD4 and NOD2/CARD15. Both NOD1/CARD4 and NOD2/CARD15 recognize the components of bacteria cell wall: ligands of NOD1/CARD4 are γ-D-glutamyl-m-diaminopimelic acid (iE-DAP) and its synthetic derivatives (particularly having hydrophobic acyl residues) (Chamaillard et al., 2003; Girardin et al., 2003), and the ligand of NOD2/CARD15 is muramyl dipeptide (MDP) (Girardin et al., 2003). These compounds are the components of peptidoglycan (PGN). They can enter the cytosol through the pores formed as a result of bacterial toxin exposure (Ratner et al., 2007), via action of the pathogen secretion systems (Ratner et al., 2007), by endocytosis (Marina-Garcia et al., 2008) or by work of transporters (Ismair et al., 2006), and they can be released in the cytosol of infected cells during a bacterial cell division or from lysosomes where PGN of phagocytosed bacteria is degraded (Shaw et al., 2010). Until the ligand binding, LRR-containing C-terminal domain of NOD1/CARD4 and NOD2/CARD15 prevents the activation of the central domain (NOD)

and its further oligomerization (Faustin et al., 2007); ligand binding causes the conformational alterations in the C-terminal region that, in turn, lead to self-oligomerization of the central domain and to the further activation of N-terminal domain (CARD) that recruits and activates specific adaptor proteins, initiating NOD signaling pathways. Such initiation results in the activation of various transcription factors and, consequently, in the production of proinflammatory mediators (Inohara et al., 1999; Ogura et al., 2001).

Although CLRs and RLRs are investigated relatively less than TLRs and NLRs, it is known that they recognize bacterial, viral, fungal, protozoan, and helminth PAMPs as TLRs and NLRs (Table 2), initiating an immune response against them through their specific signaling pathways (as their structure is not so clear as in the case with signaling pathways of TLRs and NLRs, it will be precisely depicted only in the following years). It is crucially important to note that in many steps signaling pathways of all classes of PRRs may intersect, making possible the crosstalk between them.

Receptor	Ligand
MRC1 (CD206, CLEC13D, mannose receptor)	High mannose, fucose
CD207 (CLEC4K, langerin)	Mannose, fucose, N-acetyl-glucosamine, β-glucan
CD209 (CLEC4L, DC-SIGN)	High mannose, fucose
CLEC7A (Dectin-1)	β-1, 3 glucans
CLEC6A (CLEC4N, Dectin-2)	High mannose, α-mannans
CLEC4E (Mincle)	α-mannose, glycolipids, SAP130
CLEC4A (DCIR)	Mannose, fucose
CLEC4C (BDCA-2, CD303)	Mannose, fucose
RIG-I	Nucleic acids of many viruses
MDA5	Nucleic acids of many viruses

Table 2. The ligands of CLRs and RLRs.

The receptors constituting families of PRRs are united by two general features. Firstly, they directly recognize common antigen determinants of virtually all classes of pathogens (so-called pathogen-associated molecular patterns, or simply PAMPs) and initiate immune response against them via specific intracellular signaling pathways. Secondly, they recognize endogenous ligands (since they are usually released during cell stress, they are called damage-associated molecular patterns, DAMPs), and, consequently, PRR-mediated immune response can be activated without influence of infectious agents. Therefore, PRRs may also initiate the development of aseptic inflammation caused by physical factors such as mechanical pressure, thermal damage, ionizing and non-ionizing radiation, or chemical factors (for instance, acidic damage, alkaline damage, exposure to chemical war gases, croton oil or turpentine, exposure to allergens, liberation of toxic substances during tumor disintegration, aseptic necrosis, internal bleeding, haemolysis,

autoimmune processes etc.). It may promote the further progression of inflammation or, on the contrary, prevent the hazardous infectious complications (the combination of these two effects may also be true). The final outcome of PRR working is an enhanced production of the many proinflammatory cytokines participating in a plenty of immune system processes. Expression of PRRs on different levels (transcriptomic or proteomic) was detected in a lot of cells and organs, so it gave an evidence that these receptors control many elements of the complex machinery of human immune system: they allow epithelium and endothelium to defend against infectious agents on their own, they mediate the activation of adaptive immune response by antigen-presenting cells and T-helpers, they stimulate expression of cell adhesion molecules for leukocyte rolling and for other processes of inflammation development, and, finally, they contribute to phagocytosis efficacy (Chang, 2010). As a consequence of all written above, pattern recognition receptors play the key role in realization of innate and adaptive immune response. In addition, many PRRs have a number of other vital functions apart from participation in the immune response realization: they may regulate various aspects of cell proliferation, survival, apoptosis, autophagy, reactive oxygen species generation, pyroptosis, angiogenesis and, consequently, of tissue remodeling and repair (Brown et al., 2007; Fukata et al., 2006; Kim et al., 2007; Rakoff-Nahoum and Medzhitov, 2008).

The fundamental character and diversity of PRR functions have led to amazingly rapid research in this field, and such investigations are very perspective for medicine as immune system plays a key role in vast majority if not all human diseases, and the process of discovering new aspects of the immune system functioning is rapidly ongoing. There is a plethora of papers analyzing the significance of PRRs in various diseases. One of the most actively exploring fields in PRR biology is their role in cancer aetiopathogenesis. Not surprisingly, it is (as well as tumor immunology in general) a hot spot in cancer biology as well.

1.2 The position of pattern recognition receptors in cancer biology

Since PRRs mediate immune response inducing by many immunoadjuvants (Okamoto and Sato, 2003; Seya, 2003), and many of them regulate immune response against potentially carcinogenic infectious agents (*Helicobacter pylori*, EBV, HPV, HHV-8/KSHV, CMV, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, enteropathogenic *Escherichia coli*, *Shigella flexneri*, *Salmonella typhimurium*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Campylobacter jejuni*, *Candida spp.*, *Schistosoma mansoni*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum* etc.), it seems to be possible to stimulate anti-tumor immunity through their enhanced activation. This hypothesis, originally developed for the TLRs, should be also true for the all PRRs as well (Killeen and Wang, 2006; Tsan, 2006). According to this suggestion, a reinforced PRR activation may protect from infectious agents and prevent, inhibit, or block carcinogenesis whilst disrupted functioning of these PRRs may allow infectious agents or tumor cells to avoid recognition by immune system and, consequently, not to be eliminated. At the same time, such PRR activation may promote carcinogenesis, creating a proinflammatory microenvironment (via action of respective cytokines) that is favorable for the tumor progression and chemoresistance development (Chen, 2007). It may also result in immunosuppression caused by chronic inflammation (Tsan, 2006). Chronic inflammation may promote the development of cervical, endometrial, ovarian, breast, prostate, testicular, nasopharyngeal,

lung, esophageal, gastric, colorectal, liver, pancreatic, gallbladder, kidney, bladder, lymphatic malignancies, and feasibly several other cancer types (Kinlen, 2004; Okamoto and Sato, 2003). In this case, on the contrary, lower PRR activity should minimize the effects of chronic inflammation such as enhancement of cancer initiation and promotion/progression and, consequently, decrease the probability of tumor development. So, the situation resembles a double-edged sword. The ideal variant, possibly, is the «golden mean» - the balance between low and high PRR activity. This hypothesis, developed for PRRs, may also be successfully projected on PRR intracellular signaling pathways – if their elements are overexpressed/constantly activated, it may lead to similar consequences as enhanced PRR activation. On the other hand, if the members of PRR pathways are underexpressed/inactivated/unable to do their work at the right time in the right place, it may result in the same effects that arise after decreased PRR activity, and the analogical «golden mean» in functioning of all genes encoding proteins constituting PRR signaling pathways will be the optimal variant.

1.3 Structural genomic variation and its relevance to cancer

The novel approaches in healthcare move towards the model of "personalized medicine". Advances in the healthcare service grow annually as well as their social relevance. Diagnostic tests and target therapy have become a part of our life. However, in spite of the neoteric improvements of the screening and treatment modalities, the prognosis of patients with many diseases including cancer remains poor. Thus, modern molecular biology and medicine are concerned on the developing of more and more new genomic markers that possess predictive, therapeutic, or prognostic significance. Several markers may evaluate predisposition of any person to one or another disease with a certain degree of accuracy based on the results of a simple blood test. The widespread application of these tests can reveal the risk groups in populations, and thereafter, the complex of preventive measures among the risk group subjects may be conducted. Moreover, above-mentioned genomic markers can be identified in the perinatal period, so the choice between "include" or "not to include" in the risk group on their basis can be made maximally early, and, consequently, the preventive measures can have the greatest efficacy. As a result, the integrative systems of predictive genomic markers, defined once, will allow to create the programs of cancer prevention based on them and will permit next generations to be informed and forewarned about their risks and predispositions to certain diseases.

Thereby, the discovery and development of predictive, therapeutic, or prognostic markers is the primary problem of biomedicine at the present time. However, the critical barrier for progress in this field is that it is not always easy to find an effective genomic marker that is exactly associated with a particular disease. One of the most widespread and important markers is the type of genomic markers called single nucleotide polymorphisms (SNPs). They represent a variation in the DNA sequence, when a single nucleotide differs between members of a biological species or paired chromosomes in an individual. The finishing of Human Genome Project and the widespread distribution of genotyping technologies have led to the enormous number of studies devoted to the association of the inherited gene polymorphisms with various diseases. The SNPs may result in amino acid substitutions altering protein function or splicing, and they can also change structure of enhancer sequences during splicing (Lamba et al., 2003) or affect mRNA stability (Tierney and Medcalf, 2001). SNPs may also alter transcription factor binding motifs, changing the

efficacy of enhancer or repressor elements (Thomas et al., 2006), and they can alter the structure of translation initiation codons that may lead to the downregulation of wild-type transcript (Zysow et al., 1995). Gene polymorphisms located in the leucine-rich repeats constituting ectodomain of PRRs may affect the ability of receptor to bind pathogens they normally recognize (Bell et al., 2003), SNPs in the transmembrane domain can lead to the defects of the intracellular receptor transport that do not allow to locate a receptor on the membrane (Johnson et al., 2007), and, finally, the polymorphisms in the internal domain may result in the altered interaction with the adaptor proteins or in the disrupted dimerization. So, inherited SNPs of the genes encoding PRRs may alter PRR expression and activity, modulating cancer risk and, possibly, influencing on various features of the cancer progression. The same statement should be true for the genes encoding proteins of PRR signaling pathways.

On the basis of the fundamental and epidemiological studies, it is possible to specify the two fundamental mechanisms for the modulation of cancer risk by the polymorphisms of the genes encoding PRRs and proteins of PRR pathways. The first of them is the impairment of the immune response to the certain pathogens (it can be bacteria, viruses, fungi, protozoan, and helminths) that increase the risk of the potentially carcinogenic infection and promote its development along with further chronic persistence. The second mechanism is an increase of production of proinflammatory cytokines after the binding of the ligand (exogenous or endogenous) that create a condition of carcinogenic chronic inflammation.

2. How to connect structural genomic variation in pattern recognition receptors and cancer?

2.1 Relevant malignancies: the first dimension of investigation

There is a variety of cancer types that can be associated with the inherited alterations in the genes encoding PRRs and proteins of PRR signaling pathways:

- Oral cancer (the alteration of the immune response to *Candida spp.* and other infectious agents colonizing oral cavity);
- Esophageal cancer (the variation of immune response to pathogens infecting esophagus);
- Gastric cancer (on the basis of modulation of the immune response to *Helicobacter pylori*, EBV and other infectious agents potentially causing this disease);
- Cancer of the small bowel (the modulation of the immune response to *Campylobacter jejuni*);
- Colorectal cancer (the alteration of the immune response to many infectious agents inhabiting colon and rectum);
- Liver cancer (the variation of the immune response to HBV, HCV, *Helicobacter hepaticus*, or liver flukes);
- Gallbladder cancer (the modulation of the immune response to infectious agents finding in bile);
- Pancreatic cancer (the alteration of the immune response to the pathogens inhabiting the pancreas);
- Endometrial cancer (the modification of the immune response to several kinds of infectious agents colonizing endometrium);

- Cervical cancer (the alteration of the immune response to HPV and some infectious agents colonizing cervix);
- Ovarian cancer (the variation of immune response to *Chlamydia trachomatis*);
- breast cancer (the modulation of the immune response to some viruses infecting breast including HPV and EBV)
- Prostate cancer (the variation of the immune response to *Propionibacterium acnes* and other uncertain pathogens finding in prostate tissue);
- Testicular cancer (the modification of the immune response to EBV);
- Kidney cancer (the variation of the immune response to bacteria and viruses infecting kidneys);
- Bladder cancer (the modulation of the immune response to certain viruses or *Schistosoma spp.*);
- Nasopharyngeal carcinoma (the alteration of the immune response to EBV);
- Lung cancer (the variation of the immune response to *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, and, possibly, to other infectious agents causing chronic inflammatory lung diseases);
- Lymphoma (the modification of the immune response to EBV and many other infectious agents such as *Borrelia burgdorferi* or *Helicobacter pylori*);
- Kaposi sarcoma (the variation of the immune response to HHV-8/KSHV-infection);
- Brain tumors (the alteration of the immune response to CMV and other viruses).

2.2 Selection of valuable polymorphisms: the second dimension of investigation

It is important to remember that there are two main components determining the importance of the SNP in the programs of cancer prevention based on genomic risk markers: the value of odds ratio (OR) between cases and controls (as in the whole population as in subgroups) and the prevalence of the polymorphism in population, and they both may vary in different geographic regions. It is desirable to develop not the one general program, but a number of the individual programs for the different countries/populations/environmental conditions. At the moment, it is possible only to recommend a list of polymorphisms for the further investigation since only small number of studies with perfect design was carried out. The list of relevant polymorphisms that can be admitted as the most perspective for the further oncogenomic investigations may be created according to the following rules:

Gene polymorphism may be included into the short list for the further oncogenomic studies if:

- The SNP leads to the substantial functional consequences on the molecular level (for instance, it strongly affects transcription, splicing, translation, stability and transport of pre-mRNA, mRNA, non-coding RNA or protein encoding by the gene, or it noticeably influences signaling of synthesized protein);
- It is associated with risk of cancer in the population studies;
- It has any functional consequences on the molecular level and it is strongly (threshold OR value may be individual for each cancer type) associated with condition that significantly increases risk of cancer.
- The gene polymorphism can be also included into the extended list if:
- It is characterized by more subtle functional alterations in the gene that, however, still result in qualitative or quantitative alterations of the encoding protein (or non-coding RNA);

- It is associated only with condition that substantially increases risk of cancer but not with risk of cancer.

One question may immediately arise: how to distinguish «substantial» and «more subtle» functional changes on the molecular level? It seems to be difficult to answer only on the basis of general principles of molecular biology since for one gene even the smallest alteration in its structure may lead to critical consequences, for another one converse statement can be true, and the effect also greatly depends on the position of the polymorphism. Therefore, an assessment of power of functional alteration should be individual for each gene, and although conclusions obtained in various investigations may differ, these discrepancies would not distort the general picture: if the polymorphism has «serious» functional consequences according to the results of one research, it definitely should be added into the short list until these conclusions will not be subverted. In any case, the general value of creation of such short and extended lists of the prescriptive polymorphisms seems to overcome difficulties related to these complications. It is important that many polymorphisms can be simply in the linkage disequilibrium with truly functional variants, and fundamental investigations are needed to determine are they only markers of association or indeed causal variants. All polymorphisms that are only in the linkage disequilibrium with functional ones should be excluded from both lists.

In concordance with this conception, the following SNPs of the genes encoding PRRs and proteins of PRR signaling pathways may be accepted as the most valuable for the further oncogenomic investigations on the basis of the analysis of relevant published literature (Table 3):

Gene	Polymorphism
TLR1-TLR6-TLR10 gene cluster:	rs10008492, rs4833103, rs5743815, rs11466657
TLR2	rs3804100, rs4696480, -196 - -174 del (Delta22), GT-microsatellite polymorphism
TLR4	rs4986790, rs4986791, rs16906079, rs11536891, rs7873784, rs1927911, rs10759932, rs10116253, rs11536889, rs11536858
TLR9	rs5743836, rs352140
TIRAP/MAL	rs8177400, rs8177399, rs8177374, rs7932766
MyD88	rs1319438, rs199396
IRAK1	rs1059703, rs3027898, rs10127175
TRAF3	rs7143468, rs12147254, rs11160707
TRAF6	rs331455, rs331457
TOLLIP	rs5743867
IRF3	rs7251
IRF5	rs2004640, rs2280714, rs10954213, 5 bp indel (CGGGG) polymorphism
NOD1	rs2075820, ND(1)+32656
NOD2	rs2066842, rs2066844, rs2066845, rs2006847
MRC1	rs1926736, rs2478577, rs2437257, rs691005
CD209	rs2287886, rs735239, rs735240, rs4804803
CLEC7A	rs16910526
RIG-I	rs36055726, rs11795404, rs10813831

Table 3. The short list of polymorphisms of the genes encoding PRRs and proteins of their signaling pathways promising for the further oncogenomic studies.

The following polymorphisms of the genes encoding PRRs and proteins of PRR signaling pathways may be added into the extended list for the further oncogenomic investigations (Table 4):

Gene	Polymorphism
TLR1-TLR6-TLR10 gene cluster:	rs4833095, rs5743551, rs5743618, rs4129009
TLR2	rs5743704, rs62323857, rs1219178642
TLR3	rs5743305, rs3775291, rs121434431, rs5743316
TLR4	rs1927914, rs2149356
TLR5	rs5744168
TLR7	rs179008
TLR8	rs3764880, rs2407992
TLR9	rs352139, rs187084, rs41308230, rs5743844
TIRAP/MAL	rs7932976, rs595209, rs8177375
MyD88	rs156265, rs7744
IRAK1	rs1059702, rs7061789, rs2239673, rs763737, rs3027907, rs5945174
IRAK3	rs1732886, rs1732888, rs10506481, rs1624395, rs1370128
IRAK4	rs1461567, rs4251513, rs425155
TRAF1	rs6920220, rs10818488, rs3761847, rs7021206
TRAF2	rs7852970
TRAF6	rs540386
TOLLIP	rs5743854
IRF1	rs11242115, rs839, rs9282763
IRF3	rs2304204, rs2304206
IRF5	rs4728142, rs41298401, rs13242262, rs10488631, rs729302, rs3807306
IRF7	rs1131665
IRF8	rs17824933
NOD1	rs72551113, rs72551107, rs6958571, rs2907749, rs2907748, rs2075822, rs2075819, rs2075818
NOD2	rs104895493, rs104895476, rs104895475, rs104895474, rs104895473, rs104895472, rs104895462, rs104895461, rs104895460, rs104895438, rs5743291, rs5743260, rs2076756, rs2066843, Pro371Thr, Ala794Pro, Gln908His
MRC1	rs692527, rs2477664, rs691005, rs2253120, rs2477637
CD209	rs735240
RIG-I	rs3824456, rs669260
MAVS/VISA/IPS-1	rs11905552, rs17857295, rs2326369, rs7269320

Table 4. The extended list of the polymorphisms of the genes encoding PRRs and proteins of their signaling pathways promising for the further oncogenomic studies.

2.3 How to organize the study: the third dimension of investigation

The drawing-up of a rigorous study protocol is the crucial moment in the molecular epidemiology, and in some cases the complexity of the research is considerable. Even if

the investigation has a valuable aim, sufficient funding and is carried out in an excellent laboratory, errors in the study design may lead to the misrepresentation of the research results and, hence, to the reduction of their usefulness. All moments that can distort the study accuracy should be taken into account, and certain, the most relevant of them, are discussed below. Obviously, the methods of the sample collection, DNA extraction, and PCR conduction should be reliable enough. Modern methods such as automated DNA extraction, real-time PCR, and pyrosequencing should be used, although traditional methods such as allele-specific PCR with visualization in the agarose gel can be exploited as well, and their application definitely will be continued for the next decade. Anyway, automated methods should be of choice compared to methods where a subjective factor is substantial and can influence the results. The improvement of existing technologies and the development of new ones may elevate the accuracy of DNA extraction and PCR, leading to increase of validity of the results and, consequently, to the further progress in the field.

Other important aspects of the study design also should be considered. To differentiate the impact of the chronic inflammatory conditions from the contribution of the other mechanisms in the association of the polymorphisms of the genes encoding PRRs and proteins of PRR signaling pathways with cancer risk, the stratification of cases and controls by infectious agent status and chronic inflammation status should be mandatory in the further studies devoted to this problem. The sample size should be sufficient, and it depends on the frequency of target polymorphism – if it is high, sample size can be less than in the studies where target SNP frequency is low. There is also a lack of studies investigating functional consequences of the polymorphisms of the genes encoding PRRs and proteins of PRR pathways on molecular level (for instance, alterations in the promoter activity, in the gene expression on the transcriptomic and proteomic levels, in stability or/and localization of the non-coding RNA, pre-mRNA, mRNA and protein inside the cell, in protein structure and functions, etc.). It is important since many polymorphisms can be simply in linkage disequilibrium with the other, truly functional variants, and thus such fundamental studies are necessary to clarify their role (are they only markers of association or indeed causal variants?). In addition, in certain populations replication studies should be conducted to prove results that were obtained in prime investigations, particularly if the sample size was not large.

There are certain disparities in different population studies investigating the association of the polymorphisms of the genes encoding PRRs and proteins of their signaling pathways with various aspects of cancer development. General reasons for these discrepancies may include confounding host, bacterial, or environmental factors in different ethnicities modulating the penetrance of the variant allele and affecting risk of condition increasing cancer risk (such as autoimmune diseases, precancerous gastric lesions, tuberculosis, recurrent pneumonia etc.), different bacterial impact in aetiology of such conditions in different populations (that will be reflected in different features of PRR-mediated immune response because of specific PRR-ligand interaction), differences in the sample size, in age/gender/BMI/ethnicity/TNM stage/other clinicopathological characteristics between the study samples, in the prevalence of infectious agent (e.g. HP or EBV) in case and control groups, differences in diagnostics, stratification, genotyping methods, and chance. In addition, certain studies in which negative results were obtained could never been published (so-called file drawer effect) that may create a significant bias and distort a

picture that we can observe at the moment. Unfortunately, although some genome-wide association studies (GWAS) relevant to the discussing problem were performed, it is usually not possible to compare them with the non-GWAS on the same cancer type since there are no non-GWAS investigating association of the same SNPs with similar malignancies. It may be feasible in future when the number of studies devoted to this issue will be enough for correct comparative analysis.

3. Hot spots in the field

The most intriguing moments in the problem of the association of inherited structural variation in the genes encoding PRRs and proteins of PRR signaling pathways with features of cancer development are:

- Are SNPs in the genes encoding PRRs or proteins of PRR signaling pathways associated with the features of cancer progression or only with cancer risk? Existing studies have shown controversial results, and the results of most of them allow to suggest that there is no or weak correlation between such polymorphisms and peculiarities of cancer progression.
- Are the polymorphisms of the genes encoding CLRs, RLRs, or specific proteins of their signaling pathways associated with risk or progression of cancer? If yes, would be appropriate to include them in the list of polymorphisms using in programs of cancer risk determination and further cancer prevention? As it was shown above, there are some premises to think that these SNPs may be associated with cancer risk. Further fundamental and population studies are necessary to answer this question.
- Do the polymorphisms of genes encoding PRRs or proteins of PRR signaling pathways (particularly TLRs and TLR pathway) correlate with altered prostate cancer risk or progression? Despite there are some fundamental mechanisms allowing to hypothesize that *TLR* gene polymorphisms may play a role in prostate cancer aetiology, and a number of comprehensive projects on large samples in various countries was conducted, the reliable associations of these SNPs with prostate cancer risk or with features of prostate cancer progression were not detected, and results vary in different populations.
- Are the polymorphisms of the genes of PRR signaling pathways associated with cancer risk or progression to the same extent as polymorphisms of the genes encoding PRRs? It is logical that if SNP of gene encoding specific PRR is associated with risk or progression features of certain malignancies, polymorphisms in the genes encoding specific signaling molecules constituting pathways of this receptor should correlate with similar neoplasms, if they have substantial functional consequences on the molecular level. In contrast to the polymorphisms of the genes encoding TLRs, whose association with solid tumors is a subject of investigation in a lot of genetic association studies, the polymorphisms of the genes encoding proteins of TLR pathway are investigated mostly in relation to leukemia and lymphoma, and their association with epithelial tumors is discovered very poorly. SNPs affecting functional parts of TLR pathway central elements (MyD88, TRIF/TICAM1, TIRP/TRAM/TICAM2, TIRAP/MAL, IRAKs, TRAF3, TRAF6, TAK1, TAB1, TAB2, PKR, IRF3, IRF7) should be the most significant for the oncogenomic studies analyzing this problem.

- How the polymorphisms of the genes encoding PRRs and proteins of PRR signaling pathways interact with each other in relation to determination of cancer risk and progression? Particularly, how SNPs of positive and negative regulators of PRR activity (especially, miRNA) influence on cancer risk or progression if they are inherited together? Answers to these questions remain elusive at present time, and should be obtained from the fundamental and population studies in the future.

- Which the SNPs of the genes encoding PRRs and proteins of PRR pathways have independent significance, and which are just in the linkage disequilibrium? Knowledge of it may help in listing of the polymorphisms useful in the programs of cancer risk determination and further prevention.

- Which SNPs of the genes encoding PRRs and proteins of PRR pathways should be included in such list? Which of them have universal effect for each cancer type, and which influence on risk or/and progression of one cancer type but have no effect in relation to another malignancy? Differences in the association of the same SNP with different malignancies should be explained by features of specific PAMP-PRR interaction (probably, certain characteristics of ligand binding), or, possibly, on peculiarities of DAMP-PRR interaction. List of SNPs prescriptive for the further oncogenomic investigations may be created according to the conception suggested above.

- How SNPs of the genes encoding PRRs and proteins of PRR pathways affect cancer risk or progression in different populations and their subgroups? How this information may be adjusted for application in the creation of the programs of cancer risk determination and further prevention? Only large, comprehensive, well-designed population studies may give answer to these questions.

- Do the polymorphisms of the genes encoding PRRs and proteins of PRR pathways influence on cancer risk only through increase of risk of chronic inflammatory conditions, or they can affect it also through other mechanisms? How this information may be used in the programs of cancer risk determination and further prevention? To answer these questions, control group in population studies should include not only healthy controls, but also controls with the chronic inflammatory conditions predisposing to investigating cancer type.

- Which infectious agents recognizing by various PRRs are carcinogenic, and which are not? It may help to define the cancer types associated with the SNPs of the genes encoding specific PRRs and proteins constituting PRR signaling pathways. Fundamental studies devoted to the investigation of infectious agent-PRR interactions, to the investigation of carcinogenicity of known infectious agents and to the discovery of new, possibly carcinogenic, infectious agents, should answer this question.

No doubt, the determination of the role of SNPs in genes encoding PRRs and proteins of PRR signaling pathways in fields of tumor immunology and molecular epidemiology of cancer may open new pages in the cancer biology and cancer prevention.

4. Acknowledgements

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Recent Advances in Immunology to Target Cancer, Inflammation and Infections

Edited by Dr. Jagat Kanwar

ISBN 978-953-51-0592-3

Hard cover, 520 pages

Publisher InTech

Published online 09, May, 2012

Published in print edition May, 2012

Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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