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T cells in Immunobiology of Tumors and Immunotherapy

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Abstract

Recent studies indicate that functional T-lymphocyte defects compromise anti-tumor responses in various cancers. It appears that tumors not only effectively bypassed the host immune system, but have also actively corrupted the host anti-tumor response *via* several distinct mechanisms. Cancer Immunotherapy has made significant strides in recent years, due to improved understanding of the underlying principles of tumor biology and immunobiology. This review attempts to identify strategic factors involved in anti-cancer immune impairment, understand the mechanisms underlying reported immunosuppression and highlight some of the most promising present day immunotherapy approaches progressing successfully in clinics.

Keywords: Immune response; T-cell receptor; Immune escape; Immunotherapy

Introduction

Tumors effectively bypass the host immune system by altering the immunogenic potential, *via* secretion of immunosuppressive factors and inhibition of immunomodulatory cell types. Immunotherapy, also called biological therapy, designed to boost the body's natural defenses to fight cancer has become an important part of treating some types of cancer in the last few decades. Immunotherapy shows better responses in some cancers than others either as a single agent or in combination with other types of treatment. Despite the advancements made in cancer therapies over the decades, there has been no significant improvement in the survival rate and morbidity for many types of malignant neoplastic diseases [1,2]. This is frequently due to limited understanding of the biology of the tumor and late diagnosis calling for further in-depth studies to identify early-stage diagnostic markers and novel treatment modalities. It is hoped that newer studies in immunotherapy would provide more impetus for understanding tumor biology and design effective treatment modes for management of cancers. In this review, we focus on the role of T cells in immunomodulation and immunotherapy as evidenced from studies carried out by the authors and others.

Studies carried out in Regional cancer centre, Trivandrum by the authors. T-lymphocyte numbers and function correlate with immunological dysfunction and poor treatment responses [3]. The major observations made were imbalance of lymphocyte populations [4,5] lymphocyte functions as evidenced by cellular assays and molecular alterations [3,6], inhibitory effects of lymphocyte functions mediated by serum factors [6] and impairment of cytokine and cytotoxic functions. In our study, in oral cancer patients, we have noticed that T-Lymphocytes with cellular and molecular defects correlate with immunological function and treatment response [3].

Preliminary studies reported by our group, among others, reveal gross immunological alterations on various cancers such as imbalance of lymphocyte population [4,5] lymphocyte function [3,6] and inhibitory effects of lymphocyte function in cancer patient serum [6]. These findings indicate that cancer patients generally display impaired tumor response. Numerous investigators have reported imbalance in T-lymphocyte numbers and signal transduction abnormalities as the origin of immune defects in cancer [7,8]. Altered T-cell signal transduction is reported to be demonstrated as the reason for reduced IL-2 secretion and IFNγ responses [9]. Moreover, reduced expression of the T-cell receptor zeta chain has been shown as a clear predictive marker of poor survival [3,10]. Many *in-vivo* and *in-vitro* experiments demonstrate the restoration of impaired T-cell function with the administration of IL-2 [11]. Cytokines such as IL-2, CSF, IFN, TNF-alpha have also been tested as cancer immunotherapy agents. However, IL-2 was approved as an immunotherapeutic agent for metastatic renal cell carcinoma [12] with clinical trials having an overall favorable response rate of 20% [13].

Since 1990 onwards more than 25 immunotherapeutic products have received regulatory approval based on anticancer activity as single agents and/or in combination with chemotherapy. All these products are widely using against various malignancies. Very recently immunotherapy is rising as a major treatment option because of the recent success of using monoclonal antibodies (mAbs) targeting various proteins. There have been a number of studies by using gene-engineered TCRs or CARs for the treatment of cancer across the world [14] demonstrated that receptor-engineered T cells mediate long-term remissions of solid and hematologic cancers [15].

T cell signal transduction

Recent progressions in basic immunology and tumor biology have rendered tremendous amounts of information about crosstalk between tumor cells and the immune system. Identification of novel antigens and exploitation of various immunological pathways have provided

new and innovative immunotherapy strategies. The ability of T-lymphocytes to recognize antigen and transduce signal to the nucleus successfully is a key component in the initiation and maintenance of the immune response [16,17].

TCR-ζ protein is an essential component of the TCR complex that binds zap 70 and transduces signals following TCR activation [18]. The protein tyrosine kinase zap-70 is implicated, together with Src kinase p56 Lck, in controlling the early steps of the T cell antigen receptor (TCR) signaling cascade. TCR ligation by antigen/ MHC or by anti-CD3 monoclonal antibodies induce rapid tyrosine phosphorylation of the immunoreceptor tyrosine-based activated motifs (ITAMS) present in their cytoplasmic tails, an event essential for activation of lymphokine genes. ITAM phosphorylation allows recruitment of the ZAP70 to the TCR *via* binding to the two tandemly arranged ZAP-70 SH2 domains to the two phosphorylated tyrosine residues, a modification contributing as catalytic activation. T-cell activation leads to translocation of Rel-A, a component of NFκB to the nucleus and plays a role in the transcription of a variety of genes including IL2. Inability to translocate Rel-A has been observed in lymphocytes of Oral cancer patients, cervical cancer patients and Renal Cell Carcinoma patients' cells & culture model [3,5,18].

Protein tyrosine phosphorylation is a major step in T cell signaling and it must be carefully controlled. This is achieved mainly by the action of the tyrosine kinase Csk which phosphorylates a critical Tyr at the C-terminal domain of Lck rendering it inactive [19]. The role of the tyrosine kinase cascade in T cell signaling is demonstrated by the use of tyrosine kinase inhibitors such as Genistein and Staurosporine which are able to block T cell function both *in vitro* and *in vivo* [20,21]. Elevated intracellular $Ca2^+$ levels need to be maintained for several hours in order to permit downstream signaling events such as NFAT translocation to the nucleus [22]. This sustained $Ca2^+$ elevation is accomplished by the concerted action of several receptors, kinases and ion channels [23]. PKC and Ras activation results in the activation of several members of the mitogen-activated protein kinase (MAPK) superfamily. The MAPKs are serine/threonine kinases that activate kinases (and other) signaling cascades that result in the activation of the transcription factors NF-κB and AP-1, both of which are necessary for the transcription of several key genes involved in the T cell immune response.

Studies from several laboratories suggest that alterations in function and expression of signal transduction molecules associated with TCR are responsible for the deficiencies observed in various cancers [7,24,25]. A reduced expression of the signaling molecules of T-cell receptor (TCR-ζ, CD3-ε, Zap-70 and PKC) was reported by us in oral cancer patients as well as cervical cancer patients on stimulation with anti-CD3 [3,5]. Down regulation of TCR-ζ has been reported in various pathologies and is considered crucial for receptor assembly, expression and signaling [26,27]. Zap-70 has been reported to be an indispensible link in the activation of the T cells by regulating the intracellular events [26].

Immune escape

Immune escape is indicative of the failure of the immune cell to actively respond to the abnormally proliferating tumor cell. The major obstacles for the development of an effective immunotherapy approach are the complicated interactions of host-tumor and various tumor escape mechanisms. These tumor cells escape the immune response due to the mechanism of immune editing [28,29], the inefficiency of T-helper and cytotoxic cells [3,5], soluble factors and other tumor-derived immunosuppressive factors [30,31], impairment of T cell signal transduction and cytokine production [3,5], activation-induced cell death of T cells [32] and exosome-induced immunosuppression [30]. These are the notable tumor escape mechanisms which require further clinical research.

In immunized animals, tumor cells administrated in sufficiently low doses develop into cancers where greater doses are rejected, that is, under conditions theoretically optimized for rejection, tumor cells may 'sneak through' and not be recognized until growth is established and beyond recall. A recent approach to this aspect has been to model mathematically the kinetic interrelationship between tumor and various cell types that would be involved in tumor elimination. This illustrates well the point that this kinetic argument can account for many features of tumor escape mechanisms such as development of cell mediated suppression, soluble factors and other tumor derived immunosuppressive factors [33,34]. IL-10 produced by Th2 cells and Tregs but also by tumors such as non-small cell lung cancer, pancreatic cancer, and squamous cell carcinomas of the head and neck, impairs DC function and effector T-cell activity and is involved in skewing T-cell helper responses to the Th2 subtype. Prostaglandins, particularly PGE2 , generated by cyclooxygenase-2 (COX-2), which is over expressed in many cancers, suppress T- and B-cell proliferation, inhibit NK cell-mediated cytotoxicity, and inhibit TNF production [33,34].

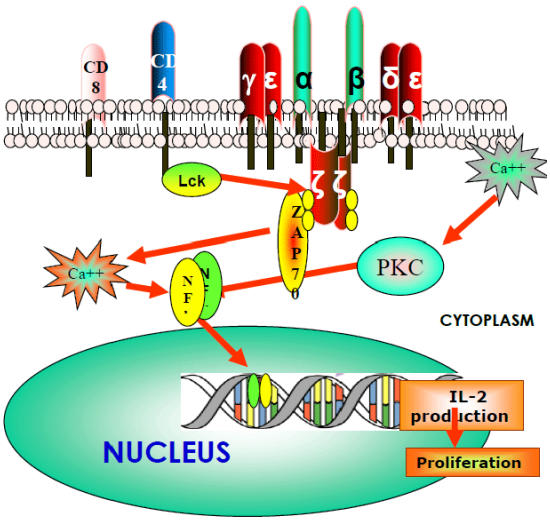

Figure 1: TCR signal transduction pathway.

Defects in T cell signaling

Defects in the TCR signaling pathways, particularly the loss of the zeta chain portion of the CD3-receptor complex, have been reported in patients with melanoma, renal cell carcinoma, ovarian carcinoma, cervical carcinoma, colon carcinoma, and prostate cancer [35-38]. The zeta chain is an important component of T-cell activation *via* the TCR and NK cells *via* the FcyRIII. Defects in signaling ultimately result in lower proliferative responses to antigen, lower cytotoxic function, and lower production of Th1 cytokines. Decreased levels of TCR-ζ expression correlate with prognosis in terms of tumor progression and aggressiveness [39]. The mechanism for zeta chain loss is not clear, but hydrogen peroxide production by tumor-associated macrophages, cleavage by caspases, and granzyme B have all been suggested [40-42].

Finally, some patients may experience defects in the T cell signaling mediated by nuclear factor κB, which is important for regulating expression of IL-2, TNF, GM-CSF, MCSF, and IFNγ [18,43] (Figure 1).

The authors in a study carried out in 112 oral cancer patients T-lymphocytes, noticed a stage-wise and histology-wise reduction in the lymphocyte response to anti-CD-3 in terms of defects in proliferation, decreased expression of TCR signal transduction protein and reduced secretion of IL-2 (Table 1). These demonstrate that oral cancer patients are immunocompromised resulting in reduced efficiency of the oral cancer patient's immune system to mount a response against tumor attack [3]. Researchers have pointed out a subset of suppressive T cells known as $CD4^+CD25^+$ regulatory T cells (Tregs) contribute to the observed immune suppression in patients with HCC by inhibiting the beneficial antitumor immunity [44-46]. Clinically, a high number of Treg number is an indicator of poor prognosis, while a low number of Treg correlates with improved survival [47]. Researchers have also shown that Tregs derived from patients with HCC are functionally more suppressive [48]. The importance of Treg cells in the dynamics of tumor immunity make them critical elements to understand and potentially valuable targets as novel treatment options. These immunosuppressive cells express CTL-A (cytotoxic T lymphocyte–associated protein 4) which is well correlated with advancement of tumor burden [48]. Monoclonal antibodies against CTLA-4 and PD-1 were approved recently by FDA renders hope for further developments of immunotherapy against various types of cancers.

Protein	Expression in:								
	Cancer	Stage	Histology	Anti-CD3 response		rIL2 Response		Treatment Response	
				Responder	Non-Res ponder	+ve	-ve	Bad	Good
TCRζ	↓	→Control to stage III ↓stage IV	→	↑	↓	→	→	↓	↑
CD3ε	↓	→	→	↑	↓	→	→	→	→
LCK	↓	→	→	→	→	→	→	→	→
ZAP-70	↓	↓	→	↑	↓	↑	↓	↓	→
PKC	→	→	→	↑	↓	→	↓	→	→

Table 1: Table showing the status of T cell signal transducing proteins in response to stimulation by anti-CD3 and augmentation with rIL-2 [3].

Blocking factors of T-lymphocyte signal transduction

The functional role of exosomes in cancer progression has become the center of interest of cancer research, because of the apparent roles attributed to them. The great extent repertoire of proteins and nucleic acids that is assembled within exosomes appear to reflect the substantial, multiple and intricate signaling potential of these nano-vehicles. Exosomes are tumor-derived microvesicles released into the extracellular milieu having a vital role in immune regulation. Exosomes generate a pro-tumor micro-environment which regulates immune response and favors carcinogenesis. Apoptosis of cytotoxic T cells and reducing proliferation of the NK cells are the major mechanisms by which exosomes regulate the immune response. Various reports have shown that tumor-derived exosomes induce differentiation of T helper cells to regulatory T cells, which may potentially be a possible mechanism for immune surveillance. NK cells exposed to tumor-derived exosomes fail to respond to IL-2 [49-51]. Apoptosis of T cells was also induced by tumor-derived exosomes, which contains pro-apoptotic proteins like Fas-L and TNF-alpha [51,52]. Tumor-derived exosomes from the ascites of ovarian adenocarcinoma were found to be immunosuppressive by affecting T cell signal transduction mechanism [30].

Use of exosomes as vehicles for drug administration has generated tremendous attention recently because of their tolerance, bioavailability and their targetability to specific tissues. Researchers have shown that exosomes can deliver drugs, micro RNAs and antigens to target receptors. Exosomes are also used to target Si RNA and micro-RNA to regulate the gene expression within the target cells. Studies have also shown that exosomes can also be an option for the delivery of tumor-derived antigens to mount an effective immune response [31,53]. Exosomes secreted from dendritic cells could present antigens to T cells to induce an anti-tumor immune response in mice [30] these findings progressed further by using peptide loaded dexosomes as a cancer vaccine and which are presently in the clinical trial phase.

Exosomes secreted by tumor cells circulate in the blood and contain specific antigens potentially useful for immunotherapeutic purposes. The ability of these factors to modulate lymphocyte and monocyte functions has been analyzed in several tumors [30,54-56]. The shed membrane vesicles have been demonstrated to exhibit the ability to modulate lymphocyte and monocyte functions in several tumor models [30,56,57]. The tumor-derived factors were also shown to suppress lymphocyte activation with phytohemagglutinin, Concanavalin A, or anti-CD3 [58]. The nature of regulation of the signal transduction proteins in T-lymphocytes, which could proceed to an impairment/enhancement of T cell function by these exosomes is not confirmed to date.

Immunotherapy

Cancer has surpassed heart diseases as the leading cause of death across the world [60]. Most of the cancers are now highly treatable and curable, but cancer induced mortality is mainly associated with the metastatic nature of the disease. For most of the distant metastatic

cancers, disease management is the only vital option. Immunotherapy is an emerging treatment option for patients with advanced cancers.

The immune system is unique and dynamic in specificity, mode of action, and memory. The immune response provides long-lasting protection against specific antigens. Researchers over the decades have tried to utilize or manipulate the immune response in the fight against cancer or other diseases because of its safety, efficacy, specificity and long lasting effects. The initial experiments of immunotherapy for cancer was done by William Coley [59], used bacterial products to treat Ewing sarcoma, though the cellular and molecular mechanisms underlying the process were unknown. There are several feasible immune strategies to achieve these goals; one of these strategies is the use of cytokines to augment anticancer immune effector mechanisms [60]. Interferon-α and interleukin-2 are the two cytokines successfully using in the clinic at present. Later a series of monoclonal antibodies were added to the clinic few notable products are rituximab, ofatumumab, alemtuzumab, trastuzumab, bevacizumab, cetuximab, and panitumumab; the radiolabeled antibodies Y-90 ibritumomab tiuxetan and I-131 tositumomab. The anti-CTLA-4 monoclonal antibody ipilumumab, which blocks regulatory T-cells [61] and programmed cell death protein-1 (PD-1) [62] were effective against several malignancies like melanoma [61,62], renal cell carcinoma [62], lung cancer [62,63], bladder cancer [64], ovarian cancer [65], Hodgkin's lymphoma [66], and gastrointestinal cancers [67]. Recently FDA approved the prostate cancer antigen specific vaccine sipuleucel-T for the treatment of advanced prostate cancer [68]. In spite of the fact that the immune system has long been identified with the works of various researchers as a preferred strategy to treat cancers, the full capacity to develop into the mainstream therapy has not been accomplished to date.

Adoptive Cell Therapy

A number of new strategies have been developed which use T cells as immunotherapeutic tools against tumors. Adoptive cell therapy is the utilization of tumor infiltrating lymphocytes (TIL) from neoplastic lesions, which mainly consist of T cells. Tumor-specific T cells were expanded by co-culture with patient tumors in the presence of cytokine IL-2 [69]. Administration of the activated T cells in the patient's body resulted in a significant response. 72 % patients expressed objective response and 40 % patients experienced complete regression [69]. In most of the cases the response appeared to be durable. Among the metastatic melanoma patients who achieve a complete tumor regression (22% of the patients, n=20), 95% of them have ongoing complete regressions beyond 5 years and may be cured [70]. Unmodified T cells can also be used to treat EBV or HPV-associated cancers. Autologous EBV-specific T cells showed promising response in nasopharyngeal carcinoma [71,72] and Hodgkin disease [73,74].

Genetically modified T cells

Adoptive cell transfer of T-cells engineered to express artificial receptors that target tumor cells is an exciting innovative approach. The progresses in genetic engineering and cellular immunology enabled to generate T-lymphocytes that successfully target the tumor. These methodologies radically change the immunotherapy and leads to the latest entry of the drug industry. There is cumulative attention in harnessing regulatory T cells (Tregs) to deregulate the unwanted immune responses. This approach was successful in autoimmune and allograft rejection. The principles of engineering T-reg cells show promise in preclinical models of autoimmunity.

Engineered T cell receptors against MART-1 (Melanoma Ag) and gp 100 produced objective response 30% and 19% respectively [75]. Chimeric antigen receptors (CARs) composed of antigen binding fragments and T cells signaling domains from CD3-z, CD-28, and other signaling molecules are the further progression of the approach [76]. Recruiting B cell leukemia cells expressing CD-19 have shown positive response in the clinic [77] by inducing a significant response against tumor burden by completely eliminating or producing an objective response. In chronic lymphocytic leukemia (CLL), of 23 patients treated with CD-19 CAR T cells, 17 % achieved a partial response, with an overall response rate of 39% [77]. During July 2014, the FDA granted the breakthrough therapy designation to CD-19 CARs for relapsed/ refractory ALL. Chimeric antigen receptor T-cell therapy has generally shown positive response against advanced types of leukemias and lymphomas with long disease-free survival periods. In solid tumors, results have been disappointing. Although engineered T cell therapy is very promising, it has several limitations, including toxicity, applicability, and efficacy. Researchers are actively working to improve production of the T cells and are looking for alternative ways to use them. Studies progressing to assess the feasibility of this technique in other types of cancers.

Conclusions

Immunological responses have a very important role to play in the initiation and progression of various cancers. The impairment of immunity in patients with cancer indicates the possibility that significant immune depression develops well in advance of malignancy. The impairment may be enhanced by the presence of the tumor. The exact nature of the T cell defect is still not entirely clear even though defects in receptor integrity, signal transduction mechanism and cytokine production have been proposed as major factors. Immunotherapy using biologic mediators is being extended with varying degrees of success in various parts of the world. Failures in some cases could be due to a proportion of the patients harboring defective T cell receptors or signal transduction mechanisms.

Adoptive cell transfer immunotherapy showed very significant response in advanced stages of cancer patients. Even though adoptive cell transfer had Striking success, treatment strategies are still is in the beginning stage. Effectiveness of this strategy to a big extend depends up on the quality and quantity of the activated T cells. Researchers are still improving how they make the activated T cells and are learning the best ways to use them. Further optimization and preconditioning methods has to be established for the successful conversion of this technology in to a treatment regime. Vast and growing understanding of immunogenic principles, mechanism by which tumor evades the immune response has served as a foundation for further resolution of these dangerous international health concerns.

References

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, et al. (2004) Cancer statistics, 2004. CA Cancer J Clin 54: 8-29.
2. Scully C (2010) Cancers of the oral mucosa treatment & management. Medscape drugs diseases and procedures.
3. Cheriyan VT, Cessal Thomas, Balaram P (2011) Augmentation of T-cell immune responses and signal transduction proteins in oral cancer patients: potential for IL-2-mediated immunotherapy. J Cancer Res Clin Oncol 137:1435-1444.

4. Balaram P, Vasudevan DM (1983) Quantitation of Fc receptor-bearing T-lymphocytes (TG and TM) in oral cancer. Cancer 52: 1837-1840.
5. Cheriyan VT, Krishna SM, Kumar A, Jayaprakash PG, Balaram P (2009) Signaling defects and functional impairment in T-cells from cervical cancer patients. Cancer Biother Radiopharm 24: 667-673.
6. Prabha B, Kumary, Vasudevan DM (1984) Leucocyte adherence inhibition assay (LAI) in cancer of the oral cavity. Eur J Cancer Clin Oncol 20: 891-897.
7. Kulkarni DP, Wadia PP, Pradhan TN, Pathak AK, Chiplunkar SV (2009) Mechanisms involved in the down-regulation of TCR zeta chain in tumor versus peripheral blood of oral cancer patients. Int J Cancer 124: 1605-1613.
8. Pappas J, Wolfson AD, Jung WJ, Olezak EL, Helm CW, et al. (2009) Differential expression of CD3? message and protein in tumor infiltrating lymphocytes from solid tumor specimens and malignant ascites from patients with ovarian carcinoma. Anticancer Res November 29: 4673-4682.
9. Rabinowich H, Reichert TE, Kashii Y, Bell MC, Whiteside TL (1998) Lymphocyte apoptosis induced by Fas ligand-expressing ovarian carcinoma cells: implications for altered expression of TcR in tumour-associated lymphocytes. J Clin Invest 101: 2579-2588.
10. Reichert TE, Day R, Wagner EM, Whiteside TL (1998) Absent or low expression of the zeta chain in T cells at the tumor site correlates with poor survival in patients with oral carcinoma. Cancer Res 58: 5344-5347.
11. Dooms H, Wolslegel K, Lin P, Abbas AK (2007) Interleukin-2 enhances CD4+ T cell memory by promoting the generation of IL-7R alpha-expressing cells. J Exp Med 204: 547-557.
12. McDermott DF, Regan MM, Atkins MB (2006) Interleukin-2 therapy of metastatic renal cell carcinoma: update of phase III trials. Clin Genitourin Cancer 5: 114-119.
13. Fisher RI, Rosenberg SA, Fyfe G (2000) Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am 6 Suppl 1: S55-S57.
14. Bridgeman JS, Hawkins RE, Hombach AA, Abken H, Gilham DE (2010) Building better chimeric antigen receptors for adoptive T cell therapy. Curr Gene Ther 10: 77-90.
15. Robbins PF, Kassim SH, Tran TL, Crystal JS, Morgan RA, et al. (2015) A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. Clin Cancer Res 21: 1019-1027.
16. Kim R, Emi M, Tanabe K (2007) Cancer immunoediting from immune surveillance to immune escape. Immunology 121: 1-14.
17. Algarra I, García-Lora A, Cabrera T, Ruiz-Cabello F, Garrido F (2004) The selection of tumor variants with altered expression of classical and nonclassical MHC class I molecules: implications for tumor immune escape. Cancer Immunol Immunother 53: 904-910.
18. Ling W, Rayman P, Uzzo R, Clark P, Kim HJ, et al. (1998) Impaired activation of NFkappaB in T cells from a subset of renal cell carcinoma patients is mediated by inhibition of phosphorylation and degradation of the inhibitor, IkappaBalpha. Blood 92: 1334-1341.
19. Hermiston ML, Xu Z, Majeti R, Weiss A (2002) Reciprocal regulation of lymphocyte activation by tyrosine kinases and phosphatases. J Clin Invest 109: 9-14.
20. Trevillyan JM, Lu YL, Atluru D, Phillips CA, Bjorndahl JM (1990) Differential inhibition of T cell receptor signal transduction and early activation events by a selective inhibitor of protein-tyrosine kinase. J. Immunol 145: 3223-3230.
21. O'Connor TP, Liesen DA, Mann PC, Rolando L, Banz WJ (2002) A high isoflavone soy protein diet and intravenous genistein delay rejection of rat cardiac allografts. J Nutr 132: 2283-2287.
22. Lewis RS (2001) Calcium signaling mechanisms in T lymphocytes. Annu Rev Immunol 19: 497-521.
23. Krasznai Z (2005) Ion channels in T cells: from molecular pharmacology to therapy. Arch Immunol Ther Exp (Warsz) 53: 127-135.
24. Sebzda E, Mariathasan S, Ohteki T, Jones R, Bachmann MF, et al. (1999) Selection of the T cell repertoire. Annu Rev Immunol 17: 829-874.
25. Kurt RA, Urba WJ, Smith JW, Schoof DD (1998) Peripheral T-lymphocytes from woman with breast cancer exhibit abnormal protein expression of several signaling molecules. Int J Cancer 78:16-20.
26. Taylor DD, Edwards RP, Case CR, Gerçel-Taylor C (2004) Modulation of CD3-zeta as a marker of clinical response to IL-2 therapy in ovarian cancer patients. Gynecol Oncol 94: 54-60.
27. Blanchard N, Di Bartolo V, Hivroz C (2002) In the immune synapse, ZAP-70 controls T cell polarization and recruitment of signaling proteins but not formation of the synaptic pattern. Immunity 17: 389-399.
28. Khong HT, Restifo NP (2002) Natural selection of tumor variants in the generation of "tumor escape" phenotypes. Nat Immunol 3: 999-1005.
29. Zitvogel L, Tesniere A, Kroemer G (2006) Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 6: 715-727.
30. Taylor DD, Gerçel-Taylor C (2005) Tumour-derived exosomes and their role in cancer-associated T-cell signalling defects. Br J Cancer 92: 305-311.
31. Wahlgren J, De L Karlson T, Brisslert M, Vaziri Sani F, Telemo E, et al. (2012) Plasma exosomes can deliver exogenous short interfering RNA to monocytes and lymphocytes. Nucleic Acids Res 40: e130.
32. Green DR, Droin N, Pinkoski M (2003) Activation-induced cell death in T cells. Immunol Rev 193: 70-81.
33. Harris SG, Padilla J, Koumas L, Ray D, Phipps RP (2002) Prostaglandins as modulators of immunity. Trends Immunol 23: 144-150.
34. Pockaj BA, Basu GD, Pathangey LB, Gray RJ, Hernandez JL, et al. (2004) Reduced T-cell and dendritic cell function is related to cyclooxygenase-2 overexpression and prostaglandin E2 secretion in patients with breast cancer. Ann Surg Oncol 11: 328-339.
35. Finke JH, Zea AH, Stanley J, Longo DL, Mizoguchi H, et al. (1993) Loss of T-cell receptor zeta chain and p56lck in T-cells infiltrating human renal cell carcinoma. Cancer Res 53: 5613-5616.
36. Gunji Y, Hori S, Aoe T, Asano T, Ochiai T, et al. (1994) High frequency of cancer patients with abnormal assembly of the T cell receptor-CD3 complex in peripheral blood T lymphocytes. Jpn J Cancer Res 85: 1189-1192.
37. Nakagomi H, Petersson M, Magnusson I, Juhlin C, Matsuda M, et al. (1993) Decreased expression of the signal-transducing ? chains in tumor-infiltrating T-cells and NK cells of patients with colorectal carcinoma. Cancer Res 53: 5610-5612.
38. Dworacki G, Meidenbauer N, Kuss I, Hoffmann TK, Gooding W, et al. (2001) Decreased zeta chain expression and apoptosis in CD3+ peripheral blood T lymphocytes of patients with melanoma. Clin Cancer Res 7: 947s-957s.
39. Zea AH, Curti BD, Longo DL, Alvord WG, Strobl SL, et al. (1995) Alterations in T cell receptor and signal transduction molecules in melanoma patients. Clin Cancer Res 1: 1327-1335.
40. Schmielau J, Finn OJ (2001) Activated granulocytes and granulocyte-derived hydrogen peroxide are the underlying mechanism of suppression of T-cell function in advanced cancer patients. Cancer Res 61: 4756-4560.
41. Otsuji M, Kimura Y, Aoe T, Okamoto Y, Saito T (1996) Oxidative stress by tumor-derived macrophages suppresses the expression of CD3 zeta chain of T-cell receptor complex and antigen-specific T-cell responses. Proc Natl Acad Sci U S A 93: 13119-13124.
42. Wieckowski E, Wang GQ, Gastman BR, Goldstein LA, Rabinowich H (2002) Granzyme B-mediated degradation of T-cell receptor zeta chain. Cancer Res 62: 4884-4889.
43. Li X, Liu J, Park JK, Hamilton TA, Rayman P, et al. (1994) T cells from renal cell carcinoma patients exhibit an abnormal pattern of kappa B-specific DNA-binding activity: a preliminary report. Cancer Res 54: 5424-5429.
44. Li H, Zhao H, Yu J, Su Y, Cao S, et al. (2011) Increased prevalence of regulatory T cells in the lung cancer microenvironment: a role of thymic stromal lymphopoietin. Cancer Immunol Immunother 60: 1587-1596.

45. Feng X, Li B, Ye H, Long D (2011) Increased frequency of CD4+CD25(high)FoxP3+ regulatory T cells in patients with hepatocellular carcinoma. Arch Immunol Ther Exp (Warsz) 59: 309-314.
46. Kobayashi N, Hiraoka N, Yamagami W, Ojima H, Kanai Y, et al. (2007) FOXP3+ regulatory T cells affect the development and progression of hepatocarcinogenesis. Clin Cancer Res 13: 902-911.
47. Zhou J, Ding T, Pan W, Zhu LY, Li L, et al. (2009) Increased intratumoral regulatory T cells are related to intratumoral macrophages and poor prognosis in hepatocellular carcinoma patients. Int J Cancer 125: 1640-1648.
48. Cabrera R, Ararat M, Eksioglu EA, Cao M, Xu Y, et al. (2010) Influence of serum and soluble CD25 (sCD25) on regulatory and effector T-cell function in hepatocellular carcinoma. Scand J Immunol 72: 293-301.
49. Whiteside TL (2013) Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes). Biochem Soc Trans 41: 245-251.
50. Wieckowski EU, Visus C, Szajnik M, Szczepanski MJ, Storkus WJ, et al. (2009) Tumor-derived microvesicles promote regulatory T cell expansion and induce apoptosis in tumor-reactive activated CD8+ T lymphocytes. J Immunol 183: 3720-3730.
51. Andreola G, Rivoltini L, Castelli C, Huber V, Perego P, et al. (2002) Induction of lymphocyte apoptosis by tumor cell secretion of FasL-bearing microvesicles. J Exp Med 195: 1303-1316.
52. Huber V, Fais S, Iero M, Lugini L, Canese P, et al. (2005) Human colorectal cancer cells induce T-cell death through release of proapoptotic microvesicles: role in immune escape. Gastroenterology 128:1796-804.
53. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, et al. (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol 29: 341-345.
54. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, et al. (1998) Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. Nat Med 4: 594-600.
55. Taylor DD, Bender DP, Gerçel-Taylor C, Stanson J, Whiteside TL (2001) Modulation of Tcr/CD3-zeta chain expression by a circulating factor derived from ovarian cancer patients. Br J Cancer 84: 1624-1629.
56. Andre F, Schartz NE, Movassagh M, Flament C, Pautier P, et al. (2002) Malignant effusions and immunogenic tumour-derived exosomes. Lancet 360: 295-305.
57. Gerçel-Taylor C, Bazzett LB, Taylor DD (2001) Presence of aberrant tumor-reactive immunoglobulins in the circulation of patients with ovarian cancer. Gynecol Oncol 81: 71-76.
58. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62: 10-29.
59. Coley WB (1907) SARCOMA OF THE LONG BONES: THE DIAGNOSIS, TREATMENT AND PROGNOSIS, WITH A REPORT OF SIXTY-NINE CASES. Ann Surg 45: 321-368.
60. Kammula US, Marincola FM (1999) Cancer immunotherapy: is there real progress at last? BioDrugs 11: 249-260.
61. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723.
62. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al. (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366: 2443-2454.
63. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 373: 123-135.
64. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, et al. (2014) MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 515: 558-562.
65. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, et al. (2015) Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol 33: 4015-4022.
66. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, et al. (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372: 311-319.
67. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 372: 2509-2520.
68. Drake CG (2010) Prostate cancer as a model for tumour immunotherapy. Nat Rev Immunol 10: 580-593.
69. Rosenberg SA (2011) Cell transfer immunotherapy for metastatic solid cancer--what clinicians need to know. Nat Rev Clin Oncol 8: 577-585.
70. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, et al. (2011) Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 17: 4550-4557.
71. Louis CU, Straathof K, Bollard CM, Ennamuri S, Gerken C, et al. (2010) Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. J Immunother 33: 983-990.
72. Comoli P, Pedrazzoli P, Maccario R, Basso S, Carminati O, et al. (2005) Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes. J Clin Oncol 23: 8942-8949.
73. Bollard CM, Aguilar L, Straathof KC, Gahn B, Huls MH, et al. (2004) Cytotoxic T lymphocyte therapy for Epstein-Barr virus+ Hodgkin's disease. J Exp Med 200: 1623-1633.
74. Bollard CM, Gottschalk S, Torrano V, Diouf O, Ku S, et al. (2014) Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. J Clin Oncol 32:798-808.
75. Johnson LA, Morgan RA, Dudley ME, Cassard L, Yang JC, et al. (2009) Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood 114: 535-546.
76. Kochenderfer JN, Rosenberg SA (2011) Chimeric antigen receptor-modified T cells in CLL. N Engl J Med 365: 1937-1939.
77. Porter DL, Frey NV, Melenhorst JJ (2014) Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL. Blood 124:1982.

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