PERSPECTIVES

C-type lectin receptors and RIG-I-like receptors: new points on the oncogenomics map

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Abstract: The group of pattern recognition receptors includes families of Toll-like receptors, NOD-like receptors, C-type lectin receptors, and RIG-I-like receptors. They are key sensors for a number of infectious agents, some of which are oncogenic, and they launch an immune response against them, normally promoting their eradication. Inherited variations in genes encoding these receptors and proteins and their signaling pathways may affect their function, possibly modulating cancer risk and features of cancer progression. There are numerous studies investigating the association of single nucleotide polymorphisms within or near genes encoding Toll-like receptors and NOD-like receptors, cancer risk, and features of cancer progression. However, there is an almost total absence of articles analyzing the correlation between polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk or progression. Nevertheless, there is some evidence supporting the hypothesis that inherited C-type lectin receptor and RIG-I-like receptor variants can be associated with increased cancer risk. Certain C-type lectin receptors and RIG-I-like receptors recognize pathogen-associated molecular patterns of potentially oncogenic infectious agents, and certain polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors may have functional consequences at the molecular level that can lead to association of such single nucleotide polymorphisms with risk or progression of some diseases that may modulate cancer risk, so these gene polymorphisms may affect cancer risk indirectly. Polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors thereby may be correlated with a risk of lung, oral, esophageal, gastric, colorectal, and liver cancer, as well as nasopharyngeal carcinoma, glioblastoma, multiple myeloma, and lymphoma. The list of the most promising polymorphisms for oncogenomic investigations may include rs1926736, rs2478577, rs2437257, rs691005, rs2287886, rs735239, rs4804803, rs16910526, rs36055726, rs11795404, and rs10813831.

Keywords: C-type lectin receptors, RIG-I-like receptors, cancer, single nucleotide polymorphisms, genetic variation, inflammation

Brief description of pattern recognition receptors

Pattern recognition receptors directly recognize common antigen determinants of virtually all classes of pathogens (so-called pathogen-associated molecular patterns, or PAMPs).[1-4] In addition, they recognize endogenous ligands, usually releasing during cell stress and known as damage-associated molecular patterns.[1-4] As a result of ligand recognition, pattern recognition receptors initiate an immune response via specific intracellular signaling pathways, and so have a key role in initiation and promotion of septic and aseptic inflammation.[1-4] Pattern recognition receptors also have a number of other vital functions apart from participation in the immune response, in that they may regulate many aspects of cell proliferation, survival, apoptosis, autophagy, generation

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of reactive oxygen species, pyroptosis, angiogenesis, and, consequently, tissue remodeling and repair.[1–4] There are four main groups of pattern recognition receptors, ie, Toll-like receptors, NOD-like receptors, C-type lectin receptors, and RIG-I-like receptors, and genes encoding them are broadly expressed, eg, in epithelial cells, endothelial cells, keratinocytes, lymphocytes, granulocytes, fibroblasts, and neurons.[1–4] A summary of the most modern conceptual data about members of these groups and about their structure and function can be obtained from recent comprehensive reviews by Kawai and Akira,[1] Elinav et al,[2] Osorio et al,[3] and Loo and Gale.[4]

The completion of the human genome project and widespread distribution of genotyping technologies have led to an enormous number of studies devoted to associating inherited gene polymorphisms with various diseases. Single nucleotide polymorphisms may result in amino acid substitutions altering protein function or splicing, and they can also change the structure of enhancer sequences during splicing[5] and affect mRNA stability.[6] Single nucleotide polymorphisms may alter transcription factor binding motifs, change the efficacy of enhancer or repressor elements,[7] and alter the structure of translation initiation codons that may lead to downregulation of wild-type transcripts.[8] Gene polymorphisms located in leucine-rich repeats constituting ectodomains of many pattern recognition receptors may affect the ability of these receptors to bind pathogens they normally recognize,[9] single nucleotide polymorphisms in transmembrane domains can lead to defects of intracellular receptor transport that prevent receptors localizing to the cell membrane,[10] and, finally, polymorphisms in the cytosolic domains may result in altered interactions with adaptor proteins or in disrupted receptor dimerization. Therefore, there are many avenues by which single nucleotide polymorphisms may alter pattern recognition receptor expression and activity. Because pattern recognition receptors recognize a number of oncogenic infectious agents and launch an immune response against them, inherited variation in their structure may modulate cancer risk and, possibly, influence cancer progression. In addition, pattern recognition receptors bind a lot of endogenous ligands,[1–4] so polymorphisms of genes encoding them can affect risk and/or progression of some autoimmune disorders and, consequently, cancer risk and/or progression, given that there is a fundamental and epidemiological association between many autoimmune diseases and cancer risk.

The problem

Although there are a lot of studies investigating the association between single nucleotide polymorphisms in genes encoding Toll-like receptors and NOD-like receptors and

the risk and features of cancer progression, there is an almost complete absence of articles analyzing the correlation between polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk or progression. This can be explained by the fact that the first wave of studies devoted to the association of polymorphisms of genes encoding Toll-like receptors and NOD-like receptors with cancer risk appeared only in 2004, and the number of such papers was relatively small until 2008. In addition, known hypotheses about the infectious agents causing human cancer and their recognition by pattern recognition receptors suggested that Toll-like receptors and NOD-like receptors should play a major role in the immune response against biological carcinogens. However, more recent findings concerning specific potentially carcinogenic ligands of C-type lectin receptors and RIG-I-like receptors were only obtained in the last few years,[3,4] so there has not been enough time as yet to conduct comprehensive investigations between single nucleotide polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk.

However, there is some evidence supporting the hypothesis that inherited features of C-type lectin receptor and RIG-I-like receptor structure can be associated with increased cancer risk.

First premise: specific ligands

Certain C-type lectin receptors and RIG-I-like receptors recognize PAMPs of oncogenic infectious agents.[3,4,11,12]

C-type lectin receptors:

- MRC1 (CD206, CLEC13D, mannose receptor) and PAMPs of *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Candida albicans*, human immunodeficiency virus type-1 (HIV-1)
- CD207 (CLEC4K, langerin) and PAMPs of *Candida* spp, HIV-1
- LY75 (CD205, CLEC13B, DEC-205) and PAMPs of HIV-1
- CD209 (CLEC4L, DC-SIGN) and PAMPs of *Mycobacterium* spp, *Schistosoma mansoni*, *C. albicans*, HCV, HIV-1, cytomegalovirus
- CLEC7A (Dectin-1) and PAMPs of *Mycobacterium* spp
- CLEC1B (CLEC-2) and PAMPs of HIV-1
- CLEC6A (CLEC4N, Dectin-2) and PAMPs of *M. tuberculosis*, *C. albicans*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*
- CLEC4E (Mincle) and PAMPs of *M. tuberculosis* and *C. albicans*
- CLEC4A (DCIR) and PAMPs of HIV-1

RIG-I-like receptors:

- RIG-I and PAMPs of Epstein–Barr virus and hepatitis C virus

On the basis of known associations between inherited structural variations in Toll-like receptors and NOD-like receptors and cancer risk,[1,2] and according to data about cancer types caused by carcinogenic infectious agents,[11,12] it is possible to suggest that risk of lung cancer may be modulated by polymorphisms of the *MRC1*, *CD209*, *CLEC7A*, *CLEC6A*, and *CLEC4E* genes, oral cancer risk by single nucleotide polymorphisms of the *MRC1*, *CD207*, *CD209*, *CLEC6A*, and *CLEC4E* genes, risk of glioblastoma and colorectal cancer by polymorphisms of the *CD209* gene, hepatocellular carcinoma risk by polymorphisms of the *CD209* and *RIG-I* genes, and risk of lymphoma, multiple myeloma, nasopharyngeal carcinoma, and esophageal and gastric cancer by single nucleotide polymorphisms of the *RIG-I* gene. In addition, single nucleotide polymorphisms of *MRC1*, *CD207*, *LY75*, *CD209*, *CLEC1B*, and *CLEC4A* genes may correlate with cancer types associated with HIV-1 infection.

Second premise: polymorphisms affecting function

Certain polymorphisms of genes indicated above may have functional consequences on the molecular level that can lead to association of such single nucleotide polymorphisms with risk or progression of some diseases that may modulate cancer risk, so these gene polymorphisms may affect cancer risk indirectly. In addition, polymorphisms of these genes correlating with diseases that are not related to cancer risk may also be useful in oncogenomics because they may have functional consequences at the molecular level as well, although they have not been investigated in relation to association with cancer risk or progression.

For instance, it was suggested that variant alleles of *MRC1* rs2477637, rs2253120, rs2477664, rs692527, rs1926736, and rs691005 gene polymorphisms are associated with development of asthma[13] (eg, variant A allele of rs1926736 was connected with decreased asthma risk). In addition, Alter et al[14] found that the variant A allele (S396) of rs1926736 (G396S) polymorphism is associated with a lower leprosy risk and, conversely, G allele (G396) correlates with increased risk of this disease. Interestingly, G396 did not influence leprosy risk in combination with T399 and L407 (amino acids resulting from variant alleles of rs2478577 and rs2437257, respectively).[14] The authors noted that all three of these *MRC1* gene single nucleotide polymorphisms map

to the second C-type lectin domain (CTLD2) of the MRC1 protein, with their in vitro results suggesting that a direct interaction between CTLD2 and an accessory receptor molecule is necessary in order for microbial ligand recognition to occur.[14] It is logical to propose that such interaction would be sensitive to G396 only in the context of the A399-F407 haplotype, and not in the context of the T399-L407 haplotype.[14] Thus, rs1926736 may have substantial functional consequences at the molecular level, but this depends on its relationship with other single nucleotide polymorphisms in the same exon. Finally, Hattori et al[15] showed that a variant allele of rs691005 polymorphism, located within the 3′ untranslated region of the *MRC1* gene, is associated with a higher risk of sarcoidosis. Because of its location, it is feasible that this single nucleotide polymorphism may alter the regulatory binding sequence and influence mRNA expression.[15]

The only study investigating the association of polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors with cancer risk is a study by Xu et al.[16] They investigated single nucleotide polymorphisms of the *CD209* gene and found that the GG genotype of the rs2287886, AA genotype of the −939 promoter polymorphism, and the G allele of the rs735239 single nucleotide polymorphism were connected with higher nasopharyngeal carcinoma risk.[16] Polymorphisms in the promoter of the *CD209* gene and in the *CD209* gene were also associated with hemorrhage in patients with dengue fever (G allele of rs4804803),[17,18] modulated tuberculosis risk (G allele of rs4804803, A allele of rs735239),[19–21] higher celiac disease risk in HLA-DQ2-negative cases (G allele of rs4804803),[22] increased ulcerative colitis risk in HLA-DR3-positive patients (G allele of rs4804803),[23] higher susceptibility to cytomegalovirus infection (G allele of rs735240 and C allele of rs2287886),[24] protection from lung cavitation[20] and fever during tuberculosis[25] (GG genotype and G allele of rs4804803), decreased HIV-1 infection risk (GG genotype of rs4804803),[21] accelerated progression to acquired immune deficiency syndrome in HIV-1-infected hemophiliacs (C allele of rs2287886),[26] decreased human T-lymphotropic virus type I infection risk (G allele of rs4804803, A allele of rs2287886),[27] increased severity of liver disease during hepatitis C virus infection (G allele of rs4804803),[28] and better prognosis following severe acute respiratory syndrome (G allele of rs4804803).[29,30]

It was shown that the A allele of the rs4804803 single nucleotide polymorphism may increase gene expression in vitro,[17] and, consequently, decreased *CD209* gene

Table 1 Results of case-control studies investigating the association of polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their signaling pathways with various diseases, and conditions or features

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
mrc1 Hattori et al[13] Japanese, Afro-American populations	rs2477637 (Japanese 0.605–0.645, Afro-American 0.686–0.667)	Asthma	Japanese, 446 cases, 424 controls; Afro-American, 86 cases, 90 controls	Japanese, dominant model 1.38 (1.02–1.87) Afro-American, no association
	rs2253120 (Japanese 0.698–0.752, Afro-American 0.663–0.667)			Japanese, additive model 1.34 (1.07–1.68); dominant model 1.55 (1.16–2.09); Afro-American, no association
	rs2477631 (Japanese 0.484–0.522, Afro-American 0.238–0.267)			Japanese, no association; Afro-American, no association
	rs2477664 (Japanese 0.509–0.537, Afro-American 0.570–0.572)			Japanese, dominant model 1.47 (1.06–2.05); Afro-American, no association
	rs692527 (Japanese 0.521–0.559, Afro-American 0.581–0.389)			Japanese, additive model 1.25 (1.01–1.55), dominant model 1.39 (1.00–1.94); Afro-American, additive model 2.17 (1.40–3.37), dominant model 2.87 (1.43–5.80) recessive model 2.76 (1.34–5.70)
	rs1926736 (Japanese 0.568–0.522, Afro-American 0.855–0.861)			Japanese, additive model 0.76 (0.61–0.95), recessive model 0.61 (0.41–0.89) 0.61; Afro-American, no association
	rs691005 (Japanese 0.705–0.679, Afro-American 0.401–0.261)			Japanese, no association; Afro-American, additive model 1.81 (1.16–2.81), dominant model 2.43 (1.32–4.46)
Alter et al[14] Vietnamese, Brazilian populations	rs1926736 (in Vietnamese controls 0.35, in Brazilian controls 0.32)	Leprosy	Vietnamese, 704 cases, 396 controls; Brazilian, 384 cases, 399 controls	Vietnamese, dominant model 0.76 (0.60–0.96), in the case with multibacillary leprosy, 0.71 (0.51–0.99); Brazilian, additive model, for carriers of wild-type G allele 1.34 (1.06–1.70), in the case with multibacillary leprosy, 1.42 (1.05–1.93)
	rs2437256 (in Vietnamese and Brazilian controls 0.21)			No association
	rs2478577 (in Vietnamese controls 0, in Brazilian controls 0.21)			No association
	rs2437257 (in Vietnamese controls 0, in Brazilian controls 0.21)			For carriers of wild-type G allele, dominant model 0.75 (0.54–1.05); in the case with multibacillary leprosy 0.63 (0.41–0.97)

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Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
Hattori et al[15] Japanese population	rs2477637 (0.412–0.355, AG genotype 0.37–0.441, GG genotype 0.227–0.134)	Sarcoidosis	181 cases, 424 controls	No association
	rs2253120 (0.301–0.248, AG genotype 0.448–0.325, GG genotype 0.077–0.085)			No association
	rs2477631 (0.472–0.478, AC genotype 0.547–0.479, CC genotype 0.199–0.238)			No association
	rs2477664 (0.472–0.463, AT genotype 0.514–0.455, TT genotype 0.215–0.236)			No association
	rs692527 (0.492–0.441, AG genotype 0.464–0.505, GG genotype 0.26–0.189)			No association
	rs1926736 (0.453–0.478, AG genotype 0.475–0.521, AA genotype 0.215–0.217)			No association
	rs544995 (0.298–0.295, AG genotype 0.431–0.467, AA genotype 0.083–0.061)			No association
	rs554313 (0.34–0.396, AG genotype 0.492–0.462, AA genotype 0.094–0.153)			No association
	rs691005 (0.376–0.321, TC genotype 0.376–0.458, CC genotype 0.188–0.092)			Recessive model, 2.53 (1.47–4.37)
CD209 Xu et al[16] Cantonese population	−116 promoter polymorphism (0.006 in controls)	NPC	444 cases, 464 controls	No association
	rs2287886 (0.275 in controls)			1.42 (1.15–1.74); for carriers of AG genotype, 1.41 (1.05–1.88), for carriers of GG genotype, 2.10 (1.23–3.59)
	−190 promoter polymorphism (in controls 0.003)			No association
	rs4804803 (in controls 0.085)			No association
	rs735239 (in controls 0.154)			1.47 (1.14–1.90); for carriers of AG genotype, 1.44 (1.05–1.98)
	rs735240 (in controls 0.222)			1.43 (1.15–1.79); for carriers of AA genotype, 2.52 (1.29–4.93)
Sakuntabhai et al[17] Thai population	rs4804803 (0.093 in dengue disease patients, 0.023 in dengue fever patients, 0.116 in dengue hemorrhagic fever patients, 0.104 in controls)	Dengue disease, dengue fever, dengue hemorrhagic fever	606 cases, 696 controls	Risk of hemorrhage during dengue fever, 5.84 (2.77–12.31); risk of dengue fever, 0.204; decreased *CD209* gene expression

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Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
	rs2287886 (0.292 in dengue disease patients, 0.266 in dengue fever patients, 0.301 in dengue hemorrhagic fever patients, 0.312 in controls)			No association
	DCSIGN1.in2+11 (0.066 in dengue patients, 0.019 in dengue fever patients, 0.081 in dengue hemorrhagic fever patients, 0.083 in controls)			Risk of hemorrhage during dengue fever, 4.60 (2.07–10.22); risk of dengue fever, 0.224
	DCSIGN1.ex4SF (0.007 in dengue patients, 0.003 in dengue fever patients, 0.009 in dengue hemorrhagic fever patients, 0.003 in controls)			No association
	DCSIGN1.ex4RPT (0.008 in dengue disease patients, 0.017 in dengue fever patients, 0.005 in dengue hemorrhagic fever patients, 0.006 in controls)			No association
	DCSIGN1.in5-178 (0.064 in dengue disease patients, 0.017 in dengue fever patients, 0.079 in dengue hemorrhagic fever patients, 0.079 in controls)			Risk of hemorrhage during dengue fever, 5.30 (2.25–12.46); risk of dengue fever, 0.201
	DCSIGN1.ex6TI (0.005 in dengue disease patients, 0.003 in dengue fever patients, 0.006 in dengue hemorrhagic fever patients, 0.005 in controls)			No association
	DCSIGN1.in6-37 (0.049 in dengue disease patients, 0.023 in dengue fever patients, 0.057 in dengue hemorrhagic fever patients, 0.064 in controls)			Risk of hemorrhage during dengue fever, 2.56 (1.19–5.52); risk of dengue fever, 0.371
	DCSIGN1.2281 (0.391 in dengue disease patients, 0.42 in dengue fever patients, 0.38 in dengue hemorrhagic fever patients, 0.344 in controls)			No association
	DCSIGN1.3197 (0.112 in dengue disease patients, 0.09 in dengue fever patients, 0.119 in dengue hemorrhagic fever patients, 0.122 in controls)			No association

Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
	DCSIGN1.3852 (0.243 in dengue disease patients, 0.24 in dengue fever patients, 0.244 in dengue hemorrhagic fever patients, 0.267 in controls)			No association
Wang et al[18] Taiwanese population	rs4804803 (0.084 in dengue patients, 0.054 in dengue fever patients, 0.122 in dengue hemorrhagic fever cases, 0.028 in other non-dengue febrile illness cases, 0.038 in controls)	Dengue disease, dengue fever, dengue hemorrhagic fever	176 dengue fever cases, 135 dengue hemorrhagic fever cases, 143 patients with other non-dengue febrile illnesses, 120 controls	Risk of dengue infection, 2.34 (1.14–4.83); risk of dengue hemorrhagic fever, 3.57 (1.67–7.63); risk of hemorrhage during dengue fever, 2.44 (1.36–4.40); increased levels of TNF-α, IL-12p40, IP-10
Barreiro et al[19] South African population	rs2048022 (0,434–0.483)	Tuberculosis	351 cases, 360 controls	No association
	rs1380229 (0.361–0.384)			No association
	rs650389 (0.152–0.195)			No association
	rs870384 (0.483–0.468)			No association
	rs695982 (0.321–0.277)			No association
	rs708682 (0.118–0.123)			No association
	rs715774 (0.143–0.161)			No association
	rs1433456 (0.199–0.197)			No association
	rs807131 (0.355–0.339)			No association
	rs11672183 (0.12–0.117)			No association
	rs2024628 (0.422–0.465)			No association
	rs1028184 (0.342–0.39)			No association
	rs2056773 (0.395–0.371)			No association
	rs1479067 (0.259–0.284)			No association
	rs327747 (0.258–0.292)			No association
	rs12665321 (0.142–0.129)			No association
	rs1566838 (0.465–0.458)			No association
	rs12785524 (0.39–0.424)			No association
	rs975423 (0.351–0.378)			No association
	rs914904 (0.292–0.282)			No association
	rs876287 (0.413–0.409)			No association
	rs1582598 (0.275–0.265)			No association
	rs1364198 (0.252–0.227)			No association
	rs739259 (0.361–0.39)			No association
	rs169479 (0.133–0.115)			No association
	rs4804803 (0.454–0.402)			1.48 (1.08–2.02)
	rs735239 (0.089–0.141)			For carriers of A allele, 1.85 (1.29–2.66)
	rs735240 (0.283–0.313)			No association
	rs2287886 (0.271–0.288)			No association
Vannberg et al[20] Gambian, Guinean, Guinea-Bissauan, Malawian populations	rs4804803 (in Gambian population 0.48–0.54, in Guinean population 0.489–0.47, in Guinea-Bissauan population 0.475–0.504, in Malawian population 0.352–0.364)	Tuberculosis	Gambian: 678 cases, 327 controls Guinean: 151 cases, 180 controls Guinea-Bissauan: 162 cases, 141 controls Malawian: 244 cases, 295 controls	For Gambian population, 0.75 (0.61–0.94); overall, 0.86 (0.77–0.96); for cavitating tuberculosis, 0.42 (0.27–0.65)

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Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
Selvaraj et al[21] South Indian population	rs4804803 (0.181–0.223)	Tuberculosis, HIV	238 HIV cases, 107 HIV+ and tuberculosis cases, 157 controls	For carriers of GG genotype, risk of tuberculosis among HIV-infected patients, 9.8 (2.2–44.3)
	rs2287886 (0.471–0.468) rs7252229 (0.105–0.101) rs1544767 (0.105–0.108)			No association No association No association
Nunez et al[22] Spanish population	rs4804803 (0.23–0.21)	Celiac disease	103 cases, 312 controls	For carriers of GG genotype; for HLA-DQ2(−)-individuals compared with HLA-DQ2(+) individuals and controls, 3.73 (1.18–11.03)
Nunez et al[23] Spanish population	rs4804803 (0.25 in Crohn's disease patients, 0.22 in ulcerative colitis patients, 0.22 in controls)	Crohn's disease, ulcerative colitis	515 Crohn's disease cases, 497 ulcerative colitis cases, 731 controls	Risk of ulcerative colitis in HLA-DR3-positive patients 1.77 (1.04–3.02)
Mezger et al[24] European population	rs2287886	Human CMV reactivation and disease after allogeneic stem cell transplantation	70 patients with human CMV reactivation, 59 patients with human CMV disease, 65 controls	Risk of human CMV disease, 1.88 (0.91–3.87)
	rs735240			Risk of human CMV reactivation, 2.41 (1.22–4.75); risk of human CMV disease, 2.01 (1.05–3.86)
Zheng et al[25] Chinese population	rs4804803 (0.061–0.073)	Tuberculosis	237 cases, 244 controls	0.209 (0.058–0.758)
	rs735239 (0.207–0.234)			No association
Koizumi et al[26] Japanese population	rs2287886	AIDS progression	104 HIV-1-positive Japanese hemophiliacs	Risk of accelerated AIDS progression: 1.95 (1.039–3.677)
	rs4804803			No association
Kashima et al[27] Mixed population from different continents	rs2287886 (0.594–0.795)	HLTV-1-infection	66 cases, 33 controls	For carriers of A allele: Risk of HTLV-1-infection: 0.3758 (0.1954–0.7229) For carriers of AA genotype: Risk of HTLV-1-infection: 0.1116 (0.02168–0.5745)
	−201 promoter polymorphism (0.038–0.016)			No association
	−332 promoter polymorphism (0.03–0)			No association
	rs4804803 (0.144–0.297)			For carriers of A allele: Risk of HTLV-1-infection: 2.511 (1.218–5.179)
Ryan et al[28] Irish population	rs4804803 (0.25–0.19)	HCV infection	131 cases, 79 controls	Increased risk of advanced liver disease
Chan et al[29] Hong Kong population	rs4804803	SARS	585 cases with lower LDH level, 96 cases with higher LDH level	Risk of higher LDH level during SARS, 0.41 (0.20–0.86); decreased expression of *CD209* gene; Sp1 and AP2 proteins bind more effectively to G allele of rs4804803

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Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
Chan et al[30] Hong Kong population	rs4804803	SARS	824 cases, 471 controls	Risk of higher LDH level during SARS, 0.41 (0.20–0.86)
CLEC7A (Dectin-1)				
Plantinga et al[31] Dutch population	rs16910526 (0.078–0.076)	Rheumatoid arthritis	262 cases, 284 controls	Diminished TNF-α and IL-1β production in cells from homozygous and heterozygous individuals; the TLR2/Dectin-1 synergism was reduced in cells isolated from heterozygous and homozygous subjects
Cunha et al[32] Italian population	rs16910526	Invasive aspergillosis	205 cases with hematopoietic stem cell transplantation	Risk of invasive aspergillosis after hematopoietic stem cell transplantation, polymorphic donor + wild-type recipient, 2.50 (1.00–6.53) Polymorphic donor + polymorphic recipient: 3.89 (1.51–9.99) Unstimulated CD14-positive monocytes from polymorphic persons display a decreased surface expression of Dectin 1 in response to β-glucan or A conidia, PBMCs from heterozygous persons showed decreased production of IL-1β, IL-6, IL-10, IL-17A, and IFN-γ
Chai et al[33] Dutch and Flemish population	rs16910526 (0.19 in patients without hematopoietic transplantation with invasive aspergillosis, 0.077 in controls, 0.07 in patients with transplantation [with and without invasive aspergillosis])	Invasive aspergillosis	71 cases with invasive aspergillosis after hematopoietic stem cell transplantation, 21 cases with invasive aspergillosis without transplantation, 108 controls with transplantation	Increased risk of invasive aspergillosis in patients without hematopoietic transplantation PBMCs from variant homozygous persons had reduced proinflammatory TNF-α and IL-6 production in response to heat-killed *Aspergillus fumigatus* hyphae, *Candida albicans* blastoconidia, and live *A.fumigatus* conidia; monocyte-derived macrophages from polymorphic individuals had deficient expression of the Dectin 1 receptor; stimulation using β-glucan failed to generate a TNF-α response in the Dectin 1-deficient monocyte-derived macrophages from variant homozygotes

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Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
Plantinga et al[34] Dutch population	rs16910526 (0.106–0.138)	Colonization with *Candida* spp	142 cases with hematopoietic stem cell transplantation, 138 controls	Risk of *Candida* spp colonization, 12.0 (2.5–57.1); risk of *Candida* spp colonization after transplantation, 15.5 (1.9–125.6); monocytes from the variant homozygous individuals exhibited no Dectin 1 expression on the cell surface, whereas cells from heterozygous individuals had intermediate cell surface expression; IL-1β induction by *C. albicans* was lower in cells from individuals bearing the polymorphism; no possibility to amplify TLR2 signaling by Dectin 1 in cells isolated from variant homozygous individuals
Plantinga et al[35] East African population	I223S	Oropharyngeal candidiasis	225 cases with HIV	IFN-γ production capacity and ability to bind zymosan was markedly lower in cells from subjects bearing the polymorphism
RIG-I Ovsyannikova et al[38] US population	rs10813821	Cytokine immune response in healthy children following rubella vaccination	738 cases	Increased level of IFN-γ
	rs9650702			Increased level of IFN-γ and decreased level of GM-CSF
	rs626214			Increased level of IFN-γ
	rs592515			Increased level of IFN-γ and TNF-α
	rs6476363			Decreased level of TNF-α
	rs3739674			Decreased level of TNF-α
	rs10813829			Decreased level of TNF-α
	rs4633144			Decreased level of TNF-α
	rs3824456			Increased level of TNF-α
	rs10813831			Decreased level of GM-CSF and IL-6
Ovsyannikova et al[39] US population	rs10813831	Cytokine immune response in healthy children following rubella vaccination	738 cases	Decreased rubella-specific antibody response (median antibody level)
	rs669260			Increased rubella-specific antibody response
Hu et al[40] US population	rs10813831	Cytokine immune response to Newcastle disease	130 cases	Increased gene expression in Newcastle disease virus-infected cells
	rs12006123			No association

(*Continued*)

Table 1 (*Continued*)

Reference, population	SNP number, variant allele frequency in cases and controls	Disease or condition	Sample size	OR and 95% CI for carriers of variant allele (only positive or negative statistically significant results)
MAVS/VISA/IPS-1				
Pothlichet et al[50] Mixed population	rs11905552 (0.126–0.102 in Afro-American population, 0.013–0 in European-American population)	SLE	520 cases, 510 controls	For Afro-American population, probability of absence of anti-RNA-binding protein autoantibodies 2.6 (1.5–4.6); decreased level of NF-κB, IL-8, IFN-β and RANTES; significantly reduced interaction of MAVS with TRAF3
	Q198K (0.187–0.2 in African-American population, 0.128–0.155 in European-American population)			No association
Liu et al[51] Chinese population	rs17857295 (0.496–0.468)	SLE	123 cases, 95 controls	Risk of SLE-related renal nephritis, 0.58 [0.34–0.97]
	rs2326369 (0.272–0.232)			Risk of SLE-related arthritis, 0.27 (0.09–0.80)
	rs7262903 (0.098–0.147)			No association
	rs7269320 (0.098–0.11)			Association with patients positive for SLE-related arthritis, 0.45 (0.21–0.94); association with patients positive for SLE-related renal nephritis, 0.42 (0.18–0.98); association with patients negative for SLE-related oral ulcer, 0.40 (0.18–0.89); association with patients negative for SLE-related photosensitivity, 0.38 (0.17–0.89)

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MRC, mannose receptor C; CD, cluster of differentiation; NPC, nasopharyngeal carcinoma; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; TNF, tumor necrosis factor; IL, interleukin; IP, interferon-gamma inducible protein 10; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency virus; HTLV, human T-cell lymphotropic virus; HCV, hepatitis C virus; SARS, severe acute respiratory syndrome; LDH, lactate dehydrogenase; Sp, specificity protein; AP, activator protein; CLEC, C-type lectin domain, the next number is the family number 7, the next letter is the letter of family member; TLR, toll-like receptor; PBMC, peripheral blood mononuclear cell; IFN, interferon; RIG-I, retinoic acid-inducible gene I; GM-CSF, granulocyte-macrophage colony-stimulating factor; MAVS/VISA/IPS-1, mitochondrial antiviral signaling protein/virus-induced signaling adapter/induced by phosphate starvation-1; NF-κB, necrosis factor kappa B; RANTES, regulated on activation, normal T-cell expressed and secreted; TRAF, TNF receptor-associated factor; SLE, systemic lupus erythematosus.

expression in subjects with the G allele may result in an impaired immune response against hepatitis C virus,[28] *M. tuberculosis*,[19,21] and bacteria potentially causing celiac disease[22] and ulcerative colitis,[23] that elevates the risk of diseases caused by these infectious agents. Such a decreased immune response may protect from hemorrhage during dengue fever,[17] from lung cavitation,[20] from fever during tuberculosis,[25] and from lung injury during severe acute respiratory syndrome[29,30] as a result of less cytokine production and diminished activation of immune cells. However, from the point of view of Vannberg et al,[20] conversely, lower *CD209* gene expression as a consequence of G allele of rs4804803 polymorphism may protect against tuberculosis because of decreased production of proinflammatory cytokines such as interleukin-4. Further fundamental, translational, and clinical studies are necessary to clarify these discrepancies. Nevertheless, although there are a number of reasons for the discrepancies between studies devoted to the association between CD209 single nucleotide polymorphisms and development of tuberculosis, but confounding host, bacterial, and

environmental factors between different study populations should be taken into account. In addition, Mezger et al[24] demonstrated that alleles of rs735240 and rs2287886 polymorphisms may also influence *CD209* gene expression and thus affect transcription factor binding.

In relation to the *CLEC7A* (Dectin-1) gene, it was also found that a variant allele of rs16910526 polymorphism is associated with impaired cytokine production by macrophages[31,32] and with a defective response to *Aspergillus* and *Candida* invasion.[33,34] The variant S form of I223S polymorphism was characterized by a lower capacity of the receptor to bind zymosan.[35]

Among polymorphisms of genes encoding RIG-I-like receptors, *RIG-I* single nucleotide polymorphisms are the most investigated. Pothlichet et al[36] conducted a comprehensive study investigating the functional consequences of rs36055726 (P229fs) and rs11795404 (S183I) polymorphisms. They found that the variant allele of rs36055726 results in a truncated constitutively active RIG-I (that leads to permanent production of proinflammatory mediators, particularly antiviral), and, conversely, the variant allele of rs11795404 induces an abortive conformation of RIG-I, causing formation of unintended stable complexes between CARD modules of RIG-I and between RIG-I and its downstream adapter protein, MAVS, rendering RIG-I incapable of downstream signaling and further cytokine synthesis.[36] Moreover, Shigemoto et al identified a variant of rs11795404 as a loss-of-function allele.[37] Ovsyannikova et al[38,39] showed that a minor allele of rs10813831 polymorphism is associated with a decrease in the rubella virus-specific granulocyte-macrophage colony-stimulating factor/interleukin-6/IgG response, whilst a variant allele of rs3824456 is connected with an increase in the rubella virus-specific tumor necrosis factor alpha response, and a variant allele of rs669260 correlates with an increase in the rubella-specific antibody level. Hu et al[40] discovered that a variant allele of rs10813831 polymorphism leads to increased gene expression and, consequently, cytokine production due to an amino acid substitution in the CARD domain of RIG-I that results in functional alteration of this RIG-I-like receptor.

There are also a lot of studies investigating the role of *IFIH1/MDA5* (the gene encoding MDA5 protein that is also a RIG-I-like receptor) single nucleotide polymorphisms in the etiology of autoimmune diseases, but almost all of them are devoted to type 1 diabetes and multiple sclerosis, and data about the association of these diseases with cancer risk are conflicting, in that some studies showed an increased risk in patients with type 1 diabetes and multiple sclerosis,[41,42] and

Table 2 Polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their specific signaling pathways that have known functional consequences and may be relevant to oncogenomics

Gene	Single nucleotide polymorphism
Genes encoding CLRs	
MRC1	rs1926736*
	rs2478577*
	rs2437257*
	rs691005*
	rs2477664
	rs692527
	rs2253120
	rs2477637
CD209	rs2287886*
	rs735239*
	rs4804803*
	rs735240*
CLEC7A	rs16910526*
	I223S
Genes encoding RLRs	
RIG-I	rs36055726*
	rs11795404*
	rs10813831*
	rs3824456
	rs669260
	rs9650702
	rs626214
	rs592515
	rs6476363
	rs3739674
	rs10813829
	rs4633144
	rs10813821
Genes encoding proteins of CLR and RLR intracellular signaling pathways	
MAVS/VISA/IPS-1	rs11905552
	rs17857295
	rs2326369
	rs7269320

Note: *Single nucleotide polymorphisms that can be valued as the most promising for further oncogenomic investigation.
Abbreviations: PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; NLRs, NOD-like receptors; CLRs, C-type lectin receptors; RLRs, RIG-I-like receptors; SNPs, single nucleotide polymorphisms; MRC, mannose receptor C; CD, cluster of differentiation; CLEC, C-type lectin domain, the next number is the family number 7, the next letter is the letter of family member; HIV, human immunodeficiency virus; LY, lymphocyte antigen; DEC-205, dendritic and epithelial cells 205 kDa; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; HCV, hepatitis C virus; CMV, cytomegalovirus; DCIR, dendritic cell immunoreceptor; RIG-I, retinoic acid-inducible gene I; EBV, Epstein–Barr virus; CARD, caspase recruitment domain; MAVS, mitochondrial antiviral signaling protein; IFIH, interferon induced with helicase C domain; MDA, melanoma differentiation-associated gene; VISA, virus-induced signaling adapter; IPS-1, induced by phosphate starvation-1.

in other investigations no connection or decreased risk of cancer has been observed.[43–49] Taking into account that there are no carcinogenic infectious agents recognizing MDA5, it does not seem to be prudent to investigate *IFIH1/MDA5* gene polymorphisms from the oncogenomic point of view.

In addition, polymorphisms of genes coding for components of the Toll-like receptor signaling pathway may modulate cancer risk as single nucleotide polymorphisms of the *TLR* gene family.[1] The same statement can be true for C-type lectin receptor and RIG-I-like receptor signaling pathways. For instance, a variant allele of rs11905552, encoding MAVS/VISA/IPS-1, a key downstream signaling molecule of RIG-I and MDA5, was associated with a particular systemic lupus erythematosus phenotype.[50] It was found that this single nucleotide polymorphism leads to reduced production of type I interferon and other proinflammatory mediators, and also to the absence of anti-RNA-binding protein autoantibodies.[50] In addition, variant alleles of rs17857295 and rs2326369 polymorphisms of the *MAVS*/*VISA*/*IPS-1* gene were associated with nephritis and arthritis in patients suffering from systemic lupus erythematosus.[51] A variant allele of another single nucleotide polymorphism of this gene, rs7269320, showed associations with different clinical characteristics of this autoimmune disease.[51] All the population case-control studies mentioned above are summarized in Table 1.

Conclusion and future directions

All polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their specific signaling pathways that have known functional consequences and may be relevant to oncogenomics are summarized in Table 2. The fundamental basis for the association of the inherited coding variation in genes encoding C-type lectin receptors and RIG-I-like receptors with cancer is represented by the defects in the immune response (that are caused by various single nucleotide polymorphisms) against specific carcinogenic infectious agents. Some polymorphisms may be valued as the most promising for further oncogenomic investigations on the basis of their association with cancer risk or because of their substantial functional consequences on the molecular level according to the following concept:

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

- The single nucleotide polymorphism leads to substantial functional consequences at the molecular level (for instance, it strongly affects transcription, splicing, translation, stability and transport of pre-mRNA, mRNA, noncoding RNA, or protein encoding by the gene, or it noticeably influences signaling of synthesized protein)
- It is associated with risk of cancer in population studies
- It has functional consequences at the molecular level and it is strongly associated with a condition that

significantly increases the risk of cancer (threshold may vary for each cancer type)

The gene polymorphism can be also included on the extended list if:

- It is characterized by more subtle functional alterations in a gene that, nonetheless, result in qualitative or quantitative alterations of the encoding protein (or noncoding RNA)
- It is associated with a condition that substantially increases the risk of cancer but has not specifically been identified to increase the risk of cancer.

According to this concept, the indicated short list of polymorphisms includes rs1926736, rs2478577, rs2437257, rs691005 (all located in the *MRC1* gene), rs2287886, -939 promoter polymorphism, rs735239, rs735240, rs4804803 (all located in the *CD209* gene), rs16910526 (*CLEC7A* gene), and rs36055726, rs11795404, rs10813831 (all located in the *RIG-I* gene). Other polymorphisms mentioned in this article may be added to the extended list for further investigations. Polymorphisms with known functional effects (rs1926736, rs2437257, rs691005, rs2287886, rs735240, rs4804803, rs16910526) were associated with relatively significant modulation of risk of diseases (as shown in Table 1) which is logical and demonstrates the correctness of the studies in which functional consequences of such single nucleotide polymorphisms were analyzed. There are still no comprehensive functional investigations for other single nucleotide polymorphisms correlated with risk of disease, so it is difficult to conclude which of them have independent significance, and which of them are just in linkage disequilibrium with truly functional variants.

In addition, PAMPs of specific infectious agents recognized by each C-type lectin receptor or RIG-I-like receptor define cancer types which can be primarily associated with inherited structural variation in the receptors discussed earlier. Furthermore, if a single nucleotide polymorphism of a gene encoding a specific C-type lectin receptor or RIG-I-like receptor is associated with risk or progression features of certain malignancies, polymorphisms in genes encoding specific signaling molecules constituting pathways of these receptors should correlate with similar neoplasms, if they have substantial functional consequences at the molecular level. The issue of an association of single nucleotide polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of pattern recognition receptor pathways with various features of cancer progression is open, and only further population studies would be likely to give a definite answer.

Reasons for discrepancies in different investigations analyzing the association of polymorphisms in genes encoding C-type lectin receptors, RIG-I-like receptors, and the proteins of their signaling pathways with various aspects of cancer development may include confounding host, bacterial, or environmental factors in different ethnicities modulating penetrance of variant alleles and affecting the risk of conditions increasing cancer risk (such as autoimmune diseases, precancerous gastric lesions, tuberculosis, recurrent pneumonia), different bacterial impact on the etiology of such conditions in different populations (that will be reflected in different features of C-type lectin receptor/RIG-I-like receptor-mediated immune response because of specific C-type lectin receptor/RIG-I-like receptor-ligand interaction), differences in sample size, in clinicopathological characteristics between study samples, in prevalence of infectious agents in case and control groups, diagnostics, stratification, genotyping methods, and chance.

Another interesting issue is that associations between single nucleotide polymorphisms of genes encoding C-type lectin receptors and RIG-I-like receptors and cancer risk can be skewed by differences between cohorts in various immune responses and infections that may not influence cancer development. The problem is that the design in an epidemiological study having a large sample is very seldom ideal. Stratification by status of chronic infection is rather difficult because of their extreme diversity and because of the very high cost of such testing. Stratification by an immune response is even more complex because of innumerable peculiarities in functioning of the immune system. Therefore, if the study has a perfect funding source, stratification by infection status can be possible, but stratification by immune response status will be far from ideal.

Unfortunately, to the best of the authors' knowledge, no genome-wide association studies of the connection between polymorphisms of genes encoding the C-type lectin receptor and RIG-I-like receptors and cancer risk or progression have been performed, and this can be explained by the relative newness of the problem or perhaps by another unknown reason.

Summing up, polymorphisms of genes encoding C-type lectin receptors, RIG-I-like receptors, and proteins of their signaling pathways may be promising targets for oncogenomics and possibly could be used in programs of cancer prevention and early cancer diagnostics in the future. Population and further fundamental studies devoted to their association with cancer risk of progression should shed light on this issue.

Disclosure

The authors report no conflicts of interest in this work.

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