Breast Care

Review Article · Übersichtsarbeit

Breast Care 2012;7:267–272
DOI: 10.1159/000342166

Published online: August 13, 2012

Immunomodulation via Chemotherapy and Targeted Therapy: A New Paradigm in Breast Cancer Therapy?

John Stagg[a] Fabrice Andre[b] Sherene Loi[c]

[a]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Faculté de Pharmacie et Institut du Cancer de Montréal, Montréal, Québec, Canada
[b]INSERM Unit 981, Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France
[c]Breast Cancer Translational Research Laboratory (BCTL), Institut Jules Bordet, Brussels, Belgium

Keywords
Breast cancer · Tumor-infiltrating lymphocytes · Prognosis · Immunotherapy

Summary
Cytotoxic chemotherapy in the treatment of tumors has traditionally been thought to be immunosuppressive. Increasing evidence suggests the contrary and has introduced the concept of 'immunogenic' chemotherapy or, in other words, the concept that the innate and adaptive immune systems are critical in determining the long-term efficacy of some cytotoxic-based (and radiotherapy-based) regimens. The underlying mechanisms how these therapies can stimulate an antitumor immune response have been demonstrated recently. In this article, we review the background of this new paradigm and how combinations of traditional agents with the new immunotherapeutic therapies may significantly advance our treatment of breast cancer.

Schlüsselwörter
Brustkrebs · Tumorinfiltrierende Lymphozyten · Prognose · Immuntherapie

Zusammenfassung
Die zytotoxische Chemotherapie wurde bei der Behandlung von Tumoren traditionell als immunsuppressiv eingeschätzt. Immer mehr Hinweise belegen das Gegenteil und führten zur Einführung des Konzeptes der «immunogenen» Chemotherapie oder, mit anderen Worten, zum Konzept, dass das angeborene und das adaptive Immunsystem für die Festlegung der Langzeiteffektivität einiger Zytotoxin-basierter (und Strahlentherapie-basierter) Regime ausschlaggebend sind. Die zugrunde liegenden Mechanismen, über die diese Therapien eine Antitumor-Immunantwort auslösen können, sind kürzlich gezeigt worden. In diesem Artikel beleuchten wir den Hintergrund dieses neuen Paradigmas und bieten einen Überblick, wie Kombinationen von traditionellen Medikamenten mit den neuen immuntherapeutischen Therapien die Behandlung von Brustkrebs beträchtlich verbessern könnten.

Introduction

Traditionally, cytotoxic chemotherapy has been thought to be immunosuppressive. Increasing evidence has proposed the concept of 'immunogenic' chemotherapy or, in other words, the concept that the innate and adaptive immune systems are critical in determining the long-term efficacy of some cytotoxic-based (and radiotherapy-based) regimens. Various mechanistic aspects of the way these therapies can stimulate an antitumor immune response have been revealed recently. In this article, we review the data behind this new paradigm and how combinations of traditional cytotoxic agents with the new targeted agents may significantly advance our treatment of solid tumors and, in particular, of breast cancer.

Cancer Immunoediting

In the past decade, cancer immunology has emerged as a fundamental discipline of oncology, and immunotherapy as a reality for cancer patients [1, 2]. Immunity has 2 seemingly paradoxical effects on cancer. On the one hand, immunity prevents the development of nascent tumors, a concept known as cancer immunosurveillance [3, 4]. On the other

KARGER
Fax +49 761 4 52 07 14
Information@Karger.de
www.karger.com

1661-3791/12/0074-0267$38.00/0

Accessible online at:
www.karger.com/brc

Dr. Sherene Loi, MD, PhD
Breast Cancer Translational Research Laboratory (BCTL)
Institut Jules Bordet
Boulevard de Waterloo 121, Brussels B1000, Belgium
Tel. +32 2 541-3457/3107, Fax -3199
sherene.loi@bordet.be

hand, immunity shapes the intrinsic nature of developing tumors through immunological pressure. This combination of host-protective and tumor-sculpting functions of the immune system is termed cancer immunoediting [5]. Immunoediting is a dynamic process composed of 3 phases: elimination, equilibrium, and escape. Elimination refers to the classical concept of cancer immunosurveillance where premalignant and early-stage malignant cells are directly or indirectly removed by immune cells. The concept of cancer immunosurveillance was initially proposed by Burnet and Thomas [6] and was experimentally validated in the late 1990s using gene-engineered mouse models of immunodeficiency [7–9]. Equilibrium refers to a period of 'tumor dormancy' after incomplete immune-mediated tumor destruction, where equilibrium is reached between immune-mediated killing and survival of tumor cells [10]. Escape refers to the outgrowth of tumors that have survived and have been selected for by immunological pressure. The importance of cancer immunoediting was recently demonstrated in a carcinogen-induced mouse sarcoma model where a mutated antigen was found to be a major tumor rejection antigen that eventually led to the outgrowth of tumors lacking the immunogenic epitope [11]. Thus, despite tumor immunosurveillance, tumors develop and are shaped in a Darwinian way in the presence of a functioning immune system.

Immunogenic Chemotherapy: Mechanisms of Immune Stimulation

In addition to being involved in the natural progression of cancer, immunity can affect the activity of various anticancer agents [12]. Accordingly, recent evidence suggests that some chemotherapeutic drugs, such as anthracyclines and oxaliplatin, rely on the induction of anticancer immune responses. In mouse models of cancer, chemotherapy with anthracyclines or oxaliplatin requires the priming of interferon (IFN)-γ-producing CD8+ T cells for optimal treatment response [13]. In cancer patients, high levels of IFN-γ and CD8+ T cells are predictive of a good clinical response to anthracyclines [14]. The immune-stimulating properties of anthracyclines and oxaliplatin were shown to require preapoptotic translocation of calreticulin (CRT) on the tumor cell surface, post-apoptotic release of the chromatin-binding protein high-mobility group B1 (HMGB1), and extracellular release of adenosine triphosphate (ATP). CRT, HMGB1, and ATP act in concert to promote tumor antigen presentation by dendritic cells (DCs) via activation of CD91, Toll-like receptor (TLR)-4, and purinergic P2X7 receptors, respectively [15]. It was recently demonstrated that chemotherapy-induced autophagy is essential for the release of ATP and subsequent anticancer immunity [16]. Accordingly, autophagy-deficient tumor cells are unable to release ATP in response to anthracyclines or oxaliplatin and fail to elicit CD8+ anticancer T cells. This suggests that patients with autophagy-deficient tumor cells might benefit from therapeutic strategies designed to compensate this process in order to trigger immunogenic signaling. Extracellular ATP thus appears as a central activator of anticancer immunity. However, tumors have been shown to overexpress ecto-nucleotidases able to hydrolyze extracellular ATP to adenosine [17]. The expression of these ecto-nucleotidases, such as CD39 and CD73, will potentially have 2 major consequences: decreasing the concentration of extracellular ATP available for DC activation and increasing the concentration of extracellular adenosine, a potent suppressor of anticancer T cell functions. Several groups have now demonstrated the importance of CD73, considered as the rate-limiting enzyme in the production of extracellular adenosine, in the suppression of anticancer immunity [18]. Taken together, these studies suggest that targeted blockade of ecto-nucleotidases such as CD39 and CD73 may provide effective means to enhance antitumor immune responses.

Immunity in Targeted Therapy

Immune responses also play a major role in the efficacy of targeted therapies with monoclonal antibodies (mAbs). 9 mAbs directed against 6 cancer-associated proteins (namely human epidermal growth factor receptor 2 (HER2), CD20, EGFR (epidermal growth factor receptor), CD52, CD33, and VEGF (vascular endothelial growth factor)) are currently approved for the treatment of various types of cancer [2]. Studies have shown that mAbs such as trastuzumab (anti-HER2) and rituximab (anti-CD20) rely in part on immune-mediated killing through antibody-dependent cellular cytotoxicity (ADCC) [19]. While innate immune responses appear to be important for tumor antigen-targeted mAb therapies, recent studies in mice and correlative clinical evidence suggest that mAbs such as trastuzumab may also stimulate adaptive antitumor immunity. 2 studies in mice showed that anti-HER2 mAb therapy required adaptive CD8-dependent immunity to mediate its optimal effect [20, 21]. Experimental evidence supports a model whereby trastuzumab activates MyD88-dependent TLR signaling (most likely via the release of HMGB1 following ADCC), stimulates the release of type I IFNs and primes adaptive IFN-γ-producing CD8+ T cells. These studies raise the possibility that combination strategies may be used to capitalize on the adaptive tumor-specific immunity generated by anti-HER2 mAbs. Consistent with this notion, Stagg et al. [21] demonstrated that anti-PD-1 and anti-CD137 mAbs can each synergize with anti-HER2 mAb therapy. Similar synergistic activity between anti-CD137 and anti-HER2 mAbs was reported by a different group [22]. Notably, it was also shown that immunosuppressive chemotherapeutic drugs, such as paclitaxel or cyclophosphamide, can dramatically interfere with the tumor-specific immune memory generated by anti-HER2 mAb [20]. Taken together, these studies suggest that first-line chemotherapeutics should be carefully considered to prioritize those that directly or indirectly prime

or alter tumor-specific immunity, and need careful attention when used in combination with mAb therapies. They also suggest that one of the mechanisms of synergy between pro-immunogenic anthracyclines and trastuzumab may be through increased antitumor immune responses [21]. Recent evidence suggests that targeted therapies with small inhibitors may also benefit from antitumor immune responses. Accordingly, the administration of a BRAF inhibitor in advanced melanoma patients has been reported to increase the level of tumor-infiltrating T cells within 7 days of treatment, with CD8+ T cells increasing significantly more than CD4+ T cells [23]. This increase in CD8+ T cells correlated with a decrease in tumor size. This suggests that the combined use of small-molecule inhibitors, such as BRAF inhibitors, and immunotherapy might be synergistic.

T Cell Infiltration, Immune Signatures, Prognosis, and Chemotherapy Response

Overwhelming data reveals the importance of tumor immune infiltrates in the survival of cancer patients, including breast cancer. Increased infiltration of tumors with CD8+ CD45RO+ memory T cells has been associated with a better prognosis in a variety of epithelial cancers [24–26]. Likewise, an increased ratio of CD8+ to CD4+ T cells (T helper 2 (Th2) cells or T regulatory cells (Tregs)) correlates with a good clinical outcome in several types of cancers [27, 28]. In colorectal cancers, T cell infiltration measured by immunohistochemistry has shown superior prognostic power than standard tumor, node, metastasis (TNM) staging [29]. In breast cancer, 2 large series, both in newly diagnosed or early-stage breast cancer, also support a correlation with better clinical outcomes [30, 31].

Tumor lymphocytic infiltration can also be determined by gene expression signatures. In breast cancer, unsupervised expression profiling of cancer-associated stroma revealed a gene signature predictive of good prognosis that was enriched for CD8+ T cell responses [32]. Also, in over 1,500 newly diagnosed breast cancer samples, a metagene of *STAT1* signaling was associated with better outcomes in specific breast cancer subtypes: the 'triple-negative' (negative for expression of the estrogen receptor, progesterone receptor, and HER2) and HER2/neu-overexpressing subtypes [33, 34]. Other independent groups have also observed this [35, 36]. Together this data supports that immune modulation may be most important for these breast cancer subtypes.

Other solid cancer types have been traditionally considered more responsive to immunotherapies, such as melanoma and renal cell carcinoma. Why is this association not considered in breast cancer? We speculate that perhaps the immune system is more effective at preventing breast cancer metastases rather than influencing growth of the primary tumor. For example, the report that transplant patients who have been treated with immunosuppressive therapies do not have an increased incidence of breast cancer, in contrast to melanoma, suggests that tumor immunosurveillance does not regulate primary breast tumor initiation and growth [37]. This is also reinforced by other reports that used breast cancer murine models, where immune effects on metastases were independent of primary tumor initiation and growth [38, 39]. Furthermore, an increase in circulating myeloid-derived suppressor cells (MDSCs) in human cancer was associated with stage 4 disease [40]. Lately, suppression of an *IRF7*-driven type I interferon innate pathway, intrinsic to breast cancer cells, was shown to restrict systemic immunosurveillance and result in increased metastases in a breast cancer murine model, further supporting this concept [41].

In addition, it has been shown in breast cancer that high levels of immune infiltrates are associated with certain breast cancer subtypes: A report in 1992 first highlighted this association with rapidly proliferating breast tumors [42]. Why this could be more relevant for breast cancers that are negative for estrogen receptor expression as well as the HER2-overexpressing breast cancer subtypes as opposed to other breast cancer subtypes is unknown; we speculate that it could be due to the poorly differentiated nature and high genomic instability of these subtypes [43]. Furthermore, HER2 is a well-described tumor antigen. However, this association with different breast cancer subtypes may explain why prognosis has been inconsistently associated with breast cancer and immune infiltrates. In the triple-negative subtype, baseline immune infiltrate is strongly associated with prognosis, independent of the adjuvant type of chemotherapy given [43, 44]. Hence, it seems that, for certain patients, immune memory has already been generated. Lately, baseline immune infiltrates at diagnosis have been shown to predict benefit from immunogenic therapies such as higher-dose doxorubicin and trastuzumab. These effects were seen only in the HER2-overepxressing subtype [43, 44]. This raises the interesting possibility that a baseline pre-existing T cell response predicts for a better outcome to immunogenic-based therapies in HER2-overexpressing disease.

Immune Checkpoint Inhibitors

Anti-CTLA-4 mAb

Several members of the immunoglobulin superfamily of receptors including CTLA-4, PD-1, BTLA (band T lymphocyte attenuator), TIM-3 (T cell immunoglobulin and mucin domain-containing protein 3) and VISTA (V-domain immunoglobulin suppressor of T cell activation) serve as inhibitory immune checkpoints that prevent uncontrolled immune reactions [45]. Much of the recent successes in cancer immunotherapy come from the generation of blocking mAbs targeting these inhibitory receptors. The anti-CTLA-4 mAb ipilimumab was the first to be tested in a phase III clinical trial [46, 47]. In 2011, the FDA approved the use of ipilimumab in patients with metastatic melanoma, either as initial therapy or after relapse. Anti-CTLA-4 mAb therapy enhances the anti-

tumor function of CD8+ T cells, increases the ratio of CD8+ T cells to Foxp3+ Tregs and inhibits the suppressive function of Tregs [1]. CTLA-4 blockade has also been shown to expand a subpopulation of tumor-infiltrating CD4+ T cells that express high levels of ICOS and secrete IFN-γ [48]. These CD4+ ICOS+ T cells might play a role in the therapeutic activity of anti-CTLA-4 mAb therapy, as their frequency correlates with survival in treated melanoma patients. The major drawback to anti-CTLA-4 mAb therapy is the generation of autoimmune toxicities due to on-target effects. It has been reported that up to 23% of patients treated with ipilimumab developed serious grade 3–4 adverse events, reflecting the importance of CTLA-4 in maintaining immune homeostasis. Unfortunately, toxicity has not always been associated with therapeutic benefit. Thus, a major challenge in the use of anti-CTLA-4 mAbs is to define favorable clinical settings that strike an optimum balance between tumor immunity and autoimmunity.

Anti-PD-1 mAb

PD-1 is another inhibitory co-receptor expressed on activated and exhausted T cells. Administration of blocking anti-PD-1 mAbs enhances adaptive antitumor immune responses by preventing T cell exhaustion. PD-1 is expressed by activated CD4+ and CD8+ T cells, B cells, monocytes and natural killer T (NKT) cells. It has two ligands, PD-L1 and PD-L2, with distinct expression profiles. Expression of PD-L1 has been shown to be associated with poor prognosis in melanoma and hepatocellular carcinoma [49, 50]. Anti-PD-1 and anti-PD-L1 mAbs have been shown to reduce the tumor burden in a number of experimental cancer models. Recently, a phase II non-randomized clinical trial evaluating anti-PD-1 mAb therapy in patients with melanoma, renal cell carcinoma, prostate cancer, non-small cell lung cancer or colorectal cancer reported that 6/16 (37.5%) evaluable patients had objective tumor responses [51]. Taken together, clinical studies with anti-PD-1 and anti-PD-L1 mAbs yield very promising results. Of interest, anti-PD-1 mAbs appear to have safer toxicity profiles than anti-CTLA-4 mAbs [52].

Combining Immune Checkpoint Inhibitors

While inhibition of a single immune checkpoint can prolong the survival of cancer patients, an important question that remains is whether combinatorial checkpoint blockade can by synergistic in promoting anticancer activity. As reported by Curran et al. [53], 'blockade of single negative costimulatory pathways often leads to enhanced effector T-cell (Teff) infiltration of tumors, but these T cells accumulate high levels of the unblocked negative coreceptors that eventually limit their expansion'. The first combination of immune checkpoint inhibitors to be tested was the combination of anti-CTLA-4 and anti-PD-1 mAbs. Curran et al. demonstrated that blockade of CTLA-4 and PD-1 allows CD8+ and CD4+ T cells to survive in the tumor microenvironment, to proliferate and to carry out effector functions. More recently, TIM-3 has been identified as another important inhibitory receptor expressed by exhausted CD8+ T cells. It was shown that the most dysfunctional tumor-infiltrating CD8+ T cells actually co-express PD-1 and TIM-3 [54]. Based on these findings, a direct comparison of the therapeutic activity of anti-CTLA-4, anti-PD-1 and anti-TIM-3 mAbs was made in various mouse models of cancer [55]. It was observed that anti-CTLA-4 mAb was only weakly effective against established tumors, which is consistent with other studies. However, the same regimen of anti-PD-1 mAb or anti-TIM-3 mAb, administered as single agent, significantly delayed established tumor growth. Most importantly, the combination of anti-PD-1 and anti-TIM-3 mAbs had the most potent anticancer effect against well-established experimental and carcinogen-induced tumors. Nevertheless, the extent of cooperative interactions between various immune checkpoints still remains largely unknown. LAG-3 is another recently identified inhibitory receptor that acts to limit effector T cell function and to augment the suppressive activity of Tregs. Woo et al. [56] recently revealed that PD-1 and LAG-3 are extensively co-expressed by tumor-infiltrating T cells and that combined blockade of PD-1 and LAG-3 provokes potent synergistic antitumor immune responses.

Other Regulators of T Cell Function

TNF Receptor Superfamily

Members of the tumor necrosis factor (TNF) receptor superfamily also play an important role as regulators of T cell function [57]. Activation of these costimulatory receptors may further enhance the generation of tumor-reactive T cells in the context of cancer therapy. Costimulatory receptors of the TNF receptor family are composed of OX40 (CD134), 4–1BB (CD137), CD27, CD30, and HVEM (herpes virus entry mediator). When activated, each of these receptors can enhance cytokine production and T cell proliferation in response to T cell receptor (TCR) signaling. OX40 and CD137 activation are particularly effective in allowing activated T cells to survive and proliferate in the late phase of immune responses. The administration of agonistic mAbs against OX40 or CD137 has been shown to enhance tumor immunity and induce regression of established mouse models of cancer [58–60]. The use of agonists to costimulatory receptors or antagonists to inhibitory receptors may rescue or enhance the activity of tumor-reactive T cells.

Blocking Tumor Immunosuppressive Factors

Targeting immunosuppression by soluble mediators is another attractive approach for cancer immunotherapy. A plethora of immunosuppressive factors has been associated with tumorigenesis, including transforming growth factor β (TGF-β), indoleamine 2,3-dioxygenase (IDO), arginase, prostaglandin-E2 (PGE2), and extracellular adenosine [3]. To determine which immunosuppressive factors are minimally required for maintaining tumor tolerance in a given patient population remains a great challenge. Recent studies in mouse models of cancer

and clinical correlative studies suggest that interleukin (IL)-23 may be a key cytokine governing the balance between pro- and antitumorigenic immune responses [61–63].

Enzymes that metabolize L-arginine (such as arginase I), the tryptophan-catabolizing enzyme IDO as well as enzymes that regulate extracellular adenosine levels (such as the ectonucleotidases CD39 and CD73) also significantly contribute to the inhibition of anticancer immune responses [17, 64]. CD73 works at a critical checkpoint in the conversion of immune-activating ATP into immunosuppressive adenosine, making it a potential therapeutic target. Tumors often overexpress CD73 as a consequence of tissue hypoxia or, in the case of breast cancer, loss of estrogen receptor expression. Proof-of-principle studies have revealed that anti-CD73 mAb therapy can reduce tumor burden and prevent metastasis in mice [65–69]. While tumor-derived CD73 is a significant contributor to the generation of adenosine, host CD73 also exacerbates tumorigenesis, highlighted by the reduced susceptibility of CD73-deficient mice against a number of transplantable and spontaneous tumors. Given the promising results of anti-CD73 targeted therapy in mice, future studies aimed at translating this approach into the clinic are warranted. Combination of these agents with immunogenic cytotoxic agents could also be a reasonable approach in order to enhance tumor antigen recognition by the host.

Conclusions and Possible Future Directions

As seen, the role of enhancing host antitumor immunity as part of cancer therapy now seems to be a feasible option, and the increased understanding of its interplay in therapies using both traditional cytotoxic and the new targeted agents suggests that combinations of these with directly immunomodulatory agents could lead to a viable new paradigm in breast cancer as well as other cancer types. The key will be the identification of those patients who require specific immune therapies and of the respective best specific therapy. We propose that breast cancer patients (the triple-negative and HER2-overexpressing subtypes) could be stratified according to the level of immune infiltrates at diagnosis as a surrogate of determining which patients have potentially already generated some antitumor immune memory. Using this stratification, we believe that immunotherapies such as the checkpoint inhibitors currently approved for melanoma will be most beneficial and could have a significant role for these breast cancer patients in combination with classical treatment, which includes cytotoxic chemotherapy, radiotherapy, and trastuzumab (fig. 1). Understanding the ligands that switch off T cells in breast cancer will also be the key to determining the T-cell immunotherapies most interesting for evaluation.

All preclinical data in mouse models, as well as prognostic and predictive data in human breast tumors, are strongly supportive of their role in determining long-term outcomes for these molecular subgroups of breast cancer.

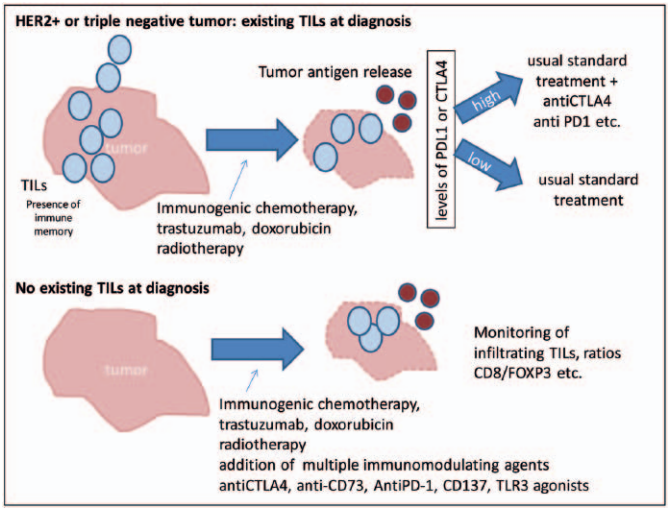

Fig. 1. Proposal for stratification of breast cancer patients for immunotherapy approaches: We propose that separate therapeutic approaches will probably be necessary for breast cancer subtypes (triple negative and HER2 overexpressing) depending on whether they have existing lymphocytic infiltrate (TILs) at diagnosis. Those that do (top) will need optimal standard cytotoxic chemotherapy including an anthraycline and radiotherapy with immunogenic capabilities. Levels of T cell-inhibitory ligands present in the tumor may dictate the need for the addition of further immunotherapy. In contrast, for patients without TILs (bottom) cancer therapy upfront must include maximum immunotherapy in combination with standard cytotoxic chemotherapy (± trastuzumab for HER2-positive patients) in order to stimulate the host immune system to see tumor antigen. This could involve immunogenic chemotherapy (provoke tumor antigen recognition), targeted mAbs (ADCC, stimulating adaptive immunity), inhibition of CD73 (inducing ATP), and TLR-3 agonists (stimulating cytokine production to expand antigen-specific CD8+ T cells and generate IFN-γ-producing CD8+ T cells).

Disclosure Statement

There are no conflicts of interest.

References

1 Sharma P, et al.: Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. Nat Rev Cancer 2011;11:805–812.
2 Mellman I, Coukos G, Dranoff G: Cancer immunotherapy comes of age. Nature 2011;480:480–489.
3 Stagg J, Johnstone RW, Smyth MJ: From cancer immunosurveillance to cancer immunotherapy. Immunol Rev 2007;220:82–101.
4 Vesely MD, et al.: Natural innate and adaptive immunity to cancer. Annu Rev Immunol 2011;29:235–271.
5 Schreiber RD, Old LJ, Smyth MJ: Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2011;331:1565–1570.
6 Burnet M: Cancer: a biological approach. III. Viruses associated with neoplastic conditions. IV. Practical applications. Br Med J 1957;1:841–847.
7 Shankaran V, et al.: IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 2001;410:1107–1111.

8 Kaplan DH, et al.: Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. Proc Natl Acad Sci USA 1998;95:7556–7561.
9 Smyth MJ, et al.: Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. J Exp Med 2000;192:755–760.
10 Koebel CM, et al.: Adaptive immunity maintains occult cancer in an equilibrium state. Nature 2007;450:903–907.
11 Matsushita H, et al.: Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature 2012;482:400–404.
12 Galluzzi L, et al.: The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 2012;11:215–233.
13 Ma Y, et al.: Contribution of IL-17-producing gamma delta T cells to the efficacy of anticancer chemotherapy. J Exp Med 2011;208:491–503.
14 Mattarollo SR, et al.: Pivotal role of innate and adaptive immunity in anthracycline chemotherapy of established tumors. Cancer Res 2011;71:4809–4820.
15 Ghiringhelli F, et al.: Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med 2009;15:1170–1178.
16 Michaud M, et al.: Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 2011;334:1573–1577.
17 Stagg J, Smyth MJ: Extracellular adenosine triphosphate and adenosine in cancer. Oncogene 2010; 29:5346–5358.
18 Beavis PA, et al.: CD73: a potent suppressor of antitumor immune responses. Trends Immunol 2012;33:231–237.
19 Ferris RL, Jaffee EM, Ferrone S: Tumor antigen-targeted, monoclonal antibody-based immunotherapy: clinical response, cellular immunity, and immunoescape. J Clin Oncol 2010;28:4390–4399.
20 Park S, et al.: The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. Cancer Cell 2010;18:160–170.
21 Stagg J, et al.: Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. Proc Natl Acad Sci USA 2011;108:7142–7147.
22 Kohrt HE, et al.: Stimulation of natural killer cells with a CD137-specific antibody enhances trastuzumab efficacy in xenotransplant models of breast cancer. J Clin Invest 2012;122:1066–1075.
23 Wilmott JS, et al.: Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Cin Cancer Res 2012;18:1386–1394.
24 Galon J, et al.: The immune score as a new possible approach for the classification of cancer. J Transl Med 2012;10:1.
25 Fridman WH, et al.: The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer 2012;12:298–306.
26 Galon J, et al.: Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960–1964.
27 Kohrt HE, et al.: Profile of immune cells in axillary lymph nodes predicts disease-free survival in breast cancer. PLoS Med 2005;2:e284.
28 Curiel TJ, et al.: Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004;10:942–949.
29 Mlecnik B, et al.: Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. J Clin Oncol 2011;29:610–618.
30 Denkert C, et al.: Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010;28:105–113.
31 Mahmoud SM, et al.: Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 2011;29:1949–1955.
32 Finak G, et al.: Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 2008;14:518–527.
33 Desmedt C, et al.: Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. Clin Cancer Res 2008;14:5158–5165.
34 Ignatiadis M, et al.: Gene modules and response to neoadjuvant chemotherapy in breast cancer subtypes: a pooled analysis. J Clin Oncol 2012;30: 1996–2004.
35 Schmidt M, et al.: The humoral immune system has a key prognostic impact in node-negative breast cancer. Cancer Res 2008;68:5405–5413.
36 Teschendorff AE, et al.: An immune response gene expression module identifies a good prognosis subtype in estrogen receptor negative breast cancer. Genome Biol 2007;8:R157.
37 Penn I: Tumors of the immunocompromised patient. Annu Rev Med 1988;39:63–73.
38 Chen Q, Zhang XH, Massagué J: Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs. Cancer Cell 2011;20:538–549.
39 DeNardo DG, et al.: CD4+ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. Cancer Cell 2009;16:91–102.
40 Filipazzi P, et al.: Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J Clin Oncol 2007;25:2546–2553.
41 Bidwell BN, et al.: Silencing of Irf7 pathways in breast cancer cells promotes bone metastasis through immune escape. Nat Med 2012, DOI: 10.1038/nm2830.
42 Aaltomaa S, et al.: Lymphocyte infiltrates as a prognostic variable in female breast cancer. Eur J Cancer 1992;28A:859–864.
43 Loi S, et al.: Evaluation of the prognostic and predictive value of tumor-infiltrating lymphocytes (TILs) in a phase III randomized adjuvant breast cancer (BC) trial (BIG 2–98) of node-positive (N+) BC comparing the addition of docetaxel to doxorubicin (A-T) with doxorubicin (A)-only chemotherapy (CT). J Clin Oncol 2011;29(suppl):abstr 556.
44 Loi S, et al.: Tumor PIK3CA mutations, lymphocyte infiltration, and recurrence-free survival (RFS) in early breast cancer (BC): Results from the FinHER trial. J Clin Oncol 2012;30(suppl):abstr 507.
45 Pardoll DM: The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–264.
46 Hodi FS, et al.: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.
47 Robert C, et al.: Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–2526.
48 Fu T, He Q, Sharma P: The ICOS/ICOSL pathway is required for optimal antitumor responses mediated by anti-CTLA-4 therapy. Cancer Res 2011;71:5445–5454.
49 Gadiot J, et al.: Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer 2011;117:2192–2201.
50 Gao Q, et al.: Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15:971–979.
51 Sznol M, et al.: Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. J Clin Oncol 2010;28(suppl 15s):abstr 2506.
52 Brahmer JR, et al.: Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167–3175.
53 Curran MA, et al.: PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA 2010;107:4275–4280.
54 Sakuishi K, et al.: Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore antitumor immunity. J Exp Med 2010;207:2187–2194.
55 Ngiow SF, et al.: Anti-TIM3 antibody promotes T cell IFN-gamma-mediated antitumor immunity and suppresses established tumors. Cancer Res 2011;71:3540–3451.
56 Woo SR, et al.: Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res 2012;72:917–927.
57 Croft M, et al.: TNF superfamily in inflammatory disease: translating basic insights. Trends Immunol 2012;33:144–152.
58 Narazaki H, et al.: CD137 agonist antibody prevents cancer recurrence: contribution of CD137 on both hematopoietic and nonhematopoietic cells. Blood 2010;115:1941–1948.
59 Palazon A, et al.: Agonist anti-CD137 mAb act on tumor endothelial cells to enhance recruitment of activated T lymphocytes. Cancer Res 2011;71:801–811.
60 Piconese S, Valzasina B, Colombo MP: OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection. J Exp Med 2008;205: 825–839.
61 Gangemi S, et al.: Clinical significance of circulating interleukin-23 as a prognostic factor in breast cancer patients. J Cell Biochem 2012;113:2122–2125.
62 Teng MW, et al.: Anti-IL-23 monoclonal antibody synergizes in combination with targeted therapies or IL-2 to suppress tumor growth and metastases. Cancer Res 2011;71:2077–2086.
63 Langowski JL, et al.: IL-23 promotes tumour incidence and growth. Nature 2006;442:461–465.
64 Singer K, et al.: Suppression of T-cell responses by tumor metabolites. Cancer Immunol Immunother 2011;60:425–431.
65 Stagg J, et al.: CD73-deficient mice are resistant to carcinogenesis. Cancer Res 2012;72:2190–2196.
66 Stagg J, et al.: CD73-deficient mice have increased antitumor immunity and are resistant to experimental metastasis. Cancer Res 2011;71:2892–2900.
67 Stagg J, et al.: Anti-CD73 antibody therapy inhibits breast tumor growth and metastasis. Proc Natl Acad Sci USA 2010;107:1547–1552.
68 Jin D, et al.: CD73 on tumor cells impairs antitumor T-cell responses: a novel mechanism of tumor-induced immune suppression. Cancer Res 2010;70:2245–2255.
69 Wang L, et al.: CD73 has distinct roles in nonhematopoietic and hematopoietic cells to promote tumor growth in mice. J Clin Invest 2011;121:2371–2382.