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Review Article

Genetics of Aberrant Immune Responses During Tumor Progression Among Iranian Population

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Abstract

The immune system has a critical tumor suppressor function via the detection and elimination of the tumor cells. Tumor cells' immune escaping is commonly observed during neoplastic transformations. Immune response suppression or aberrations facilitate immune escape that promotes tumor progression in distant or primary locations via epithelial-mesenchymal transition and angiogenesis, respectively. It has been reported that there is a rising trend of cancer incidence among the Iranian population. Since aberrant immune responses are involved in tumorigenesis; immunotherapeutic methods can be efficient for tumor cell elimination. In the present review, we discussed all of the immune-related genes that have been associated with tumor progression among the Iranian population to clarify the genetics of immune deficiency during tumor progression in this population. T regulatory and T helper related genes were the most frequently deregulated genes during tumor progression in the Iranian population. This review paves the way to suggest an immune-specific panel of genetic markers for diagnostic and immunotherapeutic purposes among Iranian cancer patients.

Keywords: Biomarker; Cancer; Diagnosis; Immune Response; Immunotherapy

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Introduction

Cancer is the second cause of human deaths globally, with about 9.6 million deaths in 2018. The most common cancers are lung, breast, and colorectal cancers. About 70% of cancer-related deaths are observed in low and middle-income countries, which can be associated with the high frequency of poor prognosis in these countries (1). Cancer is the third most frequent cause of mortality in Iran (2). Breast, stomach, colorectal, and lung cancers are the most frequent cancers in Iran; various genetic and environmental risk factors are involved in tumor progression among Iranians (3-7). Immune responses in different stages of neoplastic transformation are also associated with cancer (8, 9). Innate immune system cells have critical roles in detecting the tumor cells (10) directly. Effector and memory T cells also interact with tumor cells by Natural killer T (NKT) cells (11). Dendritic cells, like the other innate immune members, are antigen-presenting cells that connect the adaptive and innate systems to stimulate cellular and humoral immunity. Since aberrant immune responses are associated with tumorigenesis, immunotherapeutic methods such as vaccines, monoclonal antibodies, recombinant cytokines, and autologous T cells can efficiently eliminate tumor cells (12-14). The proper immunotherapeutic methods can be used to target tumor cells based on the tumor types, location, age, and stage(15). Genetic polymorphisms are also involved in the efficiency of cancer immunotherapies (16, 17). The immune system is directly associated with tumor progression and metastasis that can either suppress or promote tumor growth. Although there is considerable basic knowledge about the molecular mechanisms of tumor immune escape, there is no population-based study. Since the molecular mechanisms of tumor progressions are ethnically different (4-6, 18-20), it is required to clarify the molecular mechanisms of tumor immune escape among the Iranian population to improve the efficiency of the therapeutic methods. Identifying immune biomarkers is required to introduce more efficient immunotherapeutic methods for eliminating tumor cells. In the present review, we have discussed all of the immune-related genes reported in Iranian cancer patients to clarify the molecular biology and genetics of tumor immune responses in this population.

Regulatory and helper T cells

The levels of immune-related gene expressions (**Table 1**) and polymorphisms (**Table 2**) were involved in tumor progression among the Iranian population (**Figure 1**).

The tumor-derived antigens can be identified by the leukocytes that result in tumor cell elimination by the immune response induction. The peripheral Regulatory T (Treg) cells prevent autoimmune response (105). Treg cells exert their immune suppressor roles through the IL-10 and IL-35 productions. Forkhead box protein P3 (FOXP3) + Treg cells synthesize IL-35, increasing the number of FOXP3+Treg cells (105, 106). FOXP3 is the master regulator of Treg cells (107). Ghrelin is a hormone that promotes an anti-inflammatory response against tumor cells and induces growth hormone secretion through the growth hormone (GH) secretagogue receptor (GHS-R1a). There were significantly increased populations of Foxp3+ T and GHS-R1a cells in bladder tumor tissues among Iranian subjects. Therefore, ghrelin can be involved in the promotion of Treg cells in tumor tissue which inhibits immune response toward bladder tumor cells (21). CTLA-4 is also an immune checkpoint mainly produced by the Treg cells that are involved in immune tolerance by an inhibitory effect on activated T cells (108). There were CTLA-4 and FOXP3 up regulations among a sample of Iranian breast cancer (BC) patients compared with controls (22, 109). CTLA-4 was also upregulated through the tumor stages (I-III) among a group of Kazakh BC patients (110). It has been observed that the A allele and AA genotypes of 1661 A/G polymorphism and TGTA haplotype (-1722 T, -1661 G, +49 A, -318 T) were protective in a sample of Iranian cervical cancer cases. Moreover, the C allele and CC genotypes of 318 C/T polymorphism and TGCG haplotype increased the risk of cervical cancer in this population (65). Similarly, CTLA-4 -318T/C affected cervical cancer susceptibility among Chinese patients. The frequencies of CTLA-4 -318T allele were significantly higher in cervical cancer patients compared with controls (111). The serum IL-35 concentrations and rs3761548 polymorphism were assessed in prostate cancer (PCa) patients and the control group among the Iranian population. There were significantly increased

serum IL-35 levels in PC patients with Gleason scores of 7-10 in comparison with cases with Gleason scores of 1-6 (23).

CTLA-4 and programmed death (PD)-1 are the main regulators of self-tolerance and T-cell responses (112, 113). PD-1 is a critical mediator of tumor immune inhibition. PD-1 expression in tumor-infiltrating lymphocytes is a mechanism to suppress the host immune responses. Up-regulations of programmed death-ligand 1 (PD-L1) and PD-L2 in tumor cells suppress the CD8+T cells (114). PD-L2 as a ligand for PD-1 is a stimulator of immune tolerance in tumor tissue. PD-1/PD-L2 ligation down-regulates the Bcl-xL anti-apoptotic molecule that finally results in reduced T cell proliferation (115). There was PD-L2 upregulation in an Iranian group of colorectal cancer (CRC) patients (24). There was an increased frequency of PD-L1+CD45hi cells in tumor tissues. The levels of PD-L2 on total CD45+ lymphocytes were significantly correlated with lymph node metastasis and mortality rate in an Iranian group of BCa patients (25). STAT3 is a pivotal transcription factor involved in cell proliferation and immune response (116, 117). It induces tumor-specific immune tolerance through PD-L1 upregulation (118). STAT3 suppression downregulated PD-L1 and promoted apoptosis in colorectal tumor cells. There was also a significantly reduced number of T-reg cells in CRC patients following the treatment using STAT3 inhibitor (26).

IL-17 is mainly produced by the Th-17 lymphocytes. The anticancer immune responses can be determined by an increase in the number of CTLA4/CD4 positive lymphocytes, Th-17, Tc17, and Treg cells (119-121). There were elevated percentages of Treg cells and CTLA4+CD4+ lymphocytes in Iranian patients with salivary tumors. There was significant IL-17 upregulation in Tc17 cells of the malignant tumors compared with controls (27). There was also a significantly increased frequency of IL-17 G-197A polymorphism in Iranian GC patients compared with controls. AA allele and GA genotype carriers had an increased risk of GC. The -197A allele was also significantly associated with lower tumor grades (66). Another study showed that there were decreased and increased levels of IL-17F and IL-17B respectively in a sample of Iranian CRC patients. The levels of IL-17C and IL-17F expressions were associated with the grade of tumor differentiation. IL-17C expression had a declining trend toward advanced tumors (28).

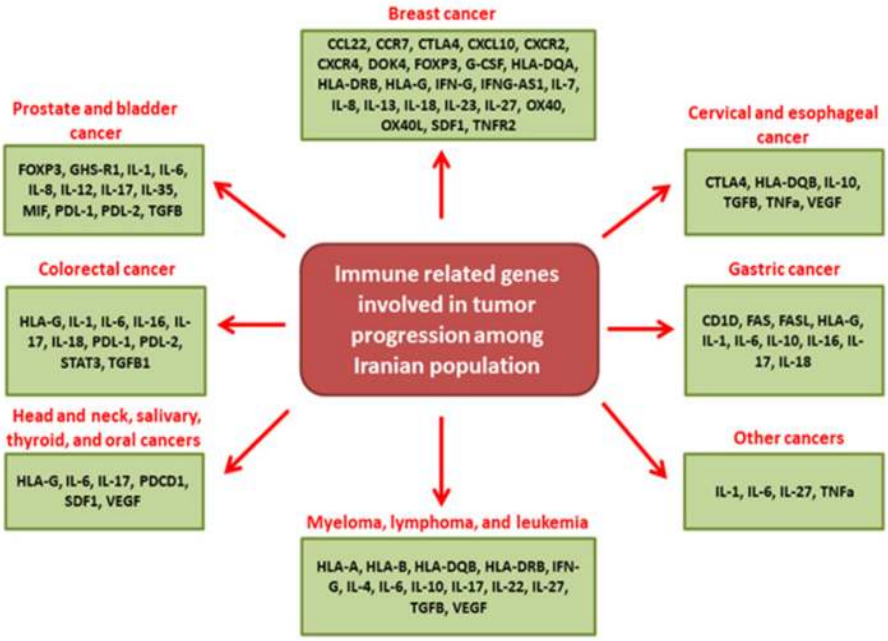

Figure 1. All of the immune-related genes are involved in the progression of different tumor types among Iranian populations.

Table 1. All of the immune-related gene expressions reported among Iranian cancer patients.

Study (et al.)	Year	Type	Gene	Population	Methods	Results
Regulatory and helper t cells						
Karimi (21)	2020	Bladder	FOXP3, GHS-R1a	40 N/T	Immunohistochemistry	Increased population of Foxp3+ T and GHS-R1a cells in tumor tissue.
Khalife (22)	2018	Breast	CTLA-4, FOXP3	20 patients 20 controls	Real time-PCR	Overexpressions
Chatrabnous (23)	2019	Prostate	IL-35, FOXP3	150 patients 150 controls	ELISA and PCR-RFLP	Overexpression
Shakerin (24)	2020	Colorectal	PD-L2	21 N/T	Immunohistochemistry	Overexpression
Ariafar (25)	2020	Bladder	PD-L2	58 patients	Flow cytometry	Was correlated with mortality.
Jahangiri (26)	2020	Colorectal	PD-L1	20 patients 20 controls	Flow cytometry	Reduced number of T-reg cells following the treatment using STAT3 inhibitor.
Haghshenas (27)	2015	Salivary gland	IL-17	8 MT** 19 BT***	FACS	Overexpression
Al-Samadi (28)	2016	Colorectal	IL-17	10 patients 10 controls	Immunofluorescence	Overexpression
Kouzegaran (29)	2018	Chronic Lymphocytic Leukemia	IL-17A, IL-22	78 patients 28 controls	ELISA, qRT-PCR, and Flow cytometry	Overexpression
Baharlou (30)	2015	Bladder	IL-17, TGF-β	37 patients 37 controls	qRT-PCR	IL-17 overexpression and TGF-β under expression.
Shokrzadeh (31)	2018	Gastric	IL-10	95 patients 90 controls	ELISA	IL-10 serum levels associated with the stage.
Shekarriz (32)	2018	Multiple Myeloma	IL-10	40 patients 20 controls	ELISA	Overexpression
Abtahi (33)	2017	Colorectal	IL-10	58 patients 30 controls	ELISA	Under expression
Hamzavi (34)	2013	Head and Neck	IL-10	30 patients 24 controls	ELISA and IHC	IL-10 serum levels were associated with stage.
Khodadadi (35)	2014	Breast	IL-23, IL-27	50 patients 50 controls	qRT-PCR	Overexpression
Ghahartars (36)	2018	Skin	IL-27	60 patients 28 controls	ELISA	Overexpression
Babadi (37)	2019	Lung	IL-27	30 patients 30 controls	ELISA	Overexpression
Monfared (38)	2013	Bladder	TGF-β	30 N/T*	Real time-PCR	Under expression
Amirzargar (39)	2005	Chronic Myelogenous Leukemia	TGF-β, IL-4, IL-10	30 patients 40 controls	SSP-PCR	TGF-β overexpression. IL-4 and IL-10 under expressions.
Bordbar (40)	2012	Breast	G-CSF, IL-7	136 patients 60 controls	ELISA	Overexpression
Major histocompatibility complex						
Imani (41)	2018	Oral	HLA-G	33 patients 30 controls	IHC	Overexpression

Farjadian (42)	2018	Gastric and colorectal	HLA-G	100 patients	IHC and ELISA	Overexpression
Esfandi (43)	2006	Colorectal	IL-6	50 patients	ELISA	Overexpression
Mojtahedi (44)	2011	Head and Neck	IL-6	65 patients 20 controls	ELISA	Overexpression
Sahebjamee (45)	2008	Oral	IL-6	9 patients 9 controls	ELISA	Overexpression
Eghtedari (46)	2019	Ocular Surface	IL-6	20 patients 20 controls	IHC	Overexpression
Nikakhlagh (47)	2015	Laryngeal	IL-6	46 patients	ELISA	Overexpression
Lotfi (48)	2015	Oral	IL-6	17 patients 17 controls	ELISA	Overexpression
Allahbakhshian Farsi (49)	2018	Acute Lymphoblastic Leukemia	IFN-G, IL-6	52 patients 13 controls	Real time-PCR	Under expression
Yaghoobi (50)	2018	Breast	IFNG-AS1	108 N/T	Real time-PCR	Overexpression
Hafezi (51)	2015	Gastric	CD1d	52 NUD[1] 53 PUD[2] 39 patients	qRT-PCR	Overexpression
Chemokines and chemoattractants						
Dayer (52)	2018	Breast	CXCR4, SDF-1		qRT-PCR	Overexpression
Lavaee (53)	2018	Head and Neck	SDF-1	60 patients 28 controls	ELISA	Overexpression
Jafarzadeh (54)	2015	Breast	CCL22, CXCL10	100 patients 100 controls	ELISA and ARMS-PCR	Overexpression
Vahedi (55)	2018	Breast	CCR7	70 N/T	IHC	Was correlated with lymph node involvement, grade, and stage
Jafarzadeh (56)	2016	Breast	CXCL10	100 patients 100 controls	PCR-RFLP	Overexpression
Dehghani (57)	2009	Prostate	IL-8	40 patients 40 BPH 34 controls	ELISA	Was correlated with the Gleason score
Tumor necrosis factor						
Ghods (58)	2019	Breast	TNFR2	40 patients	Flow cytometry	Was correlated with grade and lymph node metastasis
Boroumand-noughabi (59)	2010	Gastric	FAS, FASL	59 patients 62 controls	ELISA	Were correlated with lymph node metastasis
Hamidinia (60)	2013	Breast	FOXP3, OX40	40 patients 40 controls	qRT-PCR	Were correlated with stage.
Heidarizadi (61)	2020	Breast	DOK4	67 patients 30 controls	Real time-PCR	Under expression
Angiogenesis						
Gholamin (62)	2009	Esophageal	IL-10, TGF-β, VEGF	49 patients	Real time-PCR	Overexpression
Andisheh Tadbir (63)	2013	Salivary gland	VEGF	58 patients 30 controls	ELISA	Overexpression

Aliparasti (64)	2013	Acute Myeloid Leukemia	VEGF	27 patients 28 controls	Real time-PCR	Under expression

*** Tumor tissues and normal margins.**
**** malignant tumors.**
***** benign tumors.**
1. non-ulcer dyspepsia
2. Peptide ulcer disease

Table 2. All of the immune-related gene polymorphisms reported among Iranian cancer patients.

Study (et al.)	Year	Type	Gene	Population	Methods	Results
Regulatory and helper T cells						
Rahimifar (65)	2010	Cervical	CTLA-4	55 patients 110 controls	PCR-ARMS and -RFLP	Polymorphism was correlated with tumor progression.
Rafiei (66)	2013	Gastric	IL-17	161 patients 171 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Farjadfar (67)	2009	Lung	IL-18	73 patients 97 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Haghshenas (68)	2009	Gastric and colorectal	IL-18	232 patients 312 controls	ELISA and allele-specific PCR (AS-PCR)	Polymorphism was correlated with tumor progression.
Abdolahi (69)	2015	Thyroid	IL-18	105 patients 135 controls	PCR-RFLP and AS-PCR	Polymorphism was correlated with tumor progression.
Khalili-azad (70)	2009	Breast	IL-18	250 patients 206 controls	AS-PCR	Polymorphism was correlated with tumor progression.
Ebadi (71)	2014	Bladder	IL-12, IL-6	261patients 251 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Ghavami (72)	2018	Acute Lymphoblastic Leukemia	IL-27	200 patients 210 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Amirghofran (73)	2009	Colorectal	TGFB1	134 patients 138 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Faghih (74)	2009	Breast	IL-13	305 patients 195 controls	ELISA and PCR-RFLP	Polymorphism was correlated with tumor progression.
Razzaghi (75)	2019	Prostate	MIF	128 patients 135 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Haghshenas (76)	2017	Thyroid	PDCD1	105 patients 160 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Major histocompatibility complex						
Yari (77)	2008	Acute Lymphoblastic Leukemia	HLA-DRB1	106 patients 466 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Hojjat-farsangi (78)	2008	Chronic Lymphocytic Leukemia	HLA-DRB, HLA-DQB	87 patients 100 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Mahmoodi (79)	2012	Breast	HLA-DQA1, HLA-DRB1	100 patients 80 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Dehaghani (80)	2002	Cervical	HLA-DQB1	23 patients 36 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Ghaderi (81)	2001	Breast	HLA-DRB1	36 patients 36 controls	SSP-PCR	Polymorphism was correlated with tumor progression.

Hojjat-farsangi (82)	2014	Chronic Lymphocytic Leukemia	HLA-B	87 patients 64 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Sayad (83)	2014	Non-Hodgkin Lymphoma	HLA-A, HLA-B, HLA-DRB1	75 patients 120 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Khorrami (84)	2016	Gastric	HLA-G	100 patients 102 controls	ELISA and PCR-RFLP	Polymorphism was correlated with tumor progression.
Haghi (85)	2015	Breast	HLA-G	227 patients 255 controls	PCR	Polymorphism was correlated with tumor progression.
Attar (86)	2017	Gastric	IL-6	100 patients 361 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Dargahi abbasabad (87)	2018	Prostate	IL-6	112 patients 118 BPH 250 controls	Real time-PCR	Polymorphism was correlated with tumor progression.
Attar (88)	2016	Liver	IL-6	297 patients 368 controls	SSP-PCR	Polymorphism was correlated with tumor progression.
Kamali-sarvestani (89)	2005	Breast	IFN-G	223 patients 267 controls	AS-PCR	Polymorphism was correlated with tumor progression.
Chemokines and chemoattractants						
Razmkhah (90)	2005	Breast	SDF-1	278 patients 181 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Khademi (91)	2008	Head and Neck	SDF-1	156 patients 262 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Taheri (92)	2019	Prostate	IL-8	130 patients 200 BPH patients 200 controls	ARMS-PCR	Polymorphism was correlated with tumor progression.
Kamali-sarvestani (93)	2007	Breast	IL-8, CXCR2	257 patients 233 controls	AS-PCR	Polymorphism was correlated with tumor progression.
Azimzadeh (94)	2012	Colorectal	IL-16	249 patients 394 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Azimzadeh (95)	2011	Colorectal	IL-16	260 patients 405 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Kashfi (96)	2016	Gastric	IL-16	256 patients 300 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Tumor necrosis factor						
Azar (97)	2016	Liver	TNF-α	409 patients 483 controls	SSP-PCR	Polymorphism was correlated with
Babapour (98)	2019	Cervical	TNF-α	91 patients 161 controls	PCR	Polymorphism was correlated with tumor progression.
Vakil Monfared (99)	2018	Breast	OX40L	123 patients 126 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Angiogenesis						
Eshghyar (100)	2012	Keratocystic Odontogenic	IL-1α	38 patients 150 controls	SSP-PCR	Polymorphism was correlated with tumor progression.

Hashemi (101)	2018	Prostate	IL-1α	150 patients 155 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Ismaili (102)	2015	Gastric	IL-1β	49 patients 53 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Abbasian (103)	2018	Colorectal Gastric	IL-1	126 patients 97 controls	PCR-RFLP	Polymorphism was correlated with tumor progression.
Ibrahimi (104)	2019	Colorectal	IL-1RN	123 patients 152 controls	PCR	Polymorphism was correlated with tumor progression.

There were significantly increased IL-17A and IL-22 plasma levels in a group of Iranian Chronic Lymphocytic Leukemia (CLL) cases compared with controls (29). T helper type 1 (Th1) cells induce an immune response by Interferon-gamma (IFN-γ) production, whereas Th2 cells promote humoral immunity by IL-4 (Figure 2). Many factors such as TGF-β, IL-6, and tumor necrosis factor-alpha (TNF-α) are involved in the stimulation of Th17 differentiation (122, 123). The TGF-β and IL-6 mediate Th17 cell differentiation and suppress Treg cell differentiation (122, 124). IL-17 as the marker of Th17 cells and TGF-β and IL-6 as stimulators of Th17 cell differentiation were assessed among an Iranian subpopulation of bladder cancer patients. It was observed that IL-17 and TGF-β were up and downregulated in patients compared with controls, respectively. IL-17 overexpression in was a protective pro-inflammatory response in the early-stage patients (30).

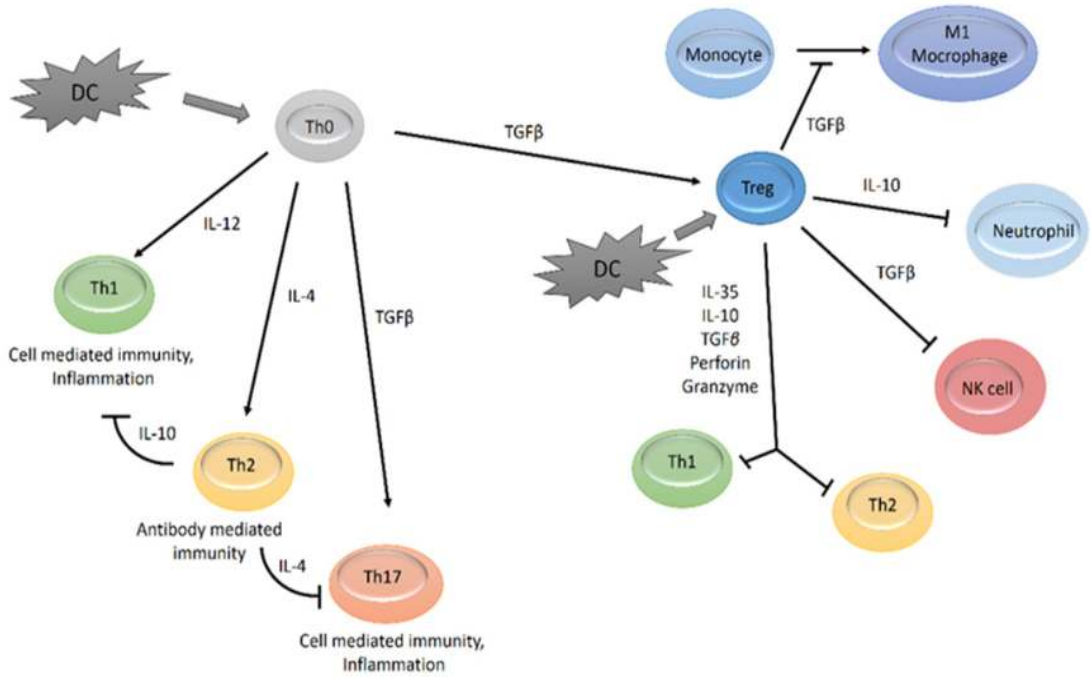

Figure 2. All of the genes involved in the maturation of T helper cells reported among Iranian cancer patients.

IL-2 is a Th1 cytokine involved in Th1/ Th2 stability and tumor-mediated inflammation (125). IL-10 is secreted by macrophages, Th2 cells, and B cells (126). A positive association has been observed between gastrointestinal tumors and increased IL-10 serum levels. The patients with advanced-stage and metastatic tumors had higher IL-10 serum levels compared with other patients (31). There were significantly increased IL-10 serum levels in a sample of Iranian multiple myeloma (MM) patients compared with healthy cases that were directly correlated with advanced tumor stages (32). There was also a significant decrease in serum IL-10 in an Iranian group of CRC patients compared with healthy cases. IL-10 downregulation mediated an aberrant innate immune response against tumor cells that resulted in tumor escape. Moreover, there was a significant association between IL-10 serum levels and vascular invasion (33). IL-10 suppresses cytokine secretion and activation of Th1 cells. It functions as an antiangiogenic factor in tumors via VEGF and MMP-9 down regulations. There was an inverse correlation between IL-10 expression and tumor stage in an Iranian group of Head and neck squamous cell carcinomas (HNSCCs) cases. Moreover, there were elevated serum IL-10 levels in patients compared with controls (34).

IL-18 exerts its tumor suppressor role through IFN-γ upregulation which stimulates Th1 differentiation, and tumor cell apoptosis while suppressing angiogenesis (127). IL-18 also prevents tumor cell recognition by immune cells and upregulates angiogenic and growth factors (128). IL-18 is produced by macrophages, kupffer cells, and thyroid cells (129). IL-18 -607(C/A) polymorphism was assessed in an Iranian group of lung cancer patients that showed a significantly increased frequency of CA and AA genotypes and A allele among squamous tumor type cases (67). Similarly, IL-18 -607 A/C polymorphism increased the Non-small-cell lung cancer (NSCLC) susceptibility in the Chinese population (130). There was a correlation between IL-18 -137G/C polymorphism and gastrointestinal cancer susceptibility among Iranian patients. Reduced frequency of CC genotype was associated with CRC risk. Moreover, -137 G/C allele frequencies were significantly different between GC patients and controls. The -607C/-137C and -607A/-137G haplotypes were more frequent among GC patients, while the -607C/-137C haplotype was more common in CRC patients compared with healthy subjects. Moreover, the -607AA/-137GC genotype was more frequent in poorly differentiated compared with well-differentiated tumors. There were increased serum IL-18 levels in CRC and GC patients compared with healthy subjects (68). Similarly, the -137C/-607A haplotype was correlated with increased CRC susceptibility among Chinese cases (131). IL-18 and IFN-γ are associated with thyroid degeneration in Hashimoto's thyroiditis (132). IL-18 656G/T polymorphism was significantly associated with thyroid cancer susceptibility in Iranian patients in which TT genotype carriers had an increased risk of thyroid cancer compared with other genotypes. In contrast, the CC genotype carriers in IL-18 127T (rs360717) polymorphism had a significantly reduced risk of thyroid cancer. Moreover, there was a significant correlation between TAGTT haplotype and thyroid cancer risk (69). Similarly, IL-18 rs360717 was significantly correlated with lymph node invasion among a Korean group of thyroid cancer patients (133). The -137 G/C polymorphism of IL-18 was assessed among an Iranian sample of BC cases compared with controls in which there was a significantly increased frequency of CC genotype in metastatic compared with non-metastatic tumors (70). The 137G/C polymorphism also contributed to increased BC susceptibility among the Brazilian population (134).

IL-6 is involved in cell growth and differentiation which is produced by monocytes, granulocytes, endothelial cells, and keratinocytes (135). It inhibits the MHC-II production by Dendritic cells (DCs) through STAT-3 activation that results in Cystatin downregulation and Cathepsin activation (136). IL-6 is involved in plasma cells to B lymphocyte differentiation. It also promotes the acute phase of inflammation and tumorigenesis (137, 138). Moreover, it upregulates the VEGF through activation of the JAK/STAT signaling pathway during tumor progression (139, 140). There were significantly increased serum and tissue levels of IL-6 in a sample of Iranian CRC patients with stage IV compared with patients in stage I-III (43). CRC tumors with IL-6 overexpression had also faster tumor growth compared with IL-6 knockout tumors in the mouse model. Moreover,

a converse association was observed between the IL-6 levels and overall survival among the Chinese population (141). Increased serum levels of IL-6 were also observed among an Iranian group of HNSCC patients compared with controls. There was a direct significant association between serum IL-6 levels and advanced tumor stage (44). There were significantly increased salivary levels of IL-6 in an Iranian subpopulation of Oral squamous cell carcinoma (OSCC) patients compared with controls (45). It has been shown that there was IL-6 upregulation in dysplastic ocular surface compared with non-neoplastic samples among Iranian subjects (46). Significant increased IL-6 serum levels were shown in an Iranian group of laryngeal cancer patients compared with healthy cases that were associated with grade and lymph node metastasis (47). Similarly, increased serum IL-6 level was associated with lymph node involvement and tumor stage among Laryngeal squamous cell carcinoma (LSCC) cases in a Chinese population (142). There were increased serum and salivary IL-6 levels among Iranian and Indian groups of OSCC patients (48, 143). IL-6 -174 G/C polymorphisms were assessed in Iranian GC subjects that showed a higher prevalence of G allele among patients compared with controls (86). There were significantly different frequencies of IL-6 -174 GG genotype and G allele among an Iranian subpopulation of metastatic PCa patients compared with healthy subjects in which the IL-6 (-174 C) allele was more frequent in PCa cases with bone metastasis (87). Similarly, the GC genotype and C allele of the IL-6 -174 polymorphism were significantly associated with PCa in Slovak patients (144). The correlation between IL-6 174G/C polymorphism and HBV infection was studied in an Iranian group of hepatocellular carcinoma (HCC) patients. There was a significantly increased frequency of G allele and G/G genotype in HBV cases in comparison with controls. G/G and C/C genotypes were also more frequent in males and females, respectively (88). IL-6 and IFN-γ down regulations were also reported in an Iranian group of Acute lymphocytic leukemia (ALL) cases (49).

IL-12 and IL-27 are the most important anti-tumor cytokines that stimulate the proliferation of naive CD4+T cells via STAT1 and STAT3 activation (145, 146). The IL-27 is mainly produced by APCs that regulate IFN-γ in CD4+ T cells (146). IL-27 is also involved in the regulation of different immune-related factors such as IL-18BP and IL-10 (147, 148). IL-27 exerts its tumor suppressor function through inhibition of angiogenesis and cell proliferation (149). It has been observed that there were IL-27 and IL-23 up regulations in the peripheral blood of BC patients compared with controls among Iranian subjects (35). The IL-12B (1188 A/C) and IL-6 (174G>C) polymorphisms were assessed in an Iranian group of bladder cancer subjects. AC and CC genotypes of 1188 A/C were correlated with an increased risk of bladder cancer in smokers. The GC and GC+CC genotype carriers at 174GC had also increased tumor susceptibility compared with GG genotype harbors (71). There were significantly higher serum levels of IL-27 in an Iranian group of Non Melanoma Skin cancer patients compared with healthy subjects (36). There was a significantly higher frequency of rs153109 AG genotype and G allele in a sample of Iranian ALL cases compared with controls. The cases with combined G variant (TG + GG) of rs17855750 had higher levels of serum IL-27 in comparison with TT genotype carriers. There were significantly increased IL-27 serum levels in patients compared with controls. Moreover, the rs153109 AG and rs17855750 TG genotype carriers had poor prognoses and a higher rate of tumor relapse (72). Similarly, another study has reported that the rs153109 AG/GG and rs17855750 GT/GG significantly increased papillary thyroid carcinoma (PTC) susceptibility among Chinese cases (150). There were higher serum IL-27 levels in Iranian lung cancer patients compared with healthy subjects. The serum IL-27 level of stage III cases was higher than stage IV patients (37).

TGF-β is a tumor suppressor cytokine involved in apoptosis stimulation and cell proliferation suppression (151). It inhibits the Th1 and Th2 cell differentiation (152). TGF-β2 is the most prevalent type in mammalian cells (153). It activates the Smad (SMAD) transcriptional regulators through binding with TGF-βR (154). The TGF-β1 -509 C/T polymorphism was assessed in a group of Iranian CRC patients, which showed that there were significantly decreased frequencies of the 509T allele and TT genotype among cases compared with controls. Therefore, TGF-β1 509T al-

lele carriers had a lower risk of CRC in comparison with C allele carriers (73). MicroRNAs (miRNAs) downregulate their target genes through mRNA degradation or translational suppression (155-157). MiR-21 is known as an oncomiR by targeting various tumor suppressors (158, 159). Bone morphogenetic protein 4 (BMP4) and TGF-β can also induce miR-21 in vascular smooth muscle cells (160). There was TGF-β down-regulation in an Iranian group of low-grade bladder cancer patients. There was a rising trend of miR-21 expression from low-grade to high-grade tumors which showed miR-21 as a differentiation factor in these cases. Moreover, there was a significant direct correlation between miR-21 and TGF-β expressions (38).

IL-4 regulates the Th2 cell differentiation (161). IL-10 is a T-cell differentiation factor that stimulates IgG, IgA, and IgM production. It has been reported that there was a significantly increased frequency of IL-4 590CC genotype and IL-10 haplotype ACC in a sample of Iranian chronic myeloid leukemia (CML) cases. There were TGF-β upregulation and IL-4 and IL-10 downregulations in CML cases compared with controls (39). TGF-β (- 509 C/T) and IL-10 (- 819 C/T) polymorphisms were also correlated with decreased GC susceptibility in a sample of Mexican cases (162). IL-7 is a pleiotropic cytokine involved in tumorigenesis, lymphocyte development, and anti-apoptotic responses in hematopoietic tissues (163). It induces the IFN-γ and TNF-α production by Th1 cells (164). Granulocyte colony-stimulating factor (G-CSF) is a stimulator of granulocyte differentiation from hematopoietic progenitors (165). There were IL-7 and G-CSF regulations among an Iranian subpopulation of BC patients. Well-differentiated and N3 tumors had the highest levels of IL-1 and G-CSF expressions, respectively. Moreover, advanced-stage tumors had higher levels of serum G-CSF compared with early-stage ones (40). IL-13 is involved in apoptosis inhibition and cell proliferation induction in CLL and Hodgkin diseases (166-168). There was a direct association between the -1512C allele and increased estrogen receptor (ER) expression, whereas the -1055C allele was inversely associated with increased ER expression among an Iranian group of BC cases (74).

MIF is a pleiotropic cytokine of the TGF-β gene family that is involved in the regulation of innate immunity (169). It also induces the TNF-α and IL-1 productions (170). The MIF-173 G/C polymorphism was assessed in an Iranian group of PCa cases and showed that MIF-173*C geno_type was associated with higher Gleason scores and advanced tumor stages (75). Similarly, the MIF-173*C allele significantly contributed to an elevated risk of PCa among Chinese patients (171). Programmed cell death (PD-1) is involved in immune tolerance via the prevention of B and T cell proliferation and activation (172, 173). Moreover, it regulates induced regulatory T-cell development (174). There was a significant association between the CT genotype and T allele of PD-1.5 and thyroid cancer in a sample of Iranian subjects in which the CT genotype carriers had an increased risk of thyroid cancer compared with other genotypes. CC genotype was also significantly more frequent among controls (76).

Major histocompatibility complex and related genes

The major histocompatibility complex (MHC) encodes HLA class I (A, B, and C) and class II (DR, DQ, and DP) alloantigens (175, 176). B-cell differentiation and proliferation are associated with MHC-related T-cell activation as an adaptive immune response. The HLA-DRB1 alleles were assessed in an Iranian subpopulation of ALL cases compared with controls. There were decreased and increased frequencies of DRB1*13 and DRB1*04 alleles in ALL patients, respectively. Their results indicated an association between the elevated DRB1*04 frequency and childhood ALL, which was similar to another study in British ALL patients (77, 177). HLA-II is involved in the regulation of antigen presentation to T lymphocytes (178). These polymorphic antigens affect the pathogenesis of B-cell or T-cell malignancies via continuous induction of antigen-specific lymphocytes (179). There was a significantly higher HLA-DRB1*07 frequency in Iranian CLL cases compared with controls. The patients had an increased frequency of DRB1*13, whereas there were decreased DRB1*11, 15, 04, and 09 frequencies in patients compared with healthy cases. There were also significant direct and inverse associations between DQB1*06 DQB1*03 and CLL, respectively. Moreover, there were significantly

increased frequencies of the DRB1*04 and DRB5 alleles in CLL patients compared with indolent cases. There were increased DRB5 and DRB1*04 allele frequencies in patients with progressive disease(78). Another study has reported that there was a significant direct association between the HLA-DQA1*0301 allele and BC progression among Iranian subjects. HLA-DQA1*0505 and 0101 as well as HLA-DRB1*1301 and 0101 alleles were also protective (79). A significant direct association was also observed between the HLA-DQB1*0601 allele and cervical cancer (80). There was a significant association between the HLA-DRB1*12 allele and BC risk in a group of Iranian cases (81). HLAs are the most polymorphic factors involved in antigen presentation to T cells. Significantly increased HLA-A11:01 frequency and reduced frequencies of HLA-A01:01 and HLA-A26:01 alleles were observed among Iranian CLL cases compared with controls. There was also a significantly increased frequency of HLA-B35:01 allele among CLL cases. However, HLA-B65:01 and HLA-B53:01 alleles were protective (82). Another study has shown that there were significant direct and inverse correlations between HLA-A*26 and HLA-B*35 alleles and non-Hodgkin lymphoma among Iranian subjects, respectively (83).

Although the immune system regulates tumor progression, it is not enough efficient for tumor recognition and elimination. HLA-G as a non-classical HLA-I antigen is a tolerogenic factor in tumor survival through interaction with IL-2 and IL-4 on immune cells that reduces the immune response against tumor cells (180). HLA-G has a critical role in the suppression of maternal immune response toward the fetus and placenta (181). It exerts immune tolerance in NK cells, T cells, APCs, and endothelial cells through regulation of differentiation, proliferation, and cytokine secretion. There were significantly different frequencies of G*01:01:03:01, G*01:01:08, and G*01:01:03:01/G*01:04:01 alleles and genotypes among Iranian GC patients compared with normal controls. The G*01:01:02:01/G*01:04:01 genotype carriers had an increased risk of GC. Moreover, there were significantly increased serum HLA-G levels in patients in comparison with healthy subjects (84). There was HLA-G upregulation in an Iranian group of OSCC cases compared with controls that were associated with the stage of tumor, survival, and distant metastasis (41). HLA-G expression was also significantly correlated with histological grade in a Chinese subpopulation of OSCC patients (182). HLA-G up regulations were also observed in Iranian GC and CRC patients compared with controls (42). The 14bp insertion/deletion (InDel) polymorphism of HLA-G was assessed in an Iranian subpopulation of BC cases in which there was an increased frequency of HLA-G 14bp del genotype in BC cases compared with controls (85). Similarly, the Del allele and Del/Del genotype confer a risk for BC in the Tunisian population (183).

Interferons are another group of immunomodulatory and anti-proliferative cytokines (184). IFN-γ as a critical innate and adaptive immune cytokine promotes MHC-II expression that is produced by NKT and Th1 cells (185). Interferon γ-antisense RNA1 (IFNG-AS1) is associated with IFNG expression in Th1 cells (186). IFN-γ has tumor suppressor function through cytotoxic T and DCs activations. It has been shown that there was a significant IFNG-AS1 overexpression in BC subjects compared with their normal margins among Iranian subjects. There was also IFNG upregulation in grade I in comparison with grade II tumors. IFNG downregulation is a probable mechanism recruited by tumor cells to escape from the immune response. HER2-negative tumors had also higher IFNG expression compared with HER2-positives. Moreover, there was IFNG-AS1 upregulation in tumor tissues in comparison with normal margins (50). There was a significant association between C874 IFN-γ polymorphism and BC risk in Iranian subjects in which the patients had increased frequency of T/T genotype compared with healthy cases (89).

CD1d is an MHC-I-like cell surface glycoprotein expressed on DCs, B cells, T cells, and epithelial cells (187). As an innate immune receptor, it is involved in H. pylori detection by gastric epithelial cells during mucosal inflammation. There were significant regulations of CD1d (V4 and V5) splice variants in an Iranian group of GC patients compared with non-ulcer dyspepsia (NUD) cases. The V4 was significantly upregulated in H. pylori-positive NUD compared with negative patients which can be associated with the induction of innate immune responses (51).

Chemokines and chemoattractants

Chemokines are involved in cell migration of leukocytes during inflammation which are produced by various leukocytes, endothelial cells, and tumor cells. They can also regulate angiogenesis tumor progression and metastasis (188). Stromal cell-derived factor 1 (SDF-1) and its receptor CXCR4 are associated with tumor growth and metastasis in different cancers (189, 190). SDF1-CXCR4 interaction is associated with prostate cancer metastasis to bone and lung through activating tumor cell migration (190). SDF-1 induces tumor cell migration through upregulation of MMP-1, TNF, and integrin (191). A significantly different frequency of SDF-1 G801A polymorphism was shown between Iranian groups of lung cancer cases and healthy subjects. The patients had significantly higher frequencies of AA and AG genotypes and A allele compared with controls. Therefore, SDF-1 G801A polymorphism upregulated the SDF-1 which resulted in cell cycle aberration and cellular transformation (192). In contrast, there was not any significant association between SDF-1 G801A polymorphism and NSCLC risk among Chinese patients (193). The SDF-1 -30A polymorphism has been assessed among BC patients in which there were higher frequencies of AA and AG genotypes and A allele among Iranian patients compared with controls. Moreover, the GG genotype was directly correlated with lymph node involvement. Decreased lymph node metastasis can be associated with SDF-1 upregulation in AA and AG genotype carriers which results in CXCR4 under expression on endothelial and tumor cells. Therefore, AA and AG carriers had an increased risk of BC compared with normal cases (90). Similarly, higher SDF-1 GA and AA genotype frequencies were observed in a group of Greece BC cases compared with healthy controls (194). Another study showed that there was a correlation between SDF1-3'A polymorphism and head and neck cancer susceptibility among Iranian cases (91). Similarly, the SDF1-3'A variant was correlated with an increased risk of laryngeal tumors among Polish cases (195). It has been reported that there was a direct association between HER-2-positive BC tumors and CXCR4 expression in a sample of Iranian patients. There was a direct association between CXCR4 upregulation and lymph node involvement. Moreover, CXCR4-SDF1 expressions were correlated with MMP-2 expression in advanced-stage tumors. E-cadherin downregulation was also associated with CXCR4-SDF1 overexpression in advanced-stage tumors (52). Another study on the Chinese population with esophageal cancer showed SDF1/CXCR4 as an important mechanism of metastatic esophageal cancer through extracellular signal-regulated protein kinase 1/2 (ERK1/2) signaling pathway (196). There were significantly increased plasma CXCL12 levels among an Iranian subpopulation of HNSCC patients compared with controls (53). Another study on HNSCC patients indicated a correlation between CXCL12 upregulation and increased overall survival in a German population (197). The Th1-related cytokines are IFN-γ and TNF-α, while the Th2-related cytokines are IL-4 and IL-10 (198, 199). CCL22 is a chemokine produced by macrophages and DCs (200). CCL22 is upregulated by IL-4 and IL-5, while inhibited by IFN-γ (200). CXCL10 is produced by neutrophils, keratinocytes, and endothelial cells (201). It binds to CXCR3 on Th1 lymphocytes and NK cells to improve immune response against tumor cells (202, 203). There were significantly increased serum CCL22 and CXCL10 levels among an Iranian subpopulation of BC patients compared with controls. The CCL22 was also directly associated with advanced tumor stages. Moreover, there were significantly higher frequencies of CC genotype and C allele at CCL22 rs223818 polymorphism in BC patients compared with controls. CC genotype or C allele carriers also increased serum CCL22 levels compared with GG genotype or G allele (54). CCR7 is a chemokine receptor involved in immune cell migration to lymphoid organs that is produced by various immune cells such as DCs and NK cells (204). It has been shown that there were significant correlations between C-C chemokine receptor 7 (CCR7) expression, lymph node metastasis, tumor grade, and stage in an Iranian group of BC subjects (55). IFN-γ induces the anti-tumor activity of tumor-infiltrating macrophages through CXCL10 secretion as an angiogenic inhibitor in tumors and Th1 cell recruitment (205). There were increased serum levels of CXCL10 among an Iranian subpopulation of BC patients compared with healthy cases. ER and PR-negative tumors had also higher CXCL10

serum levels compared with positive tumors. Moreover, genotype analysis showed that there were significantly elevated frequencies of GG genotype and G allele of rs4508917 in CXCL10 among patients in comparison with healthy cases. The GG genotype or G allele carriers had significantly higher CXCL10 serum levels compared with the AA genotype or A allele carriers. There was also a direct association between CXCL10 expression and advanced stages (56). IL-8 (CXCL8) is a pro-inflammatory chemokine involved in the regulation of tumor microenvironment including endothelial cells and tumor-associated macrophages (206). It can also be associated with immune response against tumor cells through neutrophil activation and migration. IL-8 silencing results in cell cycle arrest, apoptosis, and drug response in prostate tumor cells (207). There was a significantly decreased frequency of ATA haplotype (rs407, rs2227306, and rs1126647 respectively) in an Iranian group of PCa cases compared with benign prostatic hyperplasia (BPH). There was also a converse correlation between the A allele of rs4073 and PCa risk in the dominant model (92). Another group has observed that there were significantly different plasma levels of IL-8 among PCa patients with severe or mild disease and BPH subjects in the Iranian population. Moreover, plasma IL-8 level was significantly correlated with Gleason scores (57). Another group has reported that there was a significantly increased AA genotype of IL-8 -251 T/A frequency among BC compared with healthy subjects. CXCR2 +1208 TT genotype was also correlated with poor prognosis and ER downregulation (93). IL-16 is a lymphocyte chemoattractant belonging to the chronic inflammation cytokines that induce systemic or tissue-specific inflammation (208, 209). It upregulates the TNF-α, IL-1, and IL-6. A significant association was shown between IL-16 rs1131445 polymorphism and CRC risk in a sample of Iranian cases (94). Another study showed that there were correlations between rs11556218 T>G and rs4778889 T/C polymorphisms of IL-16 and CRC susceptibility among Iranian subjects (95). There was a significant association between IL-16 rs4072111 polymorphism and the risk of GC in a group of Iranian subjects in which CT genotype carriers elevated the risk of GC. In contrast, the TT genotype was associated with a decreased risk of GC. The men carriers of the T allele had higher GC risk compared with women. A significant correlation was also observed between the rs1131445 of IL-16 CT genotype and GC susceptibility (96).

Tumor necrosis factor

TNF-α is a cytokine produced by active macrophages that is involved in cell survival, proliferation, immune response, differentiation, and cell death (210). Tumor necrosis factor receptor 1 (TNFR1) and TNFR2 are two members of the TNF receptor family which show homologous function in extracellular domains and distinct functioning in different signaling pathways (211, 212). Both soluble and transmembrane forms of the TNF-α are bound to TNFR1 during inflammation, cytotoxicity, and apoptosis (213). The mTNF-α-TNFR2 interaction is involved in lymphocyte activation and proliferation. TNFR2 is also associated with some co-stimulatory functions in B and T (214, 215). There were significantly higher percentages of TNFR2+ B cells in lower tumor grades with less lymph node metastasis in an Iranian group of BC cases (58). TNF-α -308G>A polymorphism was assessed in Iranian HCC patients in which the A/A genotype was more frequent in HBV-infected individuals compared with the healthy subjects. The G allele and G/G genotype were correlated with HBV whereas A/A or A/G carriers were correlated with chronic HBV infection (97). Similarly, TNF-α-308 G/A polymorphism was associated with an increased risk of HCC among Taiwanese cases (216). There was also an association between TNF-308 G>A polymorphism and increased cervical cancer susceptibility in Iranian patients in which the A allele carriers had higher cervical cancer susceptibility in comparison with GG genotype harbors (98). Similarly, there was also a correlation between TNF-α-308 polymorphism and cervical cancer among Chinese subjects in which the A allele carriers had more aggressive tumors (217). Fas receptor (FAS) is also another member of TNF-family receptors that promotes apoptosis following the Fas Ligand (FASL) binding (218). FASL has a critical function in immune system homeostasis in which cytolytic T stimulates apoptosis in tumor cells using FASL (219). It has been reported that there was a rising trend of FAS serum levels from normal toward tumoral epithelium in an Iranian

group of GC patients. There was also a significantly increased serum FASL levels in non-cardiac cases compared with cardia tumor type. Moreover, they observed an inverse association between FAS serum levels and lymph node metastasis (59). OX40L is a type II glycoprotein belonging to the TNF superfamily which is produced by different cells including DCs, macrophages, endothelial cells, and activated T cells (220-222). The OX40 binding with OX40L promotes T-cell proliferation, activation, and cytokine production (223). Moreover, it induces IL-2 expression that regulates T cell survival through NF-κB and survivin (224). NF-κB is also activated by OX40 which promotes the Protein kinase B (PKB) activation leading to BCL-2 and BCL-XL expressions (225, 226). Survivin is an anti-apoptotic protein activated by the PKB pathway and improves the survival of the activated T cell (227). The OX40L rs3850641 polymorphism was assessed among an Iranian subpopulation of BC cases which showed that the rs3850641 G allele significantly increased BC susceptibility (99). Similarly, the OX40L rs3850641G allele was associated with increased BC risk in the Chinese population (228). The OX40L rs3850641 polymorphism was also assessed in BC patients and healthy controls which showed elevated frequencies of AG and GG genotypes and G allele in cases compared with healthy subjects among Iranians (99). OX40 is also produced by FOXP3+T-regs (229). FOXP3 and OX40 expressions were correlated with tumor stage in an Iranian group of BC patients (60). Docking Protein 4 (DOK4) is a scaffold protein that provides a docking platform for the assembly and regulation of multi-molecular signaling complexes. It functions as a suppressor of the tyrosine kinase pathway while promoting TNF. There was significant DOK4 downregulation in Iranian BC tissues compared with normal margins (61).

Angiogenesis

Angiogenesis is a pivotal process to provide nutrients during tumor progression and metastasis (230). The maturation and proliferation of the endothelial cells can be promoted by some angiogenic factors such as TGF-α, TNF-α, IL-6, and IL-8 (231). During the inflammatory response, immune cells produce and secrete angiogenesis-promoting factors which promote angiogenesis. In addition, the newly formed vasculature maintains inflammation by facilitating the inflammatory cells' migration to the inflammation site (232). It is significantly reported that tumor cells can secrete angiogenesis-promoting factors and mediators of inflammatory cells (233). Immune cells work synergistically with malignant and stromal cells in stimulating the proliferation and angiogenesis of the endothelial cell. These synergies might also constitute crucial mechanisms for tumor metastasis using facilitating the tumor escape (232). VEGF is one of the main angiogenic factors that is responsible for the oxygen and nutrient supply of tumor cells (234). VEGF can also be an immune suppressor through suppression of DC differentiation (235). TGF-β is involved in cell proliferation and angiogenesis induction (236). It has also an immune suppressive role by MHC-II blocking tumor cells and NK cell deactivation (237). IL-10 inhibits MHC-I in tumor cells to resist them toward cytotoxic T lymphocytes (238). IL-10 has also an antitumor activity by increasing the level of Nitric oxide (NO) (239). There were significant IL-10, TGF-β, and VEGF over expressions among an Iranian subpopulation of esophageal squamous cell carcinoma patients. Moreover, concomitant TGF-β and VEGF expressions were significantly associated with tumor size (62). A significantly elevated VEGF serum level was also observed in healthy to malignant tumors in an Iranian group of salivary tumors (63). There was a significant VEGF-C downregulation in AML cases compared with healthy subjects among the Iranian population (64).

IL-1α is an inflammatory cytokine produced by many cell types such as monocytes, macrophages, and cervical epithelium (240, 241). It upregulates different growth factors such as TNF-α, VEGF, and MMPs (242, 243). There was a correlation between IL-1α C/T-889 polymorphism and keratocystic odontogenic (KCOT) tumors in a sample of Iranian subjects in which there was a significant association between T allele and KCOT risk (100). There was an association between IL-1α rs3783553 polymorphism and PCa susceptibility among Iranian subjects in which Del/Del and Ins/Del + Del/Del genotypes and Del allele carriers had significantly increased risk of PCa (101). The TTCA ins allele of rs3783553 polymorphism was also suggested as a protective variant in PCa

susceptibility among Chinese cases (244). IL-1β is secreted by activated macrophages (245). There was a direct correlation between IL-1B+3954 polymorphism and GC in a group of Iranian patients (102). Similarly, IL-1B+3954 CT or TT variants were associated with GC susceptibility in Chinese cases (246). The IL-1RN VTNR polymorphism was also assessed in Iranian groups of GC and CRC patients. There were significant correlations between the IL-1RN*2 allele and increased CRC and GC susceptibilities. Moreover, the IL-1RN *2/*2 genotype was significantly associated with elevated GC risk (103). Another study assessed the role of IL-1RN 86bp VNTR gene polymorphism on CRC risk in a group of Iranian subjects in which there was a significant correlation between the 2R allele and 2R (1/2 and 2/4) genotypes and increased CRC susceptibility (104).

Conclusion

Genetics and environment are important risk factors involved in tumor progression. Therefore, our body is condemned to have several defense mechanisms against carcinogenic factors. The immune system is one of the most effective tumor suppressor mechanisms that is responsible for the detection and elimination of tumor cells. In the present study, we summarized all of the aberrant immune related genes that have been reported among Iranian cancer patients to clarify the molecular biology and genetics of immune deficiencies during tumor progression in this population. We observed that the Regulatory T cell and T helper cell-related genes were the most common immune gene aberrations during tumor progression in the Iranian population. This review helps to suggest a novel and efficient immune-specific panel marker for immunotherapeutic and diagnostic purposes among Iranian cancer patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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