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Review Article

Research progress on Th22 cells and related cytokines in tumors: current status and future perspectives

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Abstract: Th22 cells are a newly identified subpopulation of $CD4^+$ T lymphocytes distinct from Th1, Th2, and Th17 cells, which secretes mainly interleukin-22 (IL-22), in addition to a variety of other cytokines. The function of Th22 cells in tumors is mainly realized through IL-22, which can activate JAK/STAT and MAPK cell signaling pathways, thereby regulating the anti-tumor immune response of the body. The main function of Th22 cells is to participate in mucosal defense, tissue repair, and wound healing. However, controversial data have shown that overexpression of IL-22 can lead to pathological changes under inflammatory conditions and tumor progression. In this review, we searched the PubMed and Web of Science databases for articles and reviews published before May 6, 2022, using the keywords "Th22 cells, T helper 22 cells, cancer, tumor", and conducted a comprehensive review of the relevant literature. In addition, this article offers an overview of the relevant findings on the function of Th22 cells in tumors published in recent years, along with a more comprehensive analysis of the functions and mechanisms of Th22 cells in tumors. This article will hopefully inspire new future directions in the research on cancer therapy.

Keywords: Th22, gynecological tumors, differentiation of Th cells

Introduction

Th22 cells are a newly identified subpopulation of $CD4^+$ T lymphocytes that are distinct from Th1, Th2 and Th17 cells (**Figure 1**). They are characterized by a high level of IL-22 secretion, without IFN, IL-4 or IL-17. However, Th22 also secrets TNF-α and IL-13 [1]. Th22 cells develop from naive T cells in the presence of lineage specific cytokine cocktail including TNF-α, IL-6, IL-12, IL-21, IL-23, and under long-term culture retain the IL-22 positive phenotype [2]. It has been proposed that cooperation of TNF-α, IL-6, and plasmacytoid dendritic cells can induce the Th22 phenotype [2]. IL-6 and TNFα are required for in vitro generation of Th22 from naïve $CD4^+$ T cells [3, 4]. Aryl hydrocarbon receptor (AHR), RAR-related orphan receptor gamma (RORγt), and T. bet have been reported as the main transcription factors for Th22 cells development [5, 6]. In recent years, it has been found that even vitamin D and Langerhans cells can contribute to the expression of IL-22 [7]. In the process of differentiation, a balance is maintained between Th17 and Th22, which may be altered by certain factors. The stimulation of normal human $CD4^+$ T cells with IL-1β was found to induce the differentiation of Th17 cells, promoting the production of IL-22 and IL-17 [8, 9]. Naphthoflavone accelerated the differentiation of Th22 cells but downregulated the expression of Th7, thus inhibiting the production of Th17. In mice, the addition of βNF did not inhibit the production of Th17, but induced co-differentiation of Th17 and Th22 cells. These divergent results are likely due to differences interspecies differences between humans and mice. In this article, the general biology of Th22 cells is outlined first, followed by a review of the role of Th22 cells in promoting or inhibiting tumorigenesis.

General biological characteristics

Dumoutier et al. discovered IL-22 in 2000 [11]. It is encoded by a gene on human chromosome

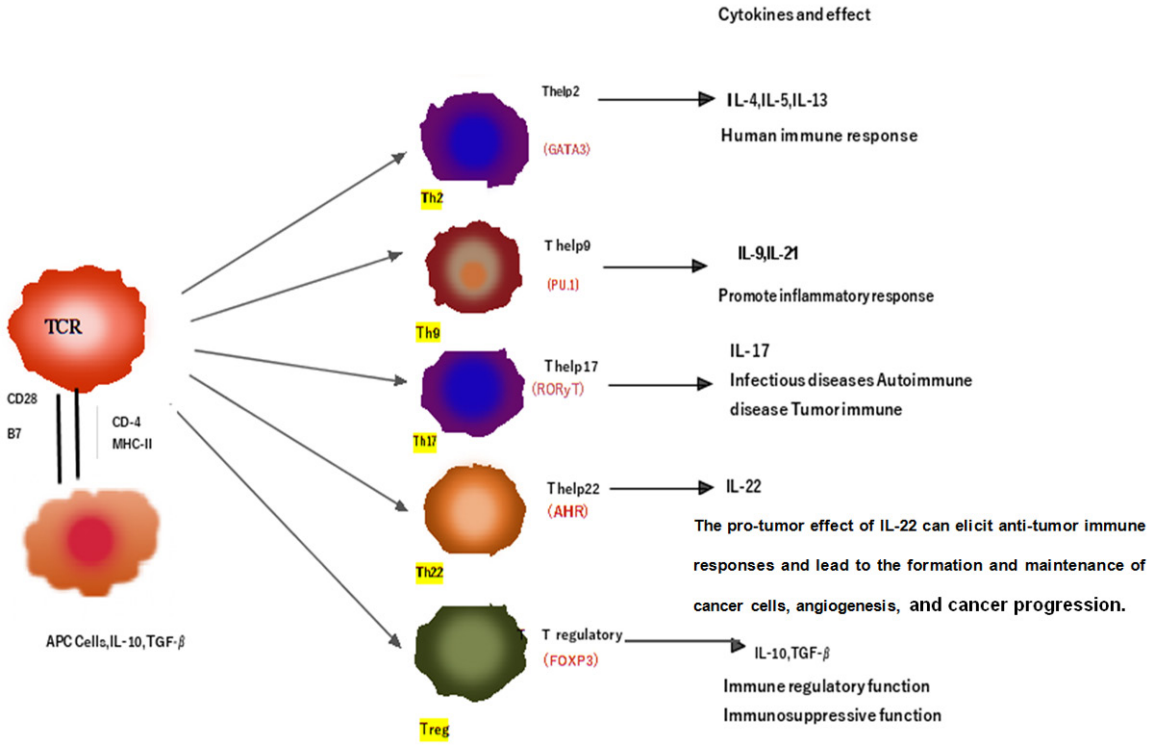

Figure 1. Diagram of differentiation and secretion of cytokines by a naïve T cell.

12q15 with a length of approximately 6 kb. It is composed of 179 amino acids and pertains to the IL-10 family of cytokines. It was firstly called IL-10-relevant T-cell-derived factor, and it is mainly excreted by Th22 cells, Th17 cells, intrinsic lymphocytes (ILCS), γST cells and natural killer cells (NKT), among which Th22 cells secrete the most IL-22, accounting for 37-63% of the total cytokines [12]. IL-22 induces a series of effects by binding to its receptor (IL-22R), which stimulates downstream signaling pathways. IL-22R is a heterodimer consisting of IL-22R1 and IL-10R2. IL-22 first binds IL-22R1 [13]. IL-22 binding to the IL-22R1-IL-10R2 complex causes stimulation of the receptor-related Jak1/Tyk2 kinase, leading to the phosphorylation of the receptor (STAT) [14].

The chief signaling mediator of IL-22 is STAT3, an oncogene relevant to cell migration and differentiation in a variety of cancers. Thus, most of the traits of Th22 cells are backed by STAT3 signaling [15-17]. To a lesser extent, IL-22 activates other signaling pathways including MEK/extracellular signal-regulated kinase (ERK), Jun amino-terminal kinases (junk), MAPKs pathway, NF-κB, p38 pathway, also increases expression of histone 3 lysine 79 (H3K79) methyltransferase DOT1L (Disruptor of telomeric silencing 1-like) and H3K27 methyltransferase Polycomb repressive complex 2 (PRC2) [15, 16]. NOTCH signaling plays an important role in the development and differentiation of T cells [18]. This signal interacts with signal transducer and catalyst of transcription 3 (STAT3) and intercede cell differentiation [19]. Recently, Zeng *et al.* also reported that NOTCH signaling or over activation of the NOTCH downstream target HES-1 causes naïve $CD4^+$ T cells to differentiate into Th22 [20]. Additionally, IL-22 weakly increases the expression of STAT1 and STAT5 [21]. The key difference between IL-22 and other cytokines is that although it is derived from immune cells, it acts on non-immune cells, suggesting that IL-22 may be a key factor in epithelial-immune cell interactions [5]. Strong evidence has demonstrated that IL-22 is crucial in preserving and rebuilding skin's epithelial and keratinocyte cells, which supports immunity against pathogen entrance. In addition, pro-inflammatory mediators such TNF-α, IL-1b, IL-6, IL-8, IL-1, GM-CSF, and G-CSF are expressed when IL-22 is present [22, 23]. Th22 cells are identified by the secretion of

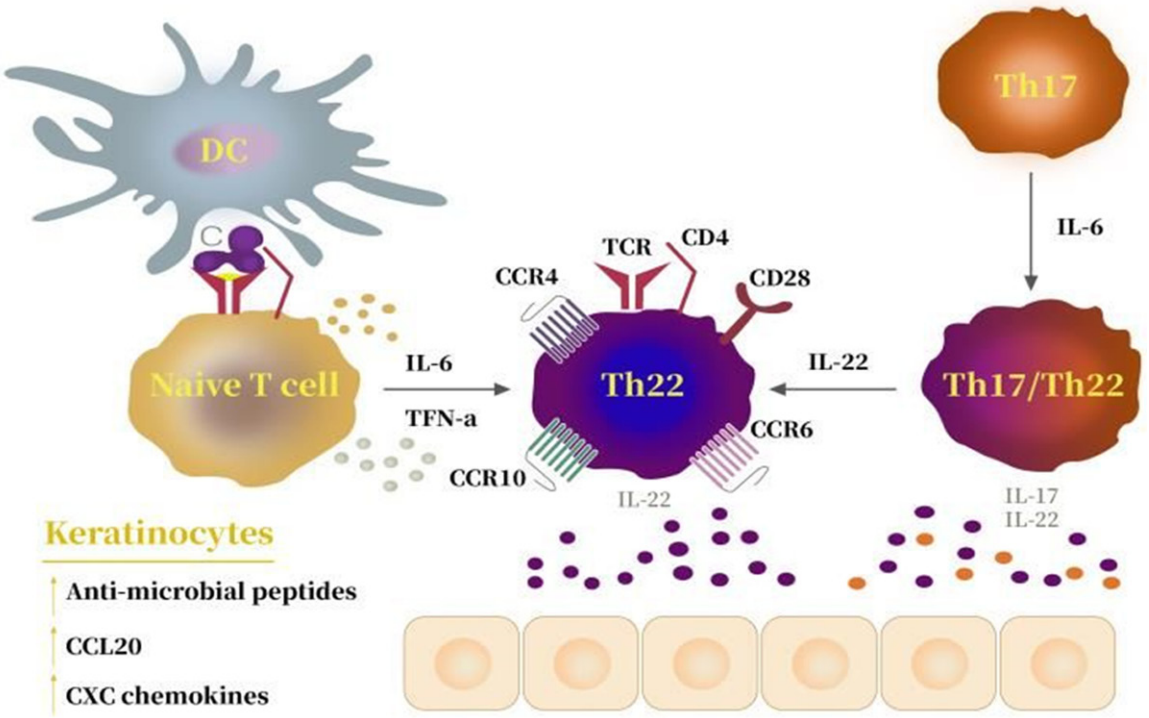

Figure 2. Characteristics and functions of T helper 22 cells in immunological disorders and malignancies [10].

IL-22, aryl hydrocarbon receptor, and expression of chemokine receptors CCR4, CCR6 and CCR10 (**Figure 2**). These chemokine receptors may be involved in the migration and retention of Th22 cell in inflammatory tissues and tumors [1, 24]. It has been shown that CCR6 and its ligand CCL20 are required for the migration of $CD4^+$ $IL\text{-}22^+$ T cells to tumor microenvironment [24]. IL-22 enhances epithelial cell repair after injury and improves the survival of epithelial cells through antiapoptotic and proliferative effects, indicating that high levels of IL-22 may have a protective effect in inflammatory and infectious diseases. Persistent high expression of IL-22 in certain illness can have pathogenic effects such as tissue damage and chronic inflammation [5]. Many studies recently confirmed the unique function of IL-22 in autoimmune diseases, infections, and tumors, which has led to studies on IL-22-related therapies in the clinic [25-27]. In a stochastic, double-blind, controlled II clinical study, an anti-IL-22 monoclonal antibody (ILV-094) showed a clinical treatment effect in patients with atopic dermatitis [28, 29]. Clinical studies on an anti-IL-22R1 antibody (ARGX-112) for the treatment of atopic dermatitis are also underway. Clinical studies on IL-22 activation for infectious diseases such as inflammatory bowel disease, pancreatitis, alcoholic hepatitis, graft-versus-host disease, and diabetic foot ulcers are also underway, suggesting that targeting IL-22 and its signaling pathways may provide new clinical options. IL-22 is associated with the occurrence, apoptosis, invasion and metastasis of skin, lung, liver, stomach, intestinal, and pancreatic cancer, as well as other malignant tumors [30, 31]. However, due to its complex protective and pathogenic functions, the effect of IL-22 in malignant neoplasms is still controversial.

The role of Th22 cells in tumors

Th22 cells in NSCLC and digestive system tumors

Most studies suggested that IL-22 can stimulate the growth of intestinal cancer, gastric cancer and lymphoma [32-34], but a small number of studies have reported that IL-22 could restrain tumor cell activity [35]. A clinical study by Jiang et al. and [36] found that in human primary hepatocellular carcinoma, the expression of peritumor lymphocytes was higher, and IL-22 was relevant to the degree of tumor spread. For

example, the presence of IL-22 in tumor tissues was significantly higher in stage III and IV patients compared to those in stage I and II. Zhuang et al. [37] found that the number of peripheral blood Th22 cells was higher in gastric cancer patients than in normal controls, and the abundance of Th22 cells was found to be associated with the degree of spread of lesions in gastric cancer patients. For instance, the presence of Th22 cells was higher in stage III and IV gastric cancer patients than in those with early gastric cancer, and the infiltration of Th22 cells in gastric carcinoma tissues was higher than in other tissues (**Table 1**). IL-22 may promote the development of human pancreatic cancer cells. Curd *et al.* found in clinical experiments that IL-22 might promote the proliferation of human pancreatic cancer cells. At the same time, it was found that peripheral blood Th22 and IL-22 levels were increased in pancreatic cancer patients, and as in many gastrointestinal tumors, the abundance of Th22 cells and IL-22 in pancreatic cancer tissues was significantly higher than in normal tissues [38]. A study by Qin et al. in 2014 showed that the frequency of circulating Th22 cells was strongly increased in hepatocellular carcinoma (HCC) patients versus healthy controls. IL-22 mRNA expression was significantly higher in stage III-IV versus stage I-II [39].

Recently, Yao *et al*. found an enrichment of Th22 cells in the peripheral blood of non-small-cell lung cancer (NSCLC) patients. The level of Th22 cells among peripheral blood mononuclear cells (PBMCs) was positively correlated with the TNM stage, lymph node metastasis, and clinical tumor biomarkers. Th22 cells and their specific cytokine IL-22 can also interact with antitumor drugs to induce apoptosis and arrest the cell cycle. Tumor cell migration and tumor tissue growth were found to be promoted, and JAK-STAT3/MAPK/AKT signaling pathway was activated, which accelerated tumor progression, resulting in a poorer prognosis in NSCLC patients. These results confirmed that Th22 cells/IL-22 might serve as a negative immune regulator in lung cancer and might provide a new therapeutic approach for NSCLC therapy [40].

Th22 cells in B-NHL, MM and BM

It has been Showned that circulating Th22 cells are increased in patients with newly-diagnosed B-cell non-Hodgkin lymphoma (B-NHL), as well as in patients with recurrent lymphoma. However, the Th22 frequency in patients after treatment was significantly lower than in patients before treatment and in patients with complete remission, and the Th22 frequency returned to normal levels after chemotherapy. Plasma IL-22 was associated with increased IL-6 levels, and plasma IL-22 was associated with plasma TNF-α in newly diagnosed patients [41]. The frequency of Th22 cells in PB and bone marrow (BM) was significantly elevated in patients with newly diagnosed and relapsed/refractory disease with multiple myeloma (MM) compared to healthy controls. The proportion of this T cell subset has also been found to be elevated in patients with stage III disease than those in stage I+II [42]. However, patients who are in complete remission after chemotherapy, the frequency of Th22 cells was significantly reduced. Data from existing literature suggest that the alteration of Th22 cells function may also contribute to the development of chronic myeloid leukaemia. Compared with the control group, the proportion of Th22, Th17 and Th1 cells as well as the expression of RORC and AHR were significantly reduced in ND patients, whereas the dysregulation of cytokines microenvironment recovers after achieving CR. Furthermore, circulating or BM Th22 are positively associated with Th17 cells [42].

Th22 cell in gynecological malignancies

Currently, research on Th22 cells is still in its initial stage. There is a lack of uniform data on the spread and control of cells in the tumor microenvironment, promotion of cancer development or inhibition of tumor metastasis. Th22 cells have been reported infrequently in gynecologic tumors. Zhang et al. [43] found that the number of Th22 cells in the peripheral blood was increased in patients with cervical intraepithelial lesions and cervical cancer compared to healthy controls. Moreover, in patients with cervical cancer, elevated Th22 cells were related to lymph node metastasis. Lu *et al.* found that the abundance of Th22 cells was higher in the peripheral blood of ovarian cancer patients than in normal controls [44]. In addition, Th22 levels in malignant ascites of ovarian cancer patients was higher than in the peripheral blood. Th22 cells might be recruited from peripheral blood to malignant ascites in ovarian cancer by chemokines and pro-inflammatory

Table 1. Levels of tumor-infiltrating Th22 cells and IL-22 cytokine in various human cancers

Tumor type	Number of patients	Author	Abundance of Th22 cells or IL-22 level	Key findings	Ref
Skin basal-cell carcinoma (BCC) and Squamous-cell carcinoma (SCC)	36	L. Nardinocchi *et al.*	↑	High levels of IL-22 and IL-17 in tumor microenvironment promote tumor progression.	[31]
Colorectal cancer	49	L. Ling, P et al.	↓	Il-22 mRNA expression in the non-tumor tissues was higher than that in the tumor tissues.	[35]
Gastric cancer	76	Zhuang Y et al.	↑	Enhanced intratumoral Th22 cells were related to tumor stage, tumor development and shorter total survival.	[37]
Pancreatic ductal adenocarcinoma	30	Curd L et al.	↑	Intratumoral IFN-γ-producing Th22 cells significantly related to TNM staging and shorter total survival.	[38]
Hepatocellular carcinoma (HCC)	45	S. Qin et al.	↑	The frequency of circulating Th22 cells was strongly increased in HCC patients versus healthy controls. IL-22 mRNA expression was significantly higher in stage IIIIV versus stage I-II.	[39]
Non-small cell lung cancer (NSCLC)		Yao *et al.*	↑	The high IL-22R1 expression is associated with primary NSCLC and patients' overall survival.	[40]
B-NHL/recurrent lymphoma	26	Lu T et al.	↑	Circulating Th22 cells are increased in patients with newly-diagnosed B-cell non-Hodgkin lymphoma (B-NHL), as well as in patients with recurrent lymphoma.	[41]
Cervical cancer	61	Zhang W et al.	↑	In cervical cancer patients, the levels of Th22 and Th17 cells were increased. Increased Th22 cell levels were related to lymph node metastasis. The mRNA expression of IL-6 and RORC was significantly higher in the lymph of cervical cancer patients compared to healthy controls.	[43]
Epithelial ovarian cancer	34	Wang T et al.	↑	The relative abundance of Th22 cells was significantly higher in the peripheral blood of EOC patients (2.57±0.88%) than in with benign epithelial ovarian tumors (0.87±0.21%) and healthy controls (0.82±0.12%).	[45]
Triple negative breast cancer	30	Wang S et al.	↑	Th22 cells were significantly more abundant in TNBC tumor tissues compared to normal breast tissue. Serum IL-22 levels were also greatly increased in patients with TNBC compared with healthy controls, and IL-22 levels were correlated with TNM phase. IL-22 levels were significantly higher in patients with stage III tumors compared to patients with stage I and II decease. In scratch healing and transwell migration assays, IL-22 was found to stimulate the migration of TNBC cells, and this effect was significantly enhanced by higher IL-22 concentrations.	[49]

IFN: interferon; IL-22: interleukin-22; TNBC: triple negative breast cancer; EOC: epithelial ovarian cancer.

cytokines. In 2018, Lei *et al*. studied the differences of Th22 cells and IL-22 levels in ovarian cancer patients and healthy controls. In addition, they analyzed the relationship between Th22 cells and ovarian cancer phase and whether it stimulates the growth of ovarian cancer via the STAT3 pathway. The results of immunohistochemistry, qPCR and western blot analysis showed that the expression of IL-22 was higher in ovarian cancer tissues than in adjacent tissues, which was positively correlated with tumor stage. The outcomes of flow cytometry revealed that the proportions of $CD4^+$ and TILS-Th22 cells in the tumor tissues of ovarian cancer patients were significantly increased, and were positively correlated with tumor stage. Immunofluorescence microscopy indicated that IL-22 was mainly excreted by $CD4^+$ cells in ovarian cancer tissues. The results of cell coculture indicated that total TILs and $CD4^+$ TILs could secrete IL-22, which could activate the STAT3 pathway and induce the expression of downstream molecules. The outcomes suggested that Th22 cells, IL-22 and the STAT3 signaling pathway might be involved in the pathogenicity of OC, which might become a new therapeutic target [45]. Wang *et al.* found that the abundance of Th22 and Th17 cells in the peripheral blood of patients with epithelial ovarian cancer was greatly higher than in healthy controls [45]. The serum levels of IL-22 and TNF-α were also greatly enhanced, and it was hypothesized that Th22 cells might be involved in epithelial ovarian carcinogenesis. Chauhan *et al.* observed massive infiltration by $PU.1^+$ cells and overexpression of IL-9R in tissue biopsy probes from cervical cancer patients [46]. Therapy with the Th9 signature cytokines IL-9 and IL-21 inhibited the migration of HeLa cells, enhanced apoptosis, and stimulated the cancer cells to express MHC-I and e-cadherin, thus exposing tumor antigens and reducing immune evasion. Tian *et al.* measured Th22 levels in the peripheral blood of healthy controls and cervical cancer patients by enzyme-linked immunosorbent experiment and flow cytometry, which revealed that the levels of IL-22 in peripheral blood were significantly higher in the cervical cancer group, indicating that Th22 cells might take part in the development of cervical cancer [47]. However, the underlying mechanism needs further investigation. Wang et al. found that the above Th22-related indicators were significantly increased in peripheral blood and tissues of cervical cancer patients compared to healthy women of the same age [48]. Th22 expression levels were also higher in cervical cancer patients with a more advanced disease stage. Th22 directly or indirectly participates in the migration, infiltration and lymph node metastasis of cervical cancer cells, greatly contributing to the pathogenesis of cervical cancer.

Wang S *et al.* found that Th22 cells and the secreted cytokine IL-22 were associated with the development of triple negative breast cancer (TNBC) [49]. High levels of IL-22 in TNBC patients suggested a poor prognosis, and IL-22 might stimulate TNBC cell migration and metastasis by stimulating the JAKSTAT3/MAPKs/AKT signaling pathway and inhibiting paclitaxel-induced apoptosis. IL-22 may be a predictor of therapeutic efficacy and prognosis for TNBC patients. Wang *et al.* revealed that in the peripheral blood of epithelial ovarian carcinoma (EOC) patients, the abundance of Th22 cells, IL-22 and TNF-α increased as the disease worsened, suggesting that Th22 cells and the associated cytokines might play a major role in the development of EOC (**Table 1**) [45].

Conclusions and outlook

Taken together, The key difference between IL-22 and other cytokines is that although it is derived from immune cells, it acts on non-immune cells, suggesting that IL-22 may be a key factor in epithelial-immune cell interactions, IL-22 production results in tissue repair, but it can also promote the growth of cancerous epithelial cells and the onset of cancer. The IL-22/IL-22R1 pathway may be a viable target for cancer therapy due to the overexpression of IL-22 or Th22 cells in several cancer types and their link to cancer progression and a poor prognosis. On the other hand, the findings of both experimental and clinical investigations support the hypothesis that IL-22 or Th22 cells may have pro-tumor activity in cancer. However, the available literature is limited by the types of tumors included and the number of studies. More investigations are needed to clarify the exact role and mechanisms of Th22 cells in different conditions regarding their manipulation in immunotherapy.

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Disclosure of conflict of interest

None.

Abbreviations

IL-22, interleukin-22; IFN, interferon; MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription; AHR, aryl hydrocarbon receptor; ERK, extracellular signal-regulated protein kinase; TILS, tumor-infiltrating lymphocytes; MHC, major histocompatibility complex; BCC, Skin basal-cell carcinoma; SCC, Squamous-cell carcinoma; TNBC, triple negative breast cancer; EOC, epithelial ovarian cancer; RORγt, RAR-related orphan receptor gamma; ILCS, Intrinsic lymphocytes; NKT, γST cells and natural killer cells; B-NHL, B-cell non-Hodgkin lymphomabone; MM, multiple myeloma; NSCLC, Non-small cell lung cancer.

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