Enhancing immunotherapy using chemotherapy and radiation to modify the tumor microenvironment

Michael H Kershaw1,2,*, Christel Devaud1, Liza B John1, Jennifer A Westwood1, and Phillip K Darcy1,2

1Cancer Immunology Research Program; Sir Peter MacCallum Department of Oncology; University of Melbourne; Parkville, VIC Australia
2Department of Immunology; Monash University; Prahran, VIC Australia

Keywords: chemotherapy, immunotherapy, radiotherapy, tumor endothelium, tumor microenvironment

The tumor microenvironment is a complex assortment of cells that includes a variety of leukocytes. The overall effect of the microenvironment is to support the growth of tumors and suppress immune responses. Immunotherapy is a highly promising form of cancer treatment, but its efficacy can be severely compromised by an immunosuppressive tumor microenvironment. Chemotherapy and radiation treatment can mediate tumor reduction through cytotoxic effects, but it is becoming increasingly clear that these forms of treatment can be used to modify the tumor microenvironment to liberate tumor antigens and decrease immunosuppression. Chemotherapy and radiotherapy can be used to modulate the tumor microenvironment to enhance immunotherapy.

Introduction

Mainstays of cancer treatment include chemotherapy and radiotherapy that are used in various regimens as first-line treatments for most malignancies. A major mechanism of tumor inhibition by chemotherapy is undoubtedly through direct toxicity to tumor cells. A range of chemical agents are used with varied mechanisms of action including their alkylating properties and their nucleoside analog properties. The use of chemotherapeutics exploits the preferential toxicity against rapidly dividing cells, such as tumor cells. Similarly, radiation can induce DNA damage in tumor cells leading to the selective elimination of malignant cells.

However, in addition to these mechanisms, chemotherapy and radiation can have a wide range of effects on tumors including modifications to the tumor microenvironment. This can lead to the induction of inflammatory cytokines and upregulation of death receptors such as Fas, which can increase antigen availability and presentation, increase the expression of major histocompatibility molecules, normalize vessels, induce danger signals and increase T cell localization.1

The tumor microenvironment is composed of cancer cells in association with a variety of other cells that comprise the stroma. Stromal cells include fibroblasts and endothelial cells in addition to a variety of leukocytes, some of which can be immunosuppressive. Such immunosuppressive leukocytes include myeloid-derived suppressor cells (MDSC),2 type 2 macrophages (M2)3 and T regulatory cells (Treg),4 which can inhibit immunity through cell contact or through the secretion of immunomodulating cytokines including transforming growth factor-β (TGF-β)

In this review, we focus on studies demonstrating the ability of chemotherapy and radiotherapy to modulate the tumor microenvironment, resulting in the enhancement of co-administered immunotherapy.

Chemotherapy to Change the Microenvironment and Enhance Immunotherapy

Although chemotherapeutic agents are generally referred to as cytotoxic, some chemotherapeutics can conserve aspects of immunity, providing opportunities to combine chemotherapy with immunotherapy. Gemcitabine is a nucleoside analog that inhibits DNA replication. One of its main side effects is neutropenia, but this can be used to advantage in the reduction of MDSC. When used in combination with cytokines or vaccine, synergistic antitumor activity can occur associated with reduction in MDSC numbers.5 An increased ratio of M1 to M2 macrophages in tumor has also been observed together with increases in the antitumor activity of CD8+ T cells and NK cells.6,7 Immunotherapeutics aimed at stimulating antigen presenting cells (APC) can also benefit from co-administration of gemcitabine, as observed in studies when combined with an anti-CD40 agonist antibody.8 Gemcitabine alone was able to increase the frequency of CD8+ T cells within tumors, which were necessary for eradication of solid tumors. Other chemotherapeutic agents including anthracyclines can also modulate recruitment and differentiation of APC to enable tumor immunity.9
Oxaliplatin, a platinum-based drug, has recently been demonstrated to induce immunogenic cell death to provide increased levels of tumor antigen presentable by APC and disrupt STAT6-mediated suppression of immune responses. Its use in combination with an inducible adenoviral IL-12 (Ad-IL-12) system was associated with a less immunosuppressive microenvironment characterized by a reduction in intratumoral MDSC and an increased ratio of CD8+ /Treg cells. Interestingly, in contrast to studies listed above, this effect was not seen when Ad-IL-12 was combined with gemcitabine, suggesting model-specific considerations in the action of chemotherapeutics. Indeed, despite demonstrations of the ability of chemotherapy to enhance immunity, this is not always the case. Indeed, even agents widely thought of as preserving immunity can, at least in some circumstances, potentiate the immunoregulatory capacity of MDSC leading to reduced tumor immunity.

The importance of the ability of chemotherapeutics to increase antigen availability is apparent in a study using 5-aza-2'-deoxycytidine, a demethylating agent, which induced de novo expression of a cancer testis antigen, leading to enhancement of adoptive immunotherapy of mouse breast cancer tumors.

In addition to changing the cellular composition of the tumor microenvironment, chemotherapeutics can change the cytokine profile and block regulatory cell function. Paclitaxel, a mitotic inhibitor, can reduce MDSC infiltration but also impair Treg function and induce intratumoral production of macrophage chemotactic protein, which was associated with increased effectiveness of a dendritic cell vaccine against 3LL tumors in mice.

IL-12 is an immunostimulatory cytokine able to induce cytokine production, cytolytic capacity and proliferation of T cells. In the presence of an immunosuppressive tumor microenvironment, the action of IL-12 can be suboptimal. However, when IL-12 is combined with cyclophosphamide, a reduction in tumor-associated MDSC and Treg can lead to enhanced antitumor activity. Importantly, the dose of cyclophosphamide in these studies is relatively low, since high doses are immunosuppressive. Similarly, costimulation of T cells through OX40 alone can lead to suboptimal antitumor responses, but when combined with cyclophosphamide a profound reduction in intratumoral Tregs can lead to eradication of established tumors in mice.

Targeted therapies using small molecules that inhibit signaling pathways represent alternative drug treatments for some malignancies with less toxic profiles, and these are also able to lead to changes in the tumor microenvironment. For example, the BRAF inhibitor, vemurafenib can reduce IL-1 secretion by melanoma cells, which can lead to reduced expression of the immune inhibitory molecules PD-L1 and PD-L2 by tumor-associated fibroblasts. Enhanced infiltration of tumors by T cells and increased recognition of melanoma by T cells has also been reported following treatment with BRAF inhibitors. Other targeted therapies, such as the epidermal growth factor receptor tyrosine kinase inhibitor lapatinib, can also enhance T cell activation and their infiltration into tumors. Therefore, targeted therapies represent attractive options for combining with immunotherapies.

Radiotherapy to Enhance Immunotherapy

Several immunopotentiating events likely operate simultaneously within tumors following irradiation and, although studies rarely look at all these events and their role in the success of immunotherapy, some important connections between microenvironment changes and success of immunotherapy have been made. For example, enhanced Fas expression following localized radiotherapy was found to be important for the increased effectiveness of adoptively transferred T cells specific for CEA. In this case, irradiation of subcutaneous mouse adenocarcinoma led to increased Fas expression and enhanced Fas-dependent CTL killing of tumor, together with a marked and significant decrease in tumor growth rate.

Similarly, two other studies demonstrated upregulation of Fas expression on tumor following localized irradiation of s.c. tumors and an enhancement of effectiveness of cancer vaccines. Both studies showed a dramatic influx of CD8+ cytotoxic T cells into the tumor, with associated tumor regression. Other changes were also noted including an increase in vascular density and an abscopal effect involving regression of distant unirradiated tumors. Interestingly, induction of high levels of T cell responses against two other antigens (gp70 and p53) overexpressed in tumor was also observed (antigen cascade effect). In the above studies, localized external beam irradiation was used, but the immunopotentiating effects have been shown to extend to other forms of radiation including brachytherapy using either 125I-seed or Yttrium-radiolabeled antibody when used in combination with vaccines.

Other immunologically important molecules upregulated by radiation include MHCI. Local tumor irradiation, demonstrated to upregulate MHCI molecules on the tumor cell surface, was combined with adoptive transfer of tumor-specific CTL to enhance the antitumor effect of transferred cells. In addition, novel proteins could be generated by the tumor, which were presented on the MHCI molecules and recognized by the CTL. Well-established tumors expressing low levels of antigen were treated with local irradiation, causing transient upregulation of MHC complexes on stromal cells and presentation of tumor antigen. Maximal antigen expression occurred 2 d later, and this was then combined with adoptive transfer of pre-activated CTL, causing tumor regression.
Other forms of immunotherapy besides vaccines and adoptive cell transfer can also benefit from radiotherapy. Blocking the CTLA-4 receptor to overcome T cell tolerance was used in conjunction with fractionated local irradiation (in which the total radiation dose is delivered in smaller fractions over time) to inhibit subcutaneous breast cancer tumors. Only fractionated (and not single dose) radiotherapy worked synergistically with the anti-CTLA-4 antibody. In addition, an abscopal effect on distant tumors was observed together with a marked increase in tumor-infiltrating lymphocytes.

Different combinations of relevant monoclonal antibodies (mAbs) to stimulate immunity (anti-(α)-CD137, α-CD40) and relieve immunosuppression (α-PD-1) have been combined with local irradiation in established orthotopic mammary tumors in mice. Complete regressions were achieved using α-CD137 combined with α-PD-1 mAb and irradiation. Interestingly, in this case, single dose irradiation performed better than fractionated radiation. In these studies, treatment was associated with a temporary intratumoral enrichment of PD-1hiCD137hiCD8+ T cells. Significant tumor regressions also occurred with the combination of α-CD137, α-CD40 and radiation.

It is worth noting as a final comment on the use of radiation to alter the tumor microenvironment, that radiotherapy may not always mediate positive immunopotentiating changes to the microenvironment. Indeed, in a study on glioblastoma multiforme, radiation induced recruitment of vasculogenic bone marrow-derived cells through stromal cell-derived factor-1 (SDF-1), which restored vasculature allowing tumor recurrence.

**Modifying Tumor Endothelium**

Irradiation and a variety of other approaches can be used to modify endothelial cells. Tumor endothelium that lines the blood vessels of tumors is composed of heterogenous cells that are organized abnormally when compared with normal blood vessel endothelium. Tumor endothelial cells have a higher proliferative rate, the blood vessels are dilated and chaotic, with discontinuous or absent basement membrane, and abnormal pericytes cover the tumor endothelium. Researchers have targeted the tumor endothelium to correct or disrupt this abnormal endothelium development.
Ganss et al. used irradiation to cause an inflammatory response in the tumor microenvironment, involving the release of cytokines and chemokines, and upregulation of adhesion molecules. This caused a remodeling of the tumor vasculature, due to upregulation of CXCL9 and CXCL10, enhancing vessel density in the tumors and changing their diameter so that they resembled normal capillaries. The irradiation was then followed by adoptive transfer of activated, tumor-specific lymphocytes, which previously had been unable to adhere to endothelium and access the tumor. Following irradiation, T cells were able to access and penetrate the tumor and induce complete tumor regression in some cases.

Shrimali et al. utilized another therapy, an anti-VEGF antibody that inhibits VEGF/VEGFR-2 interaction, to normalize the tumor vasculature endothelium prior to combination therapy. Multiple doses of anti-VEGF were essential to increase extravasation into the tumor of adaptively transferred antitumor T cells following lymphodepleting conditioning. The combination therapy was required to cause reduction in tumor growth and prolonged survival of mice.

Another way to impact on tumor endothelium is to increase adhesion molecule expression on tumor endothelial vasculature. Palazon et al. targeted CD137, which is selectively expressed on the surface of endothelial cells in response to hypoxia, with an agonist anti-CD137 monoclonal antibody. This treatment increased cell surface expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) on tumor endothelial cells, facilitating the adhesion and extravasation of adaptively transferred lymphocytes into the tumor.

Blocking new vessel formation is another way to impact on the tumor microenvironment by increasing hypoxia and inducing apoptosis and necrosis. Manning et al. utilized an anti-VEGF-R2 antibody, which decreased angiogenesis and increased tumor cell apoptosis. Combining this therapy with an

### Table 1. Examples of immunotherapies that can be combined with modification of the tumor microenvironment for effective anti-tumor responses

| Strategy                  | Microenvironment modifier | Additional immunotherapy | Effect within tumor microenvironment | Effect on tumor size and mouse survival | Ref. |
|---------------------------|---------------------------|--------------------------|--------------------------------------|----------------------------------------|------|
| 1. Chemotherapy           | Cyclophosphamide           | OX-40 agonist antibody   | Treg depletion in tumor and enhanced effector T cell level, thus decreasing Treg/Teffector ratio. | Eradication of established tumors in 75% of mice bearing s.c. B16-F10 tumors. | 22   |
|                           | Oxaliplatin                | Inducible adenoviral 1L-12 | Reduction in MDSC in tumor and increased CD8+/Treg and CD8+/MDSC cell ratios. | Rejection of tumors in > 80% of mice bearing intrahepatic MC38 tumors. | 14   |
| 2. Radiotherapy           | Local irradiation          | Adoptive cell transfer (ACT) of tumor-specific CTL | MHCI expression enhanced within tumor and increased Ag presentation and recognition by effector T cells. | Eradication of established s.c. MC38 tumors in 62% of mice. | 51   |
|                           | Fractionated local irradiation | Blocking CTLA-4 with antibody | Increased CD4+ and CD8+ TIL. | 60% survival of mice bearing TSA breast cancer, and abscopal effect on distant tumors | 35   |
|                           | Local irradiation          | Anti-CD137 with anti-CD40 or anti-PD-1 | Only effector PD-1hiCD137+CD8+ T cells were tumor specific and these were enriched in tumor. | Rejection of > 80% s.c. 4T1.2 tumors with irradiation + anti-CD137 with anti-CD40. Rejection of all orthotopic AT-3 mammary tumors with irradiation + anti-CD137 + anti-PD-1. | 36   |
| 3. Modifying tumor endothelium or stroma | Anti-VEGF | Lymphodepletion + ACT of tumor-specific CTL | Increased extravasation of adoptively transferred T cells into tumor. | Reduction in tumor growth and prolonged survival of mice bearing s.c. B16 tumors with 20% long-term survival. | 40   |
|                           | FAP+ cell ablation by diphtheria toxin (DTX) | Vaccinia-OVA immunization | 60% reduction in tumor and stroma cells in 48 h. | s.c. Lewis lung carcinoma-OVA (LL2/OVA) eradicated. | 44   |
anti-Her2 vaccine enhanced tumor regression by tumor-specific CD8+ T cells. Li et al.43 also targeted VEGF receptors, but in a different way, using a recombinant adeno-associated virus vector expressing a soluble VEGF receptor. When used in combination with GM-CSF-secreting tumor cell immunotherapy a decrease in intra-tumoral Tregs, and an increase in activated CD4+ and CD8+ infiltrating effector T cells was observed, significantly enhancing the survival of the mice.

As well as endothelial cells in the tumor microenvironment, there are mesenchymal stroma cells, identified by the expression of type II membrane dipeptidylpeptidase fibroblast activation protein-α (FAP). Their suppressive function on efficacy of vaccination was ascertained in mice following FAP+ cell ablation.44 Ablation of FAP+ stromal cells (which made up ~1% of all tumoral cells) combined with vaccination (VaxOVA) caused immediate tumor growth arrest with 60% decrease in viable cells in the tumor, which was dependent on TNFα and IFNγ.

Concluding Remarks

The above review summarizes many different approaches that have been used to change the tumor microenvironment to enhance co-administered immunotherapies (Table 1). Insight gained from mouse studies into the efficacy of combining chemotherapy and/or radiotherapy with immunotherapy has been used in the design of clinical trials. Combining paclitaxel and carboplatin with anti-CD137 for the treatment of melanoma and renal cell carcinoma was well tolerated and produced some partial responses and increases in circulating CD8+ T cells.45 Combining gemcitabine with agonist CD40 antibody induced partial tumor regression in 4 of 21 pancreatic ductal adenocarcinoma patients receiving the combined treatment.46 Histological analysis of tumors from two patients showed regression without lymphocyte infiltrate, and a potential mechanism for regression was shown in a mouse model to be due to reeducation of tumor-associated macrophages. This study demonstrated that in the tumor microenvironment is modified by one or both therapies can facilitate tumor regression.

Radiotherapy is also being used to synergize with immunotherapeutics in patients. For many years antibodies have been used to target radioisotopes to tumors, and localized modification to tumor microenvironments may well have contributed to some successes of this form of treatment.47 More recently, localized radiotherapy has been used in combination with immune modulators, and increases in tumor-specific T cell frequencies demonstrated, together with some partial tumor responses.48-50

Immunotherapy is a highly promising treatment option for cancer, and as our understanding of the tumor microenvironment increases, we can anticipate the development of enhanced therapies utilizing immune strategies. In particular, with our developing knowledge of how chemotherapeutic agents and radiation can be used to modify the immunosuppressive nature of tumors, the full potential of immunotherapy may be able to be liberated against malignant disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Kwitas AR, Donahue RN, Bernstei MB, Hodge JW. In the field: exploiting the untapped potential of immunogen modulation by radiation in combination with immunotherapy for the treatment of cancer. Front Oncol 2012; 2:104; PMID:22973551; http://dx.doi.org/10.3389/fonc.2012.00104
2. Lesokhin AM, Merghoub T, Wolchok JD. Myeloid-derived suppressor cells and the efficacy of CD8(+) T-cell immunotherapy. Oncoimmunology 2013; 2:e22764; PMID:23525353; http://dx.doi.org/10.4161/onci.22764
3. Dannenmann SR, Thielicke J, Stockli M, Matter C, von Boehmer L, Ceconi V, Hermanns T, Hefermehl L, Schraml P, Moch H, et al. Tumor-associated macrophages subvert T-cell function and correlate with reduced survival in clear cell renal cell carcinoma. Oncoimmunology 2013; 2:e23562; PMID:23687622; http://dx.doi.org/10.4161/onci.23562
4. Weiss VL, Lee TH, Jaffee EM, Armstrong TD. Concluding Remarks. Oncoimmunology 2013; 2:e23562; PMID:23687622; http://dx.doi.org/10.4161/onci.23562
5. Ko HJ, Kim YJ, Kim YS, Chang WS, Ko SY, Chang SY, Sakaguchi S, Kang CY. A combination of chemotherapy immunotherapies can efficiently break self-tolerance and induce antitumor immunity in a tolerogenic murine tumor model. Cancer Res 2007; 67:7477-86; PMID:17671218; http://dx.doi.org/10.1158/0008-5472.CAN-06-4639
6. Fridlender ZG, Sun J, Singhal S, Kapoor V, Cheng G, Suzuki E, Albeda SM. Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms. Mol Ther 2010; 18:1947-59; PMID:20683443; http://dx.doi.org/10.1038/mt.2010.159
7. Suzuki E, Kapoor V, Jasat AS, Kaiser LR, Albeda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumors, bearing animals and enhances antitumor immune activity. Clin Cancer Res 2005; 11:6731-21; PMID:16064542; http://dx.doi.org/10.1158/1078-0432.CCR-05-0883
8. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res 2003; 63:4490-6; PMID:12970962
9. Ma Y, Adjemian S, Mattaroillo SR, Yamazaki T, Aymet M, Yang L, Portela Catani JP, Hannanni D, Duter H, Steegh K, et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity 2013; 38:729-41; PMID:23562161; http://dx.doi.org/10.1016/j.immuni.2013.05.003
10. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013; 31:51-72; PMID:23157435; http://dx.doi.org/10.1146/annurev-immunol-030712-100008
11. Vaccelli E, Senovilla L, Eggermont A, Fridman WH, Galon J, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Chemotherapy with immunogenic cell death inducers. Oncoimmunology 2013; 2:e23561; PMID:23687621; http://dx.doi.org/10.4161/onci.23561
12. Tesniere A, Schlemmer F, Boige V, Kepp O, Martins I, Ghiringhelli F, Aymet M, Michaud M, Apetoh L, Barault L, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene 2010; 29:482-91; PMID:19881547; http://dx.doi.org/10.1038/onc.2009.356
13. Lesterhus WJ, Punt CJ, Hato SV, Eleveld-Trancikova D, Jensen BJ, Niekens S, Schreibelt G, de Boer A, van Herpen CM, Kaanders JH, et al. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. J Clin Invest 2011; 121:3000-8; PMID:21765211; http://dx.doi.org/10.1172/JCI43656
14. Gonzalez-Aparicio M, Alzogunen P, Maupton I, Medina-Echever J, Hervas-Stubbs S, Manchego U, Berraondo P, Cretzas J, Gonzalez-Agueuinozala G, Prieto J, et al. Oxiaplatin in combination with liver-specific expression of interleukin 12 reduces the immunosuppressive microenvironment of tumours and eradicates metastatic colorectal cancer in mice. Gut 2011; 60:341-9; PMID:20855451; http://dx.doi.org/10.1136/gut.2011.217722
15. Bruchard M, Mignot G, Derangère V, Chalmín F, Chevriaux A, Végran F, Boireau W, Simon B, Ryffel B, Connat J, et al. Chemotherapy-triggered cathep- sin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. Nat Med 2013; 19:57-64; PMID:23202296; http://dx.doi.org/10.1038/nm.2999
16. Guo ZS, Hong JIA, Irvine KR, Chen GA, Spiess PJ, Liu Y, Zeng G, Wunderlich JR, Nguyen DM, Restifo NP, et al. De novo induction of a cancer/testis anti- gen by 5-aza-2-deoxycytidine augments adoptive immunotherapy in a murine tumor model. Cancer Res 2006; 66:1105-13; PMID:16424047; http://dx.doi.org/10.1158/0008-5472.CAN-05-3020
22. Hirschhorn-Cymerman D, Rizzuto GA, Merghoub T, Montesano R, et al. Cancer Immunol Immunother 2012; 10:1193-204; PMID:22731063; dx.doi.org/10.1007/s00262-011-1136-4.

Zhong H, Han B, Tournikou IK, Lokshin A, Rosenblum A, Shirin MR, Shirin GV. Low-dose paclitaxel prior to intratumoral dendritic cell vaccine modulates intratumoral cytokine network and lung cancer growth. Clin Cancer Res 2007; 13:5457-62; PMID:17857757; dx.doi.org/10.1158/1078-0432.CCR-07-0517.

39. Gansz R, Ryschich E, Klar E, Arnold B, Hämmerling UG. Anti-apoptotic effects of TGF-beta in murine T cells. J Immunol 1991; 146:497-503; PMID:17875775; dx.doi.org/10.1158/1078-0432.CCR-07-1373.

Hodge JW, Sharp HJ, Gameiro SR. Abolitional regression of antigen disparate tumors by antigen cascade therapy with systemic tumor vaccination in combination with local tumor vaccination. Cancer Biother Radiopharm 2012; 27:12-22; PMID:22283603; dx.doi.org/10.1089/cbr.2012.1202.

37. Kioi M, Vogel H, Schultz G, Hoffman RM, Harshman J, Kasten M, Philipp S, Daschil N, Datta S, Koller JB, Tripp MH, Barni S. Targeted therapies for the treatment of cancer. Cancer Res 2010; 70:6171-80; PMID:20631075; dx.doi.org/10.1158/0008-5472.CAN-10-1733.

40. Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Finkelman FD, Bhatnagar R, Moelling K, Kim JH, Kuo HP, Wang YS, Chao CH. Tumor-associated neutrophil-granulocyte CD4+Foxp3+ regulatory T-cell impairment by paclitaxel therapy and tumor-targeted immunomodulatory mAbs. Int J Cancer 2012; 130:1876-87; PMID:22693252; dx.doi.org/10.1111/j.1365-3083.2011.03514.x.

23. Khalti JS, Liu S, Rodríguez-Cruz TG, Whittington M, Wardell S, Liu C, Zhang M, Cooper ZA, Frederick DT, Li Y, et al. Oncogenic BRAF(V600E) promotes stromal cell-mediated immunosuppression via induction of interleukin-1 in melanoma. Clin Cancer Res 2012; 18:5329-40; PMID:22850686; dx.doi.org/10.1158/1078-0432.CCR-12-1632.

28. Rossig C. Immune modulation by molecular cancer targets and targeted therapies: Rationale for novel combination strategies. Oncoimmunology 2012; 1:138-50; PMID:22737614; dx.doi.org/10.4161/1801.

29. Petrelli F, Cabiddu M, Cazzaniga ME, Cremonezi M, Barni S. Targeted therapies for the treatment of breast cancer in the post-trastuzumab era. Oncologist 2008; 13:373-81; PMID:18448551; dx.doi.org/10.1634/onthocancer.2007.0173.

38. Aird WC. Endothelial cell heterogeneity. Cold Spring Harb Perspect Med 2012; 2:006429; PMID:22335715; dx.doi.org/10.1101/cshperspect.a006429.

41. Palazón A, Tejeira A, Martinez-Foreiro I, Hervás-Stubbs S, Roncal C, Peñuela I, Dubert J, Morales-Kastreñana A, Pérez-Graciá JL, Ochoa MC, et al. Angiostatin anti-CD137 mAb act on tumor endothelial cells to enhance recruitment of activated T lymphocytes. Cancer Res 2011; 71:801-11; PMID:21266358; dx.doi.org/10.1158/0008-5472.CAN-10-1733.

46. Beatty GL, Chiorean EG, Fishman MP, Saboury EA, Teitelbaum UR, Sun W, Huhn RD, Song W, Li D, Sharp LL, et al. CD40 agonists alter tumor stromal phenotype and enhance anti-pancreatic carcinoma in mice and humans. Cancer Immunol Immunother 2012; 1:358-60; PMID:22737614; dx.doi.org/10.1158/1078-0432.CCR-12-1632.

15. Paluzza S, Zunino D, Mariotto A, Mantovani A, Ferrari S, Bono D. Hypoxia-mediated tumor invasion via matrix metalloproteinases and its control by tumor-infiltrating lymphocytes. Cancer Res 2004; 64:3428-37; PMID:15205848; dx.doi.org/10.1158/1078-0427.CAN-04-0073.

42. Manning EA, Ullman JG, Leatherman JM, Asquith MJ, Hansen TR, Armstrong TD, Hicklin DJ, Jaffee EM, Emens LA. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. Clin Cancer Res 2007; 13:3951-7; PMID:17606729; dx.doi.org/10.1158/1078-0432.CCR-07-0574.

45. Molkovskov A, Sui LL. First-in-class, first-in-human phase 1 results of targeted agents: highlights of the 2008 American society of clinical oncology meeting. J Hematol Oncol 2008; 1:20; PMID:18599794; dx.doi.org/10.1158/1756-8722.JCO.2008-119843.

48. Chi KH, Liu SJ, Li CP, Kuo HP, Wang YS, Chao CH. Induced sensitization of tumor stroma leads to eradication of established cancer by T cells. J Exp Med 2007; 204:49-55; PMID:17207351; dx.doi.org/10.1084/jem.200618225.

35. Dewan MZ, Galloway A, Kawasaki N, Dewyngaert J, Babb JS, Formenti SC, Demaria S. Fractionated but not single-dose radiotherapy induces an immune-mediated abcopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 2009; 15:5379-88; PMID:19706802; dx.doi.org/10.1158/1078-0432.CCR-09-0625.

32. Hodge JW, Sharp HJ, Gameiro SR. Abolitional regression of antigen disparate tumors by antigen cascade therapy with systemic tumor vaccination in combination with local tumor vaccination. Cancer Biother Radiopharm 2012; 27:12-22; PMID:22283603; dx.doi.org/10.1089/cbr.2012.1202.

46. Beatty GL, Chiorean EG, Fishman MP, Saboury EA, Teitelbaum UR, Sun W, Huhn RD, Song W, Li D, Sharp LL, et al. CD40 agonists alter tumor stromal phenotype and enhance anti-pancreatic carcinoma in mice and humans. Cancer Immunol Immunother 2012; 1:358-60; PMID:22737614; dx.doi.org/10.1158/1078-0432.CCR-12-1632.

17. Umanovsky V, Sykov A. Overcoming immunosuppression in the melanoma microenvironment induced by chronic inflammation. Cancer Immunol Immunother 2012; 61:275-82; PMID:22107577; dx.doi.org/10.1007/s00262-011-1164-6.

34. Zhang B, Bowerman NA, Salama JK, Schmidt H, Spastio MT, Schietinger A, Yu P, Fu YX, Weichselbaum RR, Rowley DA, et al. Inhibited sensitization of tumor stroma leads to eradication of established cancer by T cells. J Exp Med 2007; 204:49-55; PMID:17207351; dx.doi.org/10.1084/jem.200618225.

21. Hannesdóttir L, Tymoszuk P, Parajuli N, Wasmer MH, Philipp S, Asadchii N, Data S, Koller JB, Tripp MH, Barni S. Targeted therapies for the treatment of cancer. Cancer Res 2010; 70:5213-9; PMID:20951059; dx.doi.org/10.1158/0008-5472.CAN-10-0118.

Hannesdóttir L, Tymoszuk P, Parajuli N, Wasmer MH, Philipp S, Asadchii N, Data S, Koller JB, Tripp MH, Stotzner P, et al. Lapatinib and docetaxol enhance the Stat3-dependent antitumor immune response. Eur J Cancer 2013; PMID:23843024; dx.doi.org/10.1016/j.ejca.2012.02.050.

Koya RC, Mok S, Orte N, Blacker JK, Comin-Anduix B, Tumeh PC, Minasyan A, Graham NA, Graeber TG, Chodon T, et al. BRAF inhibitor vemurafenib impairs the immunogenicity of adaptive cell immunotherapy. Cancer Res 2012; 72:3928-37; PMID:22693252; dx.doi.org/10.1158/0008-5472.CAN-11-2387.

Rossig C. Immune modulation by molecular cancer targets and targeted therapies: Rationale for novel combination strategies. Oncoimmunology 2012; 1:138-50; PMID:22737614; dx.doi.org/10.4161/1801.
Author/s: Kershaw, MH; Devaud, C; John, LB; Westwood, JA; Darcy, PK

Title: Enhancing immunotherapy using chemotherapy and radiation to modify the tumor microenvironment

Date: 2013-09-01

Citation: Kershaw, M. H., Devaud, C., John, L. B., Westwood, J. A. & Darcy, P. K. (2013). Enhancing immunotherapy using chemotherapy and radiation to modify the tumor microenvironment. ONCOIMMUNOLOGY, 2 (9), https://doi.org/10.4161/onci.25962.

Persistent Link: http://hdl.handle.net/11343/265641

File Description: Published version

License: CC BY-NC