



REVIEW

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The immunoregulatory mechanisms of carcinoma for its survival and development

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Abstract

The immune system in patients detects and eliminates tumor cells, but tumors still progress persistently. The mechanisms by which tumor cells survive under the pressure of immune surveillance are not fully understood. This review is to present the evidence from clinical studies, showing a significant correlation of clinicopathological features of carcinoma with: (1) the loss of classical human leukocyte antigen class I, (2) the up-regulation of non-classical human leukocyte antigen class I, pro-apoptotic Fas ligand and receptor-binding cancer antigen expressed on SiSo cells I, and (3) the formation of immunosuppressive microenvironment by up-regulation of transforming growth factor-beta, Galectin-1, inhibitory ligand B7s, indoleamine 2,3-dioxygenase and arginase, as well as by recruitment of tumor-induced myeloid-derived suppressor cells and regulatory T cells. All of these factors may together protect carcinoma cells from the immune-cytotoxicity.

Introduction

Carcinoma is the most commonly type of cancer transformed from epithelial cells. It has been noted for a while that the immune-mediated spontaneous regression of cancer occurs in patients [1]. Recent clinical studies have demonstrated that anti-carcinoma immunity is activated along with rise and progression of carcinoma, indicated by: (1) the tumor-infiltrating immune cells (TICs), including T, B and natural killer (NK) cells, are activated [2-4], and the number of these lymphocytes and macrophages positively correlates with cancer-specific survival rate in patients with various carcinomas [5-7]; (2) both carcinoma antigen-specific cytotoxic T lymphocytes (CTLs) [8-10] and antibodies [11-13] have been identified in cancer patients; and (3) spontaneous regression has been noted in many patients with carcinoma cancers, in which the number of infiltrating immune cells, including activated CD3⁺ T cells, NK cells, antigen presenting cells (APCs), is significantly higher than that in non-regressing controls [14-16]. Therefore, the number of infiltrating immune cells becomes a reliable biomarker for predicting cancer relapse [17,18]. All these studies suggest that the immune surveillance against carcinoma is active in

patients, but how carcinoma cells still can survive and grow in some patients is not fully understood. In this review, we attempted to summarize the evidence of anti-immune functions of carcinoma from both clinical and experimental studies.

Avoidance of cytotoxic lymphocyte stimulation by attenuation of human leukocyte antigen class (HLA) molecules

Loss of HLA class I for avoidance of CD8⁺ CTL activation

Classical HLA class I constitutively expresses on epithelial cells and many carcinoma cell lines, such as non-small cell lung cancer (NSCLC) [19]. Given a central role of HLA class I in the restriction of CD8⁺ CTL recognition of carcinoma-specific antigens, loss of HLA class I expression undoubtedly becomes a major escape pathway for the evasion of CD8⁺ CTL surveillance, by which any HLA class I deficient carcinoma variants can develop to more aggressive or invasive phenotypes without stimulation of primary anti-carcinoma immunity, CD8⁺ T cell response. Indeed, as listed in Table 1, the total loss of HLA class I expression is more frequently noted with more aggressive or metastatic stages and poor differentiation phenotypes as compared to those with early stages and well to moderately differentiated lesions in patients.

A higher level of HLA class I expression in bladder carcinoma is significantly associated with a longer

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Table 1 The association of deficient HLA class I expression in carcinoma with its progression in patients

Carcinoma type	Antibodies for immunohistochemical staining	Distribution of total HLA class I expression loss (% of negative staining*)	References
Bladder	W6/32 and GRH1	The altered of HLA class I including total losses associates with higher grade lesions and tumor recurrence	[20]
	A-072	1) 16.6% in G1, 38.5% in G2, and 57.1% in G3; 2) 5-year survival: 74% with positive versus 36% with negative staining	[21]
Gastric	A-072	0% in T1 (mucosa & submucosa) versus 100% in T2-3 (muscle and fat invasion)	[22]
Esophageal	W6/32	0%: normal and benign versus 40.5% carcinoma lesions	[23]
Bronchogenic	W6/32 and HC-10	1) 13% of Diploid versus 45% of Aneuploid; 2) 17.3% in G1-2 versus 69% in G3	[24]
NSCLC	W6/32	1) 26.8% in T1-2 versus 35% in T3; 2) 20.7% in G1-2 versus 39.3% in G3; 3) 24.1% in N0 versus 34.5% in N1-2	[25]
Breast	HC-10	0% in low-grade versus 67.6% in high-grade lesions	[26]
	W6/32	24% in primary versus 64% in corresponding LN samples	[27]
Pancreatic	W6/32 and 246-E8.E7	1) 6% in primary versus 43% in metastatic tumors; 2) 0% in G1, 33% in G2 and 67% in G3	[28]
Prostate	A-072	1) 0% in Benign, 41% in primary and 66% in LN metastases; 2) 33% in low-grade versus 50% in high grade lesions	[29]

*The cutoff line for negative staining or total loss is 5 to 25% of cells stained with antibodies. W6/32 monoclonal antibody (mAb) detects monomorphic epitope of HLA class I antigen (HLA-ABC); 246-E8.E7, HC-10 and GRH1 are anti-beta2-microglobulin (β 2-m) mAbs; rA-270 is rabbit polyclonal anti- β 2-m antibody (DAKO).

survival rate in patients [21], and tumors with a normal level of HLA class I harbor more CD8⁺ T cells than those with altered HLA class I in renal cell carcinomas (RCC) [30] and cervical carcinoma [31,32]. In addition, a decrease in HLA class I expression has been noted as early as in normal mucosa surrounding the tumor or in situ lesion, and is significantly associated with subsequent development to a new primary tumor lesion [33,34]. These data indicate that the avoidance strategy may occur at early stages of carcinoma development, and suggest that by loss of HLA class I expression to avoid CD8⁺ CTL seems critical for the development of carcinoma in patients.

Heterogeneous expression of HLA class I in inactivation of NK cell cytotoxicity

Although loss of HLA class I may benefit to carcinoma resistance to CD8⁺ CTL as discussed above, it could increase the susceptibility to cytotoxicity of natural killer (NK) cells [35] because HLA class I is a ligand for inhibitory receptor family, killer cell immunoglobulin-like receptor (KIR) of NK cells [36]. Thus, loss of HLA class I expression could favor the escape of antigen-dependent cytotoxicity of CD8⁺ CTL, but at the same time carcinoma cells may become a target of NK cell cytotoxicity. To date, it is not completely clear how carcinoma cells can survive under the selection of both CD8⁺ CTLs and NK cells simultaneously. It has been suggested that carcinoma cells find a balance between maintenance of HLA class I expression for inhibition of NK cell cytotoxicity and loss of its expression for the escape from CD8⁺ CTL responses. Indeed, the complete loss of HLA class I is barely seen in carcinomas, which may be explained by its need for inhibition of NK cell

activity. The heterogeneous losses of HLA class I either positively or negatively correlate with carcinoma stages or grades in patients [24,27,28], reflecting exactly the situation of carcinoma cells; if carcinoma cancer faces more severe cytotoxicity from NK cells versus CD8⁺ CTL, certain levels of HLA class I render carcinomas resistance to NK cells; if tumor is under the pressure of CD8⁺ CTL more than NK cells, then partial loss of HLA class I becomes a key for survival, as indicated by Table 1.

In addition to heterogeneous expression of HLA class I, one has to know that other strategies are seen to avoid NK cell cytotoxicity. A clinical study with oral squamous cell carcinomas shows that HLA class I expression is either weak or absent for not stimulation of CD8⁺ CTL, but there is still no clear correlation of HLA class I expression loss with a relative proportion of NK cells, indicating that the local factors seem to down-regulate the final outcome of the cytotoxic immune response of NK cells [33]. Indeed, reduced expression of natural cytotoxicity receptor, NKG2D ligand UL16 binding protein 1 and Inter-Cellular Adhesion Molecule 1 has been seen on tumor cells [37,38], which may specifically prevent NK cell activation.

Non-classical HLA-G in inhibition of both CD8⁺ CTLs and NK cells

HLA-G is a non-classical class I antigen, originally detected in trophoblastic cells [39], where it is proposed to suppress maternal immune response against the semi-allogeneic fetus. It binds to the inhibitory receptors Ig-like transcript (ILT) 2, ILT4 or KIR2DL4, resulting in suppression of cytotoxicity of both CD8⁺ CTL and NK cells [40,41]. The protective role of HLA-G in

carcinoma survival under immune surveillance is demonstrated in many studies with patients; in contrast to its null expression in normal epithelial cells and benign adenomas, a high percentage (30-90%) of carcinoma cells expresses HLA-G in a variety of cancerous lesions, and its levels have been found to be significantly associated with clinicopathological features and shorter survival time of patients [42-45]. All these data indicate that carcinoma-expressing HLA-G could be one of important mechanisms for inhibition of both CD8⁺CTL and NK cell mediated anti-carcinoma immunity.

Induction of TIC apoptosis by expression of pro-apoptotic ligands

Fas ligand (FasL)

FasL binding to death receptor Fas triggers apoptosis of Fas-expressing cells including TICs. Two patterns of FasL expression on carcinoma cells have been shown by immunohistochemical staining: (1) up-regulation of FasL expression on carcinoma is positively associated with clinicopathological features in patients, shown by that FasL expression is an early event in epithelial cell transformation (adenoma), followed by an increase in the percentage of FasL-expressing carcinoma cells in high-stage or -grade lesions, and the poorer survival of patients with high levels of FasL expression (Table 2); and (2) high levels of FasL expression have been seen as an independent factor for clinicopathological features, indicated by the positive staining of persistent FasL expression regardless of tumor stage, histologic grade, invasion and metastasis in many studies [47,58-61]. All of these observations suggest that FasL

expression is critical for carcinoma survival by induction of TIC apoptosis. Indeed, the pro-apoptotic function of FasL on carcinoma cells has been demonstrated in both in vitro and in vivo; in co-cultures with a variety of carcinoma cell lines, FasL expressed on carcinoma cells induce apoptosis of lymphocytes in Fas-dependent manner [49,51,62-66], and in carcinoma biopsies from patients, the present of FasL on carcinoma cells is in parallel with apoptosis of TICs [53,60,67-69] or reduced number of TICs [70,71]. In the experimental studies with animal models, down-regulation of FasL expression in carcinoma significantly reduces tumor development in syngeneic immunocompetent mice [72], while persistent expression of Fas enhances tumor growth along with an increase in lymphocyte apoptosis [73,74], and is acquired for survival from active specific immunotherapy [75].

Receptor-binding cancer antigen expressed on SiSo cells (RCAS) 1

RCAS1 is a recently characterized human tumor-associated antigen expressed in a wide variety of cancer tissues, and induces cell cycle arrest and/or apoptosis in RCAS1 receptor-expressing immune cells. Like FasL on carcinoma cells, RCAS1 is expressed in a high percentage of carcinoma cells (30-100%) and is significantly correlated with clinicopathological features including a shorter survival time for patients, and with apoptosis or reduction of TICs [76-81]. In co-cultures of interleukin (IL)-2 activated peripheral blood lymphocytes with human oral squamous cell carcinomas cell line (KB cells), lymphocyte apoptosis is associated with the presence of soluble RCAS1 in the medium [77]. In addition,

Table 2 FasL expression in carcinoma cancers

Carcinoma type	Distribution of high FasL expression	References
Colorectal	19% in adenomas, 40% of stage I-II, 67% of stage III and 70% of stage IV of carcinoma	[46]
	40.9% in adenoma versus 80.8% in carcinoma	[47]
	Higher incidence of metastases and poorer patients' survival associate with FasL positive carcinomas	[48]
	0 positive in normal epithelial cells, 2/7 positive in primary tumors, 4/4 positive in hepatic metastatic tumors	[49]
Adrenocortical	37.7% in adenomas versus 100% in the carcinoma	[50]
Bladder transitional cell	1) 0% in normal urothelium, 0% in G1, 14% in G2, and 75% in G3.	[51]
	2) 13% in superficial Ta-T1 versus 81% in invasive T2-T4	
	0% in normal urothelium, 19% in T1, 21% in T2 and 49% in T3	[52]
Pancreatic ductal	1) 82% in primary versus 100% in hepatic metastases	[53]
	2) Shorter survival for patients associates with FasL positive tumors	
Nasopharyngeal	1) 0% in stage I, 57% in stage II, 58% in stage III and 82% in stage IV;	[54]
	2) A lower rate of disease-free and overall survival for patients associates with positive FasL expression.	
Gastric	36.2% in adenomas, 68.8% in early carcinoma, and 70.4% in advanced carcinoma	[55]
Cervical	1) 5/14 in inner 2/3 stromal invasion versus 10/10 outer 2/3 stromal invasion;	[56]
	2) 7/15 without LN metastasis versus 8/9 with LN metastasis;	
	3) Reduced survival times in patients with FasL-expressing tumors	
Esophageal	1) Higher incidence of LN metastasis associates with the tumors containing >25% FasL expression;	[57]
	2) All cancer metastases in LN express FasL in >50% of the cells	

LN: lymph nodes.

similar to FasL and RCAS1, CD70 overexpressed on RCC promotes lymphocyte apoptosis by binding to its receptor CD27, indicating a proapoptotic role of CD70 in the elimination of TICs as well [82]. All these observations suggest that the direct induction of TIC apoptosis by persistent expression of FasL, RCAS1 or perhaps other apoptosis-inducing ligands (e.g. CD70) on carcinoma cells plays a role in the ability of carcinoma cells to escape from the anti-carcinoma immunity.

Suppression of TIC activity by molecular and cellular factors

Immunoregulatory cytokine/cytokine-like: Transforming growth factor (TGF)- β 1 and Galectin-1 (Gal-1)

TGF- β 1 is a multifunctional cytokine involved in immunosuppression. Numerous clinical studies have demonstrated that a higher level of TGF- β 1 expression is significantly associated with an invasive phenotype of tumors or metastases in patients [83-86]. In vitro a significant amount of TGF- β 1 is produced in the poorly differentiated prostate carcinoma cell lines but not in well-differentiated cells [87]. These data imply that TGF- β 1 may increase metastasis by a paracrine matter, such as suppression of local immune response or increased angiogenesis. Indeed, in the biopsies of cervical carcinoma tumors, an inverse relationship between TGF- β 1 expression in tumor cells and the extent of TICs is demonstrated [88]. This clinical observation is further confirmed by several experimental studies. In a mouse skin explant model, TGF- β 1 is produced by progressor types but not regressor squamous cell carcinoma lines, and this tumor-derived cytokine inhibits migration of professional APCs, Langerhans cells (LCs), and keeps them in an immature form [89], or transgenic expression of TGF- β 1 enhances growth of regressor squamous carcinoma cells in vitro and in vivo just like progressor phenotype, and reduces the number of infiltrating LCs, CD4⁺ and CD8⁺ T cells [90]. A further study with invasive colon carcinoma U9A cell line shows that decreasing TGF- β 1 expression by antisense reduces the invasive activity and metastasis of tumor cells to the liver [91]. All these studies suggest that carcinoma-derived TGF- β plays an important role in the tumor metastasis, which may be caused by its immune suppressive function.

Gal-1 is a member of β -galactosidase binding protein family (galectins), and is a recently identified immunoregulatory cytokine-like molecule in cancer [92]. It has been documented that Gal-1 exhibits immunoregulatory effects by which it controls immune cell trafficking, regulates activation of dendritic cells (DCs) and induces T-cell apoptosis [93]. Up-regulation of Gal-1 expression has been seen in a variety of carcinoma biopsies, particularly in tumor-associated stroma, and is associated with tumor invasiveness or worse prognoses [94-97] and

with reduced infiltrating T cells [98], suggesting that Gal-1, produced by carcinoma and/or stromal cells surrounding the tumor, may take a part in the carcinoma immune-escape by regulation of T cell homeostasis. This hypothesis is supported by a recent study showing that tumor cell-expressing Gal-1 induces T cell apoptosis in a co-culture system [99].

Immune inhibitory ligands: B7 family members (B7-H1, -H3 and -H4)

B7-H1 (PD-L1) is a ligand for the receptor PD-1 on T cell, and is known to negatively regulate T-cell activation [100]. Similar to B7-H1, B7-H3 or -H4 ligation of T cells has a profound inhibitory effect on Th1 differentiation [101], as well as the proliferation, differentiation and cytotoxicity of T cells [102]. Over-expression of these B7 family members (B7-H1, -H3 or -H4) has been documented in various types of carcinoma as compared to healthy controls: (1) B7-H1 in pancreatic tumors [103,104], RCC [105,106], human hepatocellular carcinoma (HCC) [107,108], urothelial cell carcinoma (UCC) [109] and NSCLC [110]; (2) B7-H3 in UCC [111]; and (4) B7-H4 in NSCLC [112], breast cancer [113,114] and ovarian cancer [115]. Tumor B7-H1 expression is significantly associated with less TICs including PD-1 positive immune cells, poor tumor differentiation, advanced tumor stage and poorer survival of patients [103,104,106-110,115]. Similar correlation of B7-H4 with clinicopathological features has been reported as well [111-114].

In parallel with up-regulation of B7-H1, the number of PD-1⁺ CD8⁺ cells increases in tumor tissues, such as HCC [108,116] and prostate cancer [117], and these tumor-infiltrating CD8⁺ cells have been shown to be impaired in the granule and cytokine productions [108,117-119]. In addition, blocking the interaction of B7-H1 with PD-1 using neutralizing antibody restores the effector function of tumor-infiltrating T cells [108,119] and in a mouse model of pancreatic cancer, the antibody therapy, combined with gemcitabine, induces a complete regression of tumor growth [104]. All these studies indicate that up-regulation of B7 inhibitory molecules acts as an immunosuppressive strategy for carcinoma to escape from anti-carcinoma immunity during cell-cell contact with T cells.

Depletion of amino acids enzymes: indoleamine 2,3-dioxygenase (IDO) and arginase (ARG)

The mechanisms by which IDO induces immunosuppression have been recently reviewed [120]. IDO is a tryptophan-catabolising enzyme. Up-regulation of its synthesis has been documented in IFN- γ -stimulated cultures of KB oral carcinoma and WiDr colon adenocarcinoma [121], pancreatic carcinomal cells [122], hepatocellular carcinoma cell lines [123], and colorectal carcinoma cell lines [124]. Over-expression of IDO protein is reported in the cancerous lesions, and significantly correlates with

carcinoma metastasis and poor prognosis in patients with a variety of carcinoma cancers [122-126]. The up-regulation of IDO is associated with a significant reduction of CD3⁺ TICs [124], or with an increased number of regulatory T (Treg) cells in the metastatic carcinoma in lymph nodes (LNs) [122]. Ectopic expression of IDO enhances tumor growth of the human endometrial carcinoma cell line AMEC and suppresses cytotoxicity of NK cells in a mouse xenograft model [127]. All these observations suggest that IDO-high expression in carcinoma cells in primary tumors may defeat the invasion of effector T cells and NK cells via local tryptophan depletion as well as production of proapoptotic tryptophan catabolites. Also, IDO in metastatic carcinoma cells may enhance the differentiation of Treg cells as a potent immunosuppressive strategy.

ARG is an arginine-metabolic enzyme converting L-arginine into L-ornithine and urea [128]. It has been suggested that arginine is one of essential amino acids for T cell activation and proliferation [129], and the depletion of extracellular arginine by ARG results in the modulation of CD3 ζ chain expression and proliferative suppression in T cells [130]. A significantly high level of ARG activity has been demonstrated in the carcinomas of the prostate [131], the gallbladder [132] and the lung [133,134], but the evidence for the contribution of ARG activity to tumor immune escape is still weak; ARGII and NOSII together has been shown to participate in local peroxynitrite dependent immune suppression of prostate cancer [135], but not seen in lung cancer [136]. However, this enzyme may play a critical role in the immunosuppressive activity of tumor-induced myeloid-derived suppressor cells (MDSCs) as discussed below.

Immunosuppressive cells: CD4⁺CD25⁺Foxp3⁺ regulatory T (Treg) cells and Tumor-induced myeloid-derived suppressor cells (MDSCs)

Treg cells can inactivate both effector/helper T and B cells. After activation, Treg cells not only produce abundant anti-inflammatory cytokine IL-10 and TGF- β , but also express cell surface CTLA-4, which binds to B7 molecules on APCs, resulting in suppression of effector T cells and their dependent B cells. Numerous studies with cancer patients have demonstrated that the prevalence of Treg cells is significantly high in cancerous lesions as compared to those in healthy controls [136-141], and the percentage of Treg cells among TICs positively correlates with a significantly lower survival rate [138,139,142]. In mice challenged with pancreas adenocarcinoma cells (Pan02), depletion of Treg cells promotes a tumor-specific immune response, and significantly associates with smaller size of tumor and longer survival [143]. All these studies suggest that an increase in Treg cells in TICs may play a central role in self-tolerance to carcinoma cells, which may "hijack" these

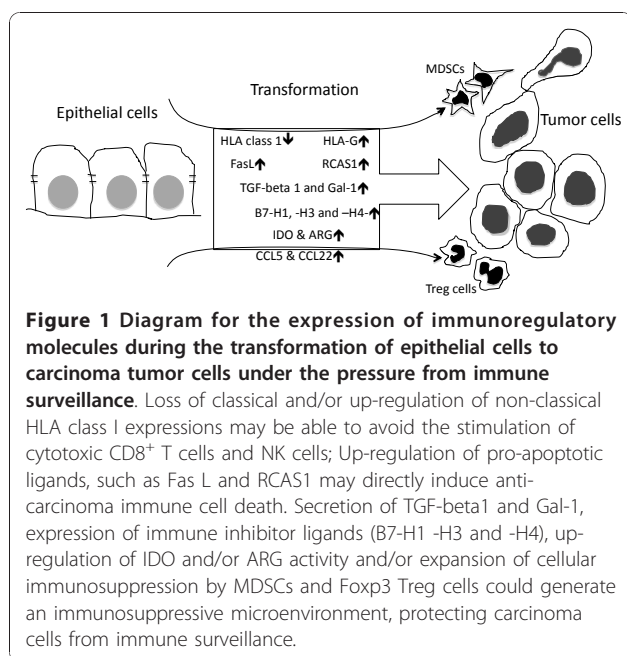
Treg cells as an effective strategy for immunoescape by suppression of anti-carcinoma immunity.

However, the mechanism of elevation of Treg cells in TICs is not fully clarified, but may be due to their local proliferation/differentiation or recruitment from circulation to cancerous lesion or to both. Indeed, the presence of Treg cells in carcinoma lesions is in conjunction with immature DCs, Th2 cytokine dominant microenvironment, prostaglandin E2 (PGE2) and IDO activity [122,144,145] or is required the function of CCL22 [146] and/or CCL5 [147]. Chemokine CCL22 and CCL5 mediate trafficking of Treg cells to the tumors, whereas immature DCs, Th2 cytokines and PGE2 favor Treg cell proliferation and/or differentiation.

MDSCs represent a heterogeneous population of immunosuppressive cells expressing a variety of surface markers, such as CD11c⁺, CD11b⁺, CD33⁺, CD34⁺ and CD15⁺. In patients with all different types of carcinomas, an increasing number of MDSCs have been found in peripheral blood [148-150] and/or intratumor lesions [151-153]. The frequency of these cells also positively correlates with the incidence of recurrence or metastatic disease in patients [153,154]. Experimental studies show that MDSCs can function as potent suppressors of cytotoxicity of both effector CD8⁺ T-cells [155] and NK cells [156]. The immunosuppressive activities of MDSCs may depend on the activity of ARG and/or reactive oxygen species they produce [150,157,158] or the induction of Foxp3⁺ Treg cells [159]. All these studies suggest that MDSCs may be one of important factors responsible not only for systemic immune dysfunction in cancer patients but also for local carcinoma immune escape.

Conclusions

The evidence from the limited literature we reviewed clearly indicates that carcinoma development in patients closely correlates to its ability to inactivate effector cytotoxic lymphocytes (i.e. CD8⁺ CTL and NK cells), to induce TIC apoptosis and/or to suppress the anti-carcinoma immune response, as indicated by: (1) down-regulation of antigen-presenting protein HLA class I; (2) up-regulation of immunosuppressive proteins, such as cell surface FasL, HLA-G, immune inhibitory ligand B7 family members, secreted cytokine TGF- β and Gal-1, enzyme IDO and perhaps ARG, and (3) induction/expansion of immunosuppressive cells: MDSCs and/or Foxp3⁺ Treg cells (Figure 1). Thus, it must be acknowledged that carcinoma develops multiple adaptation mechanisms against immune surveillance, but different types of carcinoma cancer may use different anti-immune strategies depending on the spectrum of host anti-carcinoma immunity in patients. Further understanding of these mechanisms by which



carcinomas cells resist to anti-carcinoma immunity will lead to develop more effective immunotherapy

Abbreviations

APC: Antigen presenting cell; ARG: Arginase; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; Gal: Galectin; HCC: human hepatocellular carcinoma; HLA: Human leukocyte antigen; HNSCC: Head and neck squamous cell carcinoma; IDO: Indoleamine 2,3-dioxygenase; IL: Interleukin; ILT: Ig-like transcript; KIR: Killer cell immunoglobulin-like receptor; LC: Langerhans cell; MDSC: Tumor-induced myeloid-derived suppressor cell; NK: Natural killer; NSCLC: Non-small cell lung cancer; PGE2: Prostaglandin E2; RCAS1: Receptor-binding cancer antigen expressed on SiSo cells; RCC: Renal cell carcinomas; TGF: Transforming growth factor; TIC: Tumor-infiltrating immune cell; Treg: Regulatory T cell; UCC: Urothelial cell carcinoma.

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Authors' contributions

YW initiated the concept. CD drafted the manuscript. Both authors participated in writing, read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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