Published OnlineFirst May 19, 2017; DOI: 10.1158/0008-5472.CAN-17-0428

Review

Cancer Research

Therapeutic IgE Antibodies: Harnessing a Macrophage-Mediated Immune Surveillance Mechanism against Cancer

Sophia N. Karagiannis[1,2], Debra H. Josephs[1,2,3], Heather J. Bax[1,2,3], and James F. Spicer[2,3]

Abstract

IgG monoclonal antibodies have made significant contributions to cancer therapy, but suffer from several limitations that restrict their effectiveness in unleashing host immune system components against tumors. The development of monoclonal antibodies of an alternative class, namely IgE, may offer enhanced immune surveillance and superior effector cell potency against cancer cells. In our recent article, we elaborate our proof-of-concept studies of a mouse/human chimeric IgE antibody (MOv18 IgE), which is specific for the cancer-associated antigen folate receptor alpha. We demonstrate superior antitumor efficacy for IgE compared with an otherwise identical IgG in a syngeneic immunocompetent animal, and we identify TNFα/MCP-1 signaling as an IgE-mediated mechanism of monocyte and macrophage activation and recruitment to tumors. These findings draw parallels with powerful macrophage-activating functions employed by IgE against parasites, rather than allergic IgE mechanisms. The potential clinical application of IgE-derived drugs in clinical oncology is clear if the antitumor activity of MOv18 IgE in these preclinical experiments can be replicated in patients. In particular, different IgE antibodies with specificity for many other antigens already validated as targets for IgG suggest a wide potential for development of a novel class of antibody therapy. *Cancer Res; 77(11); 2779–83. ©2017 AACR.*

Antibodies in Cancer Therapy and Their Limitations

Immunotherapy has become one of the most dynamic and rapidly expanding areas of cancer therapy in recent years. One arm of the immunotherapeutic armamentarium, namely monoclonal antibodies, has been used with considerable success over the past 20 years, and now constitutes a vital component of contemporary cancer therapy (1). Monoclonal antibodies in current clinical use variously induce their therapeutic effects either through molecular signal blockade (for example, by competitive inhibition of ligand binding to a transmembrane receptor) or through recruiting effector cells expressing the Fc-gamma receptor family members. Despite impressive results, however, antibody-based treatments continue to face limitations. Adequate binding of antibody to tumor antigens depends upon favorable pharmacokinetics, and efficient penetration and retention of the molecule in the targeted tissue. These binding properties are determined by antibody size, shape, receptor affinity, and valency. All currently approved antibodies are members of the IgG class, characterized by their large molecular size, very long serum half-life of up to 3 weeks, and poor tissue retention. As a result of these biological properties, IgG molecules do not provide very efficient surveillance of the tissue compartment, which may limit the overall efficacy of existing therapeutic antibodies.

Once bound to cell surface antigens, therapeutic antibodies have the potential to elicit immune-mediated tumor cell death, either by engaging cell lineages of the innate immune system or by activating the complement cascade. Antibody-dependent cell-mediated cytotoxicity and phagocytosis (ADCC and ADCP) are dependent on interactions between Fc receptors (FcR) expressed on the surface of immune cells and the antibody Fc domain. Indeed, Fc-mediated mechanisms of immune system engagement appear to play an important role in the antitumor efficacy of the majority of approved antibodies for cancer therapy today. However, the triggering of Fc-mediated immune effector cell engagement by therapeutic IgGs may be limited by several factors, including (i) the low affinity of IgG for its FcγRs (requiring the formation of immune complexes to achieve adequate retention and Fc signaling of antibodies by effector cells), (ii) glycosylation of antibody Fc regions (known to reduce FcγR affinity), (iii) competition with native IgGs (especially IgG4) for binding to FcγRs, and (iv) inhibitory FcRs such as FcγRIIb expressed on B cells, macrophages, dendritic cells, and neutrophils (2).

Macrophages in the tumor microenvironment

Cancer cells rely on resident and recruited "accessory cells" to support their proliferation. Such cells include those forming the vasculature and lymphatics, tissue-specific mesenchymal support

[1]St. John's Institute of Dermatology, Division of Genetics and Molecular Medicine, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom. [2]NIHR Biomedical Research Centre at Guy's and St. Thomas's Hospitals and King's College London, London, United Kingdom. [3]Division of Cancer Studies, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom.

Corresponding Author: Sophia N. Karagiannis, St. John's Institute of Dermatology, Division of Genetics and Molecular Medicine, King's College London, Guy's Hospital, Tower Wing, 9th Floor, London SE1 9RT, UK. Phone: 44-020-7188-6355; Fax: 44-020-7188-8050; E-mail: sophia.karagiannis@kcl.ac.uk

doi: 10.1158/0008-5472.CAN-17-0428

Published OnlineFirst May 19, 2017; DOI: 10.1158/0008-5472.CAN-17-0428

cells, and myeloid and lymphoid-lineage immune cells. Interactions between neoplastic cells and cellular components of the tumor microenvironment (TME) have prompted research into immunotherapeutic approaches aimed at neutralizing tumor-promoting chronic inflammation, or at releasing the cytotoxic activities of antigen-specific T cells (3).

Although the development of monoclonal antibody therapies has traditionally focused on targeting the tumor cell itself, more recently attention has shifted toward targeting the TME and its cellular components. Clinical application of IgG antibodies blocking inhibitory components of the immune checkpoint, in particular T-cell signaling mediated by CTLA-4 and PD-1, has been the most successful application of this new strategy to date (4). Reactivation or reprogramming of cells within the TME may provide the key to further success with antibody-mediated cancer immunotherapy.

Macrophages are a prominent component of the cellular TME, where they exert a profound influence over the tumor immunologic composition (5). Macrophages are phenotypically diverse members of the mononuclear phagocyte family, distributed throughout every organ of the body. Previously thought to be derived exclusively from circulating monocytes, tissue-resident macrophages have more recently been found to be established *in utero*, and to be able to replenish their numbers independently of circulating monocytes (6). These tissue-resident macrophages are maintained locally via colony-stimulating factor 1 (CSF1), a key growth factor produced by the local tissue stroma (6, 7) and may also be enhanced by recruitment and differentiation of circulating monocytes (7). Tumor-associated macrophages (TAM) are recruited into tumors following activation of their CSF1 receptor (CSF1R) by either CSF1 or IL34. In addition, the chemokine CCL2/MCP-1 may facilitate macrophage recruitment into tumors (8).

Under physiologic conditions, macrophages act as phagocytes, serving as an early line of defense against pathogens. They are specialized to engulf and digest cellular debris and drive adaptive immune responses. Despite a common progenitor, TAM populations are functionally diverse, ranging from antitumor, proinflammatory (M1) macrophages to tumor-promoting, anti-inflammatory (M2) populations (5). Macrophages are therefore implicated both as essential mediators in antitumor immune responses and as drivers of local tolerance and even tumor-promoting inflammation. Indeed, within the TME, innumerable tumor- and stromal-derived factors may suppress the tumoricidal activity of TAMs, endowing them with properties characteristic of M2 macrophages, so facilitating tumor growth, metastasis, and immune evasion. In this way, TAM infiltration may correlate with poor prognosis and disease outcome in many human cancers (9). By contrast, dense tumor infiltration by macrophages in lymphoma patients is associated with improved outcome following a rituximab-containing regimen, in contrast to inferior survival in the absence of rituximab treatment (10). This suggests that tumor macrophage infiltration may be a favorable factor specifically in the context of treatment with monoclonal antibodies.

Enhancing the Efficacy of Antibody Therapy: Harnessing the Effector Functions of IgE Antibodies

Efforts to boost the efficacy of antitumor IgGs have involved modification of the IgG constant (Fc) region to strengthen its ability to interact with the human immune system. Approaches to enhance this interaction include altering Fc region amino acid sequences (11) or changing the glycosylation pattern of the Fc region to enhance interaction with FcγRs on effector cells (12). Another strategy to optimize the antibody-immune system interaction has been exploration of antibodies with Fc regions of alternative immunoglobulin classes, such as IgE. Work in this area constitutes an important branch of the rapidly growing field of AllergoOncology, which aims to address the potential opportunities of IgE-mediated and Th2-biased cellular responses in malignant diseases (13, 14). The key hypothesis underlying IgE immunotherapy is that this antibody class can recruit a different effector cell population, utilizing the cognate FcεRs expressed on those cells. Innate immune cells such as macrophages may be reactivated and retargeted by antitumor IgE to overcome inhibitory effects of the TME.

Besides its critical role in allergy, IgE plays a physiological role in immunity against parasitic infections, by a number of different mechanisms and via a number of IgE receptor–expressing cell types including monocytes and macrophages (15). The particular properties that make IgE a key contributor to the allergic response, and permit protection against parasitic infections, suggest the potential value of antibodies in this class as therapeutic agents in cancer. The manifestations of local immune stimulation seen in parasitic infestation, with an ensuing cascade of effector cell activation and inflammation at the site of antigen provocation, might be harnessed by IgE therapies to induce tumor rejection. Macrophages are likely to be a key cell population implicated in such an IgE-mediated anticancer effect, because they are known to be pivotal effectors in the control of intracellular and extracellular parasites by IgE through engendering effector mechanisms such as ADCC and ADCP (16, 17).

The potential biological advantages of IgE antibodies outlined above, and the presence in solid tumors of many key FcεR-expressing immune effector cells including macrophages, provide a rationale for the development of tumor-specific therapeutic IgE molecules (13, 14). Work by Josephs and colleagues describes proof-of-concept studies building upon our previous studies of a mouse/human chimeric IgE antibody (MOv18 IgE) specific for the ovarian cancer–associated antigen folate receptor alpha (FRα; refs. 13, 18–20). Here, in an immunocompetent rodent model of pulmonary metastases from a syngeneic tumor expressing human FRα, we demonstrated clear superiority of antitumor activity for IgE compared with IgG, in line with our previous findings in two *in vivo* models of cancer with reconstituted human cellular immunity (21).

A role for human monocytes was previously demonstrated *in vitro* via both ADCC (mediated by the IgE high-affinity receptor FcεRI, expressed by a proportion of monocytes/macrophages) and ADCP (through CD23, the low-affinity IgE receptor, expressed on the surface of IL4-activated monocytes/macrophages). ADCC and ADCP are both known mechanisms of action for IgE in the defense against parasitic infections. This provided a rationale in favor of further exploring the IgE-mediated antitumor functions of these cells (19, 20). In a nude mouse xenograft model of FRα-positive patient-derived ovarian carcinoma with cellular immunity reconstituted using human peripheral blood mononuclear cells (PBMC), control of tumor growth using chimeric mouse/human MOv18 IgE (MOv18 IgE) was superior to that of the IgG1 anti-FRα counterpart. Tumor xenografts were infiltrated by human monocytes in MOv18 IgE–treated mice. Use of

monocyte-depleted PBMCs in this model resulted in a loss of the survival advantage conferred by MOv18 IgE (20). This indicated that monocytes may play an important role in the antitumor effect of MOv18 IgE *in vivo* (20).

Based on these findings, we sought to explore the role of the monocyte/macrophage lineage in mediating tumor cell killing by IgE in an immunocompetent model. We further hypothesized that IgE may recruit and re-educate these cells to adopt an activated phenotype.

IgE-mediated macrophage recruitment and activation

In the study recently reported in *Cancer Research*, we sought to ascertain how antitumor IgE antibodies may be applied to recruit macrophages and to reprogram these cells to eradicate cancer cells (21). Our work reveals a previously-unappreciated contribution of a TNFα/MCP-1 cascade to monocyte and macrophage re-education and recruitment in an immunocompetent rat tumor model, specifically chosen for its suitability to examine IgE effector functions (Fig. 1).

MOv18 IgE inhibited tumor growth and induced pronounced infiltration of CD68-positive monocytes/macrophages deep into rat tumors. In concordance, the degree of intratumor macrophage influx significantly correlated with prolonged survival of IgE-treated mice bearing patient-derived tumor xenografts. There is evidence to suggest that the location of TAMs in relation to tumor cells in human cancer can influence clinical outcome (22). Macrophage density within tumor islets was positively associated with survival of patients with lung cancer, whereas a concentration of these cells in the stroma, away from tumor cells, was negatively prognostic. Furthermore, the ratio of macrophage density in the tumor islets to macrophage density in the tumor stroma appeared to correlate better with survival (22). Therefore, effective MOv18 IgE–induced tumor infiltration by macrophages may represent a mechanistic explanation for the observed superior anticancer activity compared with IgG.

In the MOv18 IgE–treated immunocompetent model, the phenotype of tumor lung metastases-infiltrating macrophages is different to that of macrophages from the MOv18 IgG or buffer control groups: tumor-TAMs from MOv18 IgE–treated rats featured elevated surface expression of the macrophage maturation and co-stimulatory marker CD80, higher intracellular expression of the proinflammatory, and cytotoxic mediator TNFα, and some elevation of IL10. TNFα was also found to be a prominent cytokine within the airways of MOv18 IgE–treated rats (broncho-alveolar lavage—BAL), alongside the macrophage chemoattractant MCP-1 and IL10. This points to the presence of a distinct macrophage compartment and a specific immune mediator signature in tumor environments, both associated with IgE therapy.

In our study, we have shown that cross-linking of IgE, but not IgG, of any antigen specificity bound to monocytes triggers upregulation of TNFα expression (Fig. 1A). This is likely to be a function of the high affinity of IgE for FcεRI on macrophages, and may be facilitated by molecular patterns displayed by tumor antigens (designated tumor-associated molecular patterns, TAMP; ref. 23). TAMPs can promote cross-linking of IgE bound to FcεRs on effector cells, thereby fostering more sustained interactions of macrophages with IgE than with IgG, and leading in turn to higher levels of TNFα in the tumor microenvironment. MOv18 IgE–mediated tumor ADCC was abrogated *in vitro* by TNFα receptor–specific blockade of monocyte effector cell functions, pointing to the contribution of TNFα signaling in antitumor IgE effector functions (21).

In addition to TNFα, the other key analyte elevated in the BAL fluid from rats treated with MOv18 IgE was MCP-1, a member of the CC family of chemokines, a potent chemoattractant for macrophages, and a macrophage-related proinflammatory chemokine (24). We demonstrate that upregulation of TNFα by monocytes could promote enhanced MCP-1 expression by both monocytes and importantly by tumor cells (Fig. 1B). This IgE-specific macrophage activation and recruitment mechanism seems to be generalizable, since TNFα triggered higher MCP-1 production by a number of different tumor cell types.

Studies have suggested that MCP-1 produced by tumor cells may be responsible for chemotaxis of monocytes, mast cells, and $CD8^+$ T cells into the TME (25). The markedly increased recruitment of macrophages deep into tumors observed in animals treated with MOv18 IgE, compared with MOv18 IgG, may therefore result from the MCP-1 upregulation described above (Fig. 1C).

Taken together, our findings are consistent with a positive feedback interaction engendered by IgE-, but not IgG-, Fc engagement and cross-linking on the surface of macrophages. Initial tumor cell–macrophage interactions fostered by tumor antigen–specific IgE may trigger a TNFα-mediated MCP-1 upregulation cascade that may further mobilize macrophages or recruit additional macrophages into tumors.

Reprograming macrophages toward a tumoricidal function

The plasticity of TAMs may be exploited therapeutically in order to restore their antitumor properties. Strategies to reprogram Th2-driven myeloid cells to reduce the immunosuppressive status of macrophages, trigger antitumor immunity, or suppress tumor growth have all been pursued in several tissue-specific cancer models (Fig. 1D; refs. 26–30). For instance, CSF1-neutralizing monoclonal antibodies and small-molecule CSF1R inhibitors have been evaluated, as monotherapy or in combination with chemotherapy, radiotherapy, or other immunotherapies, for their ability to suppress macrophage survival and/or presence in tumors (26, 31). TAMs have also been therapeutically manipulated by inhibiting the macrophage transmembrane receptor kinase RON (27). Other strategies include antibody-mediated activation of costimulatory CD40 or blocking of inhibitory IL10, delivery of immunostimulatory cytokines such as IL12, or the administration of Toll-like receptor agonists including imiquimod (28–30). It may be that IgE therapies could join these other novel approaches in targeting protumorigenic immune cells including macrophages, so altering the TME in a way that fosters their cytotoxic properties.

Although pivotal in the control of parasites via IgE, physiologic macrophage activity appears to be suppressed in tumors. Our findings point to the possibility that administration of therapeutic IgE antibodies may re-direct macrophage functions, evolved to neutralize parasites, against cancer cells. TNFα, MCP-1, nitric oxide, and IL10 are all upregulated during parasiticidal activities of macrophages (17). Upregulation of TNFα and MCP-1 is detected in tumors in response to IgE therapy, but the classical Th2 cytokine IL4 is notably absent. This indicates that parasite-targeting, rather than allergic,

Published OnlineFirst May 19, 2017; DOI: 10.1158/0008-5472.CAN-17-0428

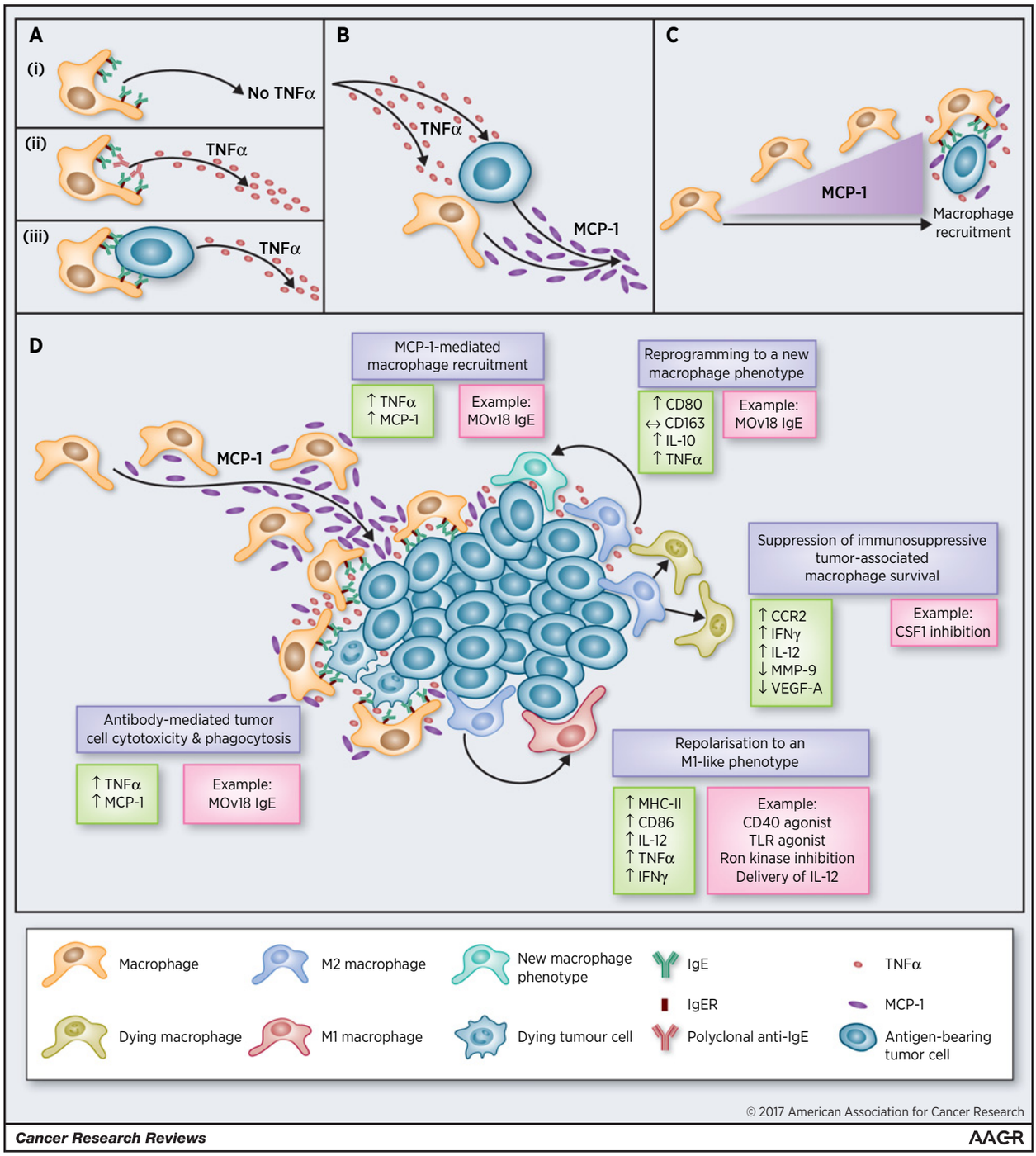

Figure 1.

Effects of anticancer strategies including antitumor IgE antibodies on macrophages. Activation of macrophages by antitumor IgE mediates a TNFα/MCP-1 axis (**A** and **B**) and promotes potent recruitment of macrophages (**C**). **A,** IgE engagement with Fcε receptors on the surface of macrophages is not sufficient for effector cell activation (**i**). Cross-linking of tumor-targeting IgE antibodies on macrophages by polyclonal anti-IgE (**ii**) or antigen-bearing tumor cells (**iii**) is necessary for upregulation of TNFα by macrophages. **B,** TNFα then stimulates production of MCP-1 by macrophages and tumor cells. **C,** MCP-1 promotes potent chemotaxis of further macrophages into tumors, resulting in enhanced tumor cell–macrophage interactions and subsequent tumor cell death. **D,** Antitumor mechanisms of established and novel anticancer therapies on macrophages include reprogramming to a new macrophage phenotype, macrophage recruitment, repolarization to an M1-like phenotype, activation to trigger antibody-mediated tumor cell death (e.g., by ADCC, ADCP, immunoactivatory cytokines), and reduced immunosuppressive tumor-associated macrophage survival.

mechanisms are dominant in this context. Furthermore, analysis of publically available ovarian gene expression libraries suggests a positive prognostic role for elevated TNFα/MCP-1 levels, as well as for macrophage and FcεR markers, highlighting the clinical significance of this mediator signature in patients with cancer (21).

In the future, it is possible that the clinical use of IgE class antibodies to combine engagement, recruitment, and activation of TAMs could ignite the tumoricidal properties of these cells and open new and compelling therapeutic opportunities. Improved understanding of relevant activating cytokine cascades, normally associated with parasite clearance, could further harness this hitherto unappreciated mechanism of human immune defense against cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research (NIHR), or the Department of Health.

Grant Support

This study was supported by Cancer Research UK (C30122/A11527; C30122/A15774); the Academy of Medical Sciences; CRUK/EPSRC/MRC/NIHR KCL/UCL Comprehensive Cancer Imaging Centre (C1519/A10331); the Medical Research Council (MR/L023091/1); Breast Cancer Now (147); CRUK/NIHR in England/DoH for Scotland, Wales, and Northern Ireland Experimental Cancer Medicine Centre (C10355/A15587). The research was also supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas's NHS Foundation Trust and King's College London.

Received February 14, 2017; revised March 3, 2017; accepted March 30, 2017; published OnlineFirst May 19, 2017.

References

1. Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer 2015;15:361–70.
2. DiLillo DJ, Ravetch JV. Differential fc-receptor engagement drives an anti-tumor vaccinal effect. Cell 2015;161:1035–45.
3. Palucka AK, Coussens LM. The basis of oncoimmunology. Cell 2016; 164:1233–47.
4. Makkouk A, Weiner GJ. Cancer immunotherapy and breaking immune tolerance: New approaches to an old challenge. Cancer Res 2015;75:5–10.
5. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell 2015;27:462–72.
6. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity 2013; 38:792–804.
7. Jakubzick C, Gautier EL, Gibbings SL, Sojka DK, Schlitzer A, Johnson TE, et al. Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. Immunity 2013;39: 599–610.
8. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature 2011;475:222–5.
9. Komohara Y, Jinushi M, Takeya M. Clinical significance of macrophage heterogeneity in human malignant tumors. Cancer Sci 2014;105:1–8.
10. Taskinen M, Karjalainen-Lindsberg ML, Nyman H, Eerola LM, Leppa S. A high tumor-associated macrophage content predicts favorable outcome in follicular lymphoma patients treated with rituximab and cyclophosphamide-doxorubicin-vincristine-prednisone. Clin Cancer Res 2007;13:5784–9.
11. Bowles JA, Wang SY, Link BK, Allan B, Beuerlein G, Campbell MA, et al. Anti-CD20 monoclonal antibody with enhanced affinity for CD16 activates NK cells at lower concentrations and more effectively than rituximab. Blood 2006;108:2648–54.
12. Kern DJ, James BR, Blackwell S, Gassner C, Klein C, Weiner GJ. GA101 induces NK-cell activation and antibody-dependent cellular cytotoxicity more effectively than rituximab when complement is present. Leuk Lymphoma 2013;54:2500–5.
13. Josephs DH, Spicer JF, Karagiannis P, Gould HJ, Karagiannis SN. IgE immunotherapy: A novel concept with promise for the treatment of cancer. MAbs 2014;6:54–72.
14. Jensen-Jarolim E, Bax HJ, Bianchini R, Capron M, Corrigan C, Castells M, et al. AllergoOncology - the impact of allergy in oncology: EAACI position paper. Allergy 2016. doi: 10.1111/all.13119.
15. Finkelman FD, Urban JF, Jr. The other side of the coin: The protective role of the TH2 cytokines. J Allergy Clin Immunol 2001;107:772–80.
16. Gounni AS, Lamkhioued B, Ochiai K, Tanaka Y, Delaporte E, Capron A, et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature 1994;367:183–6.
17. Vouldoukis I, Mazier D, Moynet D, Thiolat D, Malvy D, Mossalayi MD. IgE mediates killing of intracellular Toxoplasma gondii by human macrophages through CD23-dependent, interleukin-10 sensitive pathway. PLoS One 2011;6:e18289.
18. Gould HJ, Mackay GA, Karagiannis SN, O'Toole CM, Marsh PJ, Daniel BE, et al. Comparison of IgE and IgG antibody-dependent cytotoxicity in vitro and in a SCID mouse xenograft model of ovarian carcinoma. Eur J Immunol 1999;29:3527–37.
19. Karagiannis SN, Wang Q, East N, Burke F, Riffard S, Bracher MG, et al. Activity of human monocytes in IgE antibody-dependent surveillance and killing of ovarian tumor cells. Eur J Immunol 2003;33:1030–40.
20. Karagiannis SN, Bracher MG, Hunt J, McCloskey N, Beavil RL, Beavil AJ, et al. IgE-antibody-dependent immunotherapy of solid tumors: Cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells. J Immunol 2007;179:2832–43.
21. Josephs DH, Bax HJ, Dodev T, Georgouli M, Nakamura M, Pellizzari G, et al. Anti-folate receptor-alpha IgE but not IgG recruits macrophages to attack tumors via TNF-alpha/MCP-1 signaling. Cancer Res 2017;77:1127–41.
22. Dai F, Liu L, Che G, Yu N, Pu Q, Zhang S, et al. The number and microlocalization of tumor-associated immune cells are associated with patient's survival time in non-small cell lung cancer. BMC Cancer 2010;10:220.
23. Jensen-Jarolim E, Mechtcheriakova D, Pali-Scholl I. The Targets of IgE; allergen-associated and tumor-associated molecular patterns. In: Penichet M, Jensen-Jarolim E, editors. Cancer and IgE. New York, Dordrecht, Heidelberg, London: Springer; 2010. pp. 231–54.
24. Yadav A, Saini V, Arora S. MCP-1: Chemoattractant with a role beyond immunity: A review. Clin Chim Acta 2010;411:1570–9.
25. Brown CE, Vishwanath RP, Aguilar B, Starr R, Najbauer J, Aboody KS, et al. Tumor-derived chemokine MCP-1/CCL2 is sufficient for mediating tumor tropism of adoptively transferred T cells. J Immunol 2007;179:3332–41.
26. Moughon DL, He H, Schokrpur S, Jiang ZK, Yaqoob M, David J, et al. Macrophage blockade using CSF1R inhibitors reverses the vascular leakage underlying malignant ascites in late-stage epithelial ovarian cancer. Cancer Res 2015;75:4742–52.
27. Eyob H, Ekiz HA, Derose YS, Waltz SE, Williams MA, Welm AL. Inhibition of ron kinase blocks conversion of micrometastases to overt metastases by boosting antitumor immunity. Cancer Discov 2013;3:751–60.
28. Smith KJ, Hamza S, Skelton H. Topical imidazoquinoline therapy of cutaneous squamous cell carcinoma polarizes lymphoid and monocyte/macrophage populations to a Th1 and M1 cytokine pattern. Clin Exp Dermatol 2004;29:505–12.
29. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science 2011;331:1612–6.
30. Guiducci C, Vicari AP, Sangaletti S, Trinchieri G, Colombo MP. Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection. Cancer Res 2005;65:3437–46.
31. Escamilla J, Schokrpur S, Liu C, Priceman SJ, Moughon D, Jiang Z, et al. CSF1 receptor targeting in prostate cancer reverses macrophage-mediated resistance to androgen blockade therapy. Cancer Res 2015;75:950–62.

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

AACR American Association for Cancer Research

Therapeutic IgE Antibodies: Harnessing a Macrophage-Mediated Immune Surveillance Mechanism against Cancer

Sophia N. Karagiannis, Debra H. Josephs, Heather J. Bax, et al.

Cancer Res 2017;77:2779-2783. Published OnlineFirst May 19, 2017.