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Double-edge Role of B Cells in Tumor Immunity: Potential Molecular Mechanism

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Summary: B cells are a heterogeneous population, which have distinct functions of antigen presentation, activating T cells, and secreting antibodies, cytokines as well as protease. It is supposed that the balance among these B cells subpopulation (resting B cells, activated B cells, Bregs, and other differentiated B cells) will determine the ultimate role of B cells in tumor immunity. There has been increasing evidence supporting opposite roles of B cells in tumor immunity, though there are no general acceptable phenotypes for them. Recent years, a new designated subset of B cells identified as Bregs has emerged from immunosuppressive and/or regulatory functions in tumor immune responses. Therefore, transferring activated B cells would be possible to become a promising strategy against tumor via conquering the immunosuppressive status of B cells in future. Understanding the potential mechanism of double-edge role of B cells will help researchers utilize activated B cells to improve their anti-tumor response. Moreover, the molecular pathways related to B cell differentiation are involved in its tumor-promoting effect, such as NF-κB, STAT3, BTK. So, we review the molecular and signaling pathway mechanisms of B cells involved in both tumor-promoting and tumor-suppressive immunity, in order to help researchers optimize B cells to fight cancer better.
Key words: B cells; tumor immunity

The importance of T cells in tumor immunity has been extensively studied and well established. However, the underlying role of B cells in tumor immunity is less defined. In fact, a series of literatures describe two opposite effects on the significance of B cells on cancer, that is, B cells can positively or negatively affect tumor growth and patients' prognosis[1]. Nevertheless, the mechanism behind this phenomenon has still remained largely elusive. Except for traditional immunologic mechanism of B cells such as antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, presenting antigens and providing co-stimulation[2], this review highlights recent findings on molecular or signaling pathway mechanisms of B cells involved in both tumor-promoting and tumor-suppressive functions, and gives some reasonable explanations for this paradox.

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1 MOLECULAR MECHANISMS ON PROTUMORIGENIC EFFECT OF B CELLS

1.1 NF-κB Signaling Pathway

NF-κB proteins normally exist as components on inactive cytoplasmic complexes bound by members of the inhibitor of κB (IκB) family. The non-canonical NF-κB pathway plays a central role in the B cell immune response[3, 4]. Ammirante *et al* reported that androgen ablation induced infiltration of regressing androgen-dependent tumors with leukocytes, including B cells; and IkappaB kinase (IKK) β-dependent lymphotoxin produced by tumor-infiltrating B cells stimulated IKKα-dependent androgen-free survival in prostate cancer-bearing mice[5], which provided a new perspective to understand the emergence of castration-resistant prostate cancer. Another study from the above team further revealed the recurrence of androgen-deprived prostate cancer was dependent on the activation of IKKα mediated by B lymphocytes, which then operated by inducing the phosphorylation

and nuclear translocation of E2F1 to promote its recruitment to the promoters/regulatory regions of the Bmi1 and Ccne genes that encoded positive regulators of progenitor cell proliferation[6]. Collectively, NF-κB signaling is not only particularly essential for B cell activation[7], but also contributes to its protumorigenic effect.

1.2 STAT3 Signaling Pathway

The intrinsic STAT3 signaling provides a crucial axis to support cell proliferation and survival. The emerging roles of STAT3 in immune cell function of tumor development are identified[8]. Tumor-associated B cells with activated STAT3, which were mainly found in or near tumor vasculature, contribute to tumor development by promoting tumor angiogenesis in both B16 melanoma and Lewis lung cancer mouse models, but the protective effect occurs when STAT3 signaling to B cells is inactive[9]. In the same mouse melanoma B16 model, IL-6 directly bound to $CD5^+$ B cells in the absence of IL-6Rα, which then led to activation of transcription factor STAT3 via gp130 and its downstream kinase JAK2; moreover, activated STAT3 upregulated the CD5 expression, thereby forming a feed-forward loops in B cells[10]. JSI124, known as cucurbitacin Ⅰ, is a selective inhibitor of JAK/STAT3. The STAT3 levels in B cells are significantly decreased from JSI124-treated 4T1 mice, and the JSI124-treated B cells inhibit the growth of 4T1 tumors *in vivo*, however, 4T1 mice-derived B cells can enhance tumor growth[11]. These findings demonstrate a critical role of STAT3 signaling to protumorigenic effect of B cells.

STAT3 signaling to B cells is also involved in expansion of T regulatory cells (Tregs). Tumor-evoked B regulatory cells (tBregs) that constitutively express active STAT3 promote tumor growth and metastasis by TGFβ-dependent conversion of non-Tregs to Tregs in the 4T1 breast cancer mouse model; in the absence of tBregs, 4T1 tumors can not metastasize into the lungs efficiently due to poor Tregs conversion[12]. A plant-derived polyphenol (RSV), at a low and non-cytotoxic dose for immune cells, can indeed preferentially inhibit tBregs and concurrently decrease lung metastasis in mice with highly metastatic 4T1.2 cancer through blocking phosphorylation of STAT3, which underscores the therapeutic relevance to non-cytotoxic low-doses of RSV to combat cancer escape mediated by tBregs[13].

1.3 Bruton Tyrosine Kinase (BTK)

BTK, a deficiency of which leads to X-linked agammaglobulinemia, is responsible for B cell antigen receptor signaling. Gunderson *et al* illustrated that pancreas ductal adenocarcinoma (PDAC) growth depended on cross-talk between B cells and $FcR\gamma^+$ tumor-associated macrophages, resulting in T(H)2-type macrophage programming via BTK activation in a PI3Kγ-dependent manner; inhibition of BTK with ibrutinib that was approved to treat B cell lymphoma restored T cell-dependent antitumor immune responses to inhibit PDAC growth and improved responsiveness to chemotherapy[14]. BTK plays an essential role in the pathogenesis of various B cell lymphomas[15], so it deserves to further explore significance of BTK on the non-hematologic cancer-promoting role of B cells.

1.4 Cytokines

B lymphocytes that secret cytokines can be subdivided into two different subsets: Bregs, producing IL-10 or TGFβ, and B effector cells expressing distinct arrays of cytokines depending on their maturation stage and environment[16]. Bregs are mainly responsible for promoting cancer. IL-10 secreted by B cells represents a common inhibiting cytokine that leads to various tumor growth via immunosuppression. Schioppa *et al* reported that inhibition of papilloma development in $Tnf^{-/-}$ mice was associated with increased IFN-γ and $CD8^+$ T cells in skin and a significant reduction in IL-10-producing Bregs in the spleen[17]. Inoue *et al* indicated that B-cell depletion could therapeutically enhance antitumor immune responses to certain tumors by decreasing IL-10 production of B cells[18]. In addition, IL-10 removal, either by using $IL\text{-}10^{-/-}$ tumor-draining lymph nodes B cells or by systemic neutralization of IL-10, significantly augments therapeutic efficacy of adoptively transferred tumor-draining lymph node B cells[19]. Lymphoma progression and survival are reduced when endogenous host B cells are not depleted, particularly a rare IL-10-producing B cell subset (B10 cells); and adoptively transferred B10 cells dramatically suppress anti-CD20 monoclonal antibody (mAb) mediated lymphoma depletion through IL-10-dependent mechanisms[20]. Bregs from the tumor tissue suppress IFN-γ production and T cell proliferation, and support Treg expansion *in vitro* and *in vivo* inhibit $CD8^+$ cytolytic T cell activity. In the presence of Bregs within the tumor tissue, a marked decrease in both CD8 and NK cell infiltration is observed. These B regulatory properties inhibit the anti-tumor response and lead to enhanced tumor growth.

Though most of the work on Bregs has been focused on B10 cells, B cells can exert regulatory functions in an IL-10-independent manner[21]. B cells are enriched in human pancreatic intraepithelial neoplasia, and give rise to protumorigenic effect through the expression of IL-35. Furthermore, $CD19^+CD1dhighCD^{5+}$ subpopulation of B cells are crucial to promoting tumor growth[22]. Recruited B cells increase IL-8/androgen receptor (AR) signals to bladder cancer *in vitro*, which then promotes the expression of metastasis genes including MMP1, MMP13; blockage of the IL-8/AR/MMPs signals either by anti-IL-8 neutralizing antibody, AR-siRNA, or MMPs inhibitors all partially reverses the bladder cancer-promoting role of infiltrating B cells[23]. In general, cytokines play an important role in the tumor immune response of B cells.

1.5 Others

Lee *et al* unexpectedly discovered that pancreas-specific HIF1α deletion drastically accelerated *KrasG12D*-driven pancreatic neoplasia, and was accompanied by significant increase of B lymphocytes in pancreas, featuring prominent influx of a rare $CD19^{+}CD43^{+}IgM^{hi}CD5^{-}$ B cell subtype. On the contrary, B cell depletion employed with anti-CD20 mAb inhibited progression of pancreatic intraepithelial neoplasia in HIF1α-deficient mice[24]. Combined with the above two studies related to pancreas cancer[14, 22], all these data suggested that B cells contributed to PDAC progression in different ways, depending on the biological context. Thus, understanding the whole immune environment of these tumors and further dissecting the roles of B cells will be vital for development of effective immunotherapies for PDAC[25].

2 MOLECULAR MECHANISM ON ANTITUMORIGENIC EFFECT OF B CELLS

Though the tumor-suppressive effect of B cells is also witnessed on a variety of previous studies, few researcheres have concentrated on its non-traditional mechanism against tumor until now. CD73 is a cell surface enzyme that can suppress T cell-mediated immune responses by producing extracellular adenosine; a specific CD73 inhibitor, adenosine 5'-(α, β-methylene)diphosphate (APCP), induces a significant tumor regression on the presence of B cells through IL-17A in melanoma-bearing mice, however, the anti-tumor effect of APCP is ablated by administration of anti–IL-17A mAb or depletion of $CD20^{+}$ B cells, implying a critical role for B cells in the anti-tumor activity of APCP[26]. Another example of the protective effect of B cells in cancer shows that CpG-activated B cells are capable of killing tumor cells through the TRAIL/Apo-2L-dependent mechanism[27].

Using the Cancer Genome Atlas mRNA-seq data and a large microarray dataset, Iglesia *et al* evaluated adaptive immune gene expression by genomic subtype in breast and ovarian cancers, demonstrating that improved metastasis-free/progression-free survival was correlated with B-cell gene expression signatures, which was mainly restricted to the basal-like and HER2-enriched breast cancer subtypes and the immunoreactive ovarian cancer subtype[28]. Consistent with a restricted epitope-driven response, these subtypes of diseases show high expression of a low-diversity population of B cell receptor (BCR) gene segments[28]. These results indicated some BCR genes might be a new mechanism involved in the antitumorigenic effect of B cells. In short, the molecular mechanism of B cells against cancer is still poorly understood. It may be fairly interesting and valuable to further explore the molecular mechanism in this field.

3 RATIONALE BEHIND OPPOSITE EFFECTS OF B CELLS ON CANCER IMMUNITY

3.1 Distinct Animal Models

Many studies using genetically manipulated B cell-deficient mice such as $IgM^{-/-}$ B cell-deficient mice (BCDM)[29–31], including the EL4 thymoma, and the MC38 colon carcinoma in C57BL/6 mice, as well as the EMT-6 breast carcinoma in BALB/C mice, confirm that the absence of B cells significantly restricts tumor growth[32], and adoptive transfer of B cells reverses this effect. Due to abnormalities in B cell-deficient mice, for example, they might secret more pro-inflammatory cytokine IL-12, which leads to the preferential generation of short-lived splenic plasma cells, with ensuing low affinity antibodies and a diminished recall response which will contribute to tumor development[33]. Thus, the tumor growth on this kind of genetic mice model cannot be consistent with that in normal mice model or patients. Actually, previous studies had a contrary result from another mice model that adoptive transfer of tumor reactive B cells significantly inhibited tumor growth and/or lung metastasis on BALB/C mice, compared to the control group[19, 34–37]. Moreover, tumors tended to grow more fast while an acute B-cell depletion was employed via anti-CD20 mAb in 4T1 breast cancer or CT-26 BALB/C mice, and B6 melanoma mice. These results were also supported by other studies[26, 38]. Prior to syngeneic B16 melanoma tumor transfers, mature B cells are depleted from wild-type adult mice using anti-CD20 mAb. It reveals that *s.c.* tumor and lung metastasis are increased 2-fold in B cell-depleted mice[38]. However, Kim *et al* reported an incompatible result that B-cell depletion using anti-mouse CD20 antibody slowed the growth of new solid tumors (not expressing CD20) and retarded the growth of established tumors[39]. The actionable difference in the similar acute B cell depletion mice model suggests there must be other mechanisms involved in the tumor immunity of B cells.

3.2 Distinct B Cell Subsets and Activated Status

In recent years, a new designated subset of B cells identified as Bregs has emerged from immunosuppressive and/or regulatory functions in tumor immune responses and in carcinogenesis[40, 41], just like the well-established role of Tregs. Since different B cells subsets have distinct functions of antigen presentation, activating T cells, and secreting antibodies, cytokines as well as protease, such as IgG, IgM, ILs, TNFs, IFNs, TGFs, and granzyme B[42, 43], it is supposed that the balance among these B cells subpopulation (resting B cells, activated B cells, Bregs, and other differentiated B cells), will determine the ultimate role of B cells in tumor immunity, which may provide a reasonable explanation for the dual roles of B cells. Generally speaking, cancer cells can escape the immune

surveillance from T cells and B cells, so how to utilize activated B cells will be an interesting means to improve their anti-tumor response. For example, Wennhold *et al* reported that the preventive immunization of tumor-bearing mice with tumor antigen-pulsed CD40 activated B cells induced a protective anti-tumor immunity against B16.F10 melanomas and E.G7 lymphomas, leading to reduced tumor growth[44]. Therefore, just as adoptive transfer of activated T cells, transferring activated B cells would be possible to become a promising strategy against tumor via conquering the immunosuppressive status of B cells in future.

3.3 Cancer Related Clinical Factors

Different stage and metastasis status on cancer might be related to distinct roles of B cells. Shimabukuro-Vornhagen *et al* examined B-cell subsets in primary tumors (n=38), metastases (n=6) and blood (n=46) of 51 patients with colorectal cancer (CRC) and blood of 10 healthy controls, which showed peripheral blood of CRC patients contained a higher percentage of memory B cells than that of age-matched healthy controls; furthermore, the percentage of B cells within tumors was higher than that in the peripheral blood of CRC patients, but metastases were typically devoid of tumor-infiltrating B cells, and relevant proportions of regulatory B cells could only be detected in advanced cancer and metastases[45]. The tumor tissues of early-stage prostate cancer patients had a lower infiltration of B cells and a higher infiltration of $CD8^+$ T cells, but the tumor tissues of therapy-resistant and metastatic prostate cancer patients showed a higher infiltration of B cells and a lower infiltration of $CD8^+$ T cells[46, 47]. However, it is very difficult to distinguish the cause and effect between clinical characterizations and immune functional status.

4 CONCLUSION

Distinct B cells subsets that result in opposite tumor immunity effects have been recognized currently, though there are no general acceptable phenotypes for them. Apart from different subsets, the animal models, B cell activation status and clinical characterizations all contribute to the dual roles of B cells. The molecular pathways related to B cell differentiation are involved in its tumor-promoting effect, such as NF-κB, STAT3, BTK. However, the molecular mechanism of B cells in cancer immunity is still less established, particularly for anti-tumor signaling pathway mechanism. Further efforts should be paid on the molecular mechanism of B cells on tumor immunity, which will be helpful to explore the anti-cancer therapeutic promise of B cells in future.

Conflict of Interest Statement

The authors declare there is no conflicts of interest regarding the publication of this paper.

REFERENCES

1 Hu X, Zhang J, Wang J, *et al*. Landscape of B cell immunity and related immune evasion in human cancers. Nat Genet, 2019,51(3):560-567
2 Tokunaga R, Naseem M, Lo JH, *et al*. B cell and B cell-related pathways for novel cancer treatments. Cancer Treat Rev, 2019,73:10-19
3 Bonizzi G, Karin M. The two NF-kappaB activation pathways and their role in innate and adaptive immunity. Trends Immunol, 2004,25(6):280-288
4 Sun SC. The non-canonical NF-kappaB pathway in immunity and inflammation. Nat Rev Immunol, 2017,17(9):545-558
5 Ammirante M, Luo JL, Grivennikov S, *et al*. B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. Nature, 2010,464(7286):302-305
6 Ammirante M, Kuraishy AI, Shalapour S, *et al*. An IKKalpha-E2F1-BMI1 cascade activated by infiltrating B cells controls prostate regeneration and tumor recurrence. Genes Dev, 2013,27(13):1435-1440
7 Wuerzberger-Davis SM, Chen Y, Yang DT, *et al*. Nuclear export of the NF-kappaB inhibitor IkappaBalpha is required for proper B cell and secondary lymphoid tissue formation. Immunity, 2011,34(2):188-200
8 Huynh J, Etemadi N, Hollande F, *et al*. The JAK/STAT3 axis: A comprehensive drug target for solid malignancies. Semin Cancer Biol, 2017,45:13-22
9 Yang C, Lee H, Pal S, *et al*. B cells promote tumor progression via STAT3 regulated-angiogenesis. PLoS One, 2013,8(5):e64159
10 Zhang C, Xin H, Zhang W, *et al*. CD5 Binds to Interleukin-6 and Induces a Feed-Forward Loop with the Transcription Factor STAT3 in B Cells to Promote Cancer. Immunity, 2016,44(4):913-923
11 Ren Y, Yu K, Sun S, *et al*. JSI124 inhibits breast cancer cell growth by suppressing the function of B cells via the downregulation of signal transducer and activator of transcription 3. Oncol Lett, 2014,8(2):928-932
12 Olkhanud PB, Damdinsuren B, Bodogai M, *et al*. Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4(+) T cells to T-regulatory cells. Cancer Res, 2011,71(10):3505-3515
13 Lee-Chang C, Bodogai M, Martin-Montalvo A, *et al*. Inhibition of breast cancer metastasis by resveratrol-mediated inactivation of tumor-evoked regulatory B cells. J Immunol, 2013,191(8):4141-4151
14 Gunderson AJ, Kaneda MM, Tsujikawa T, *et al*. Bruton Tyrosine Kinase-Dependent Immune Cell Cross-talk Drives Pancreas Cancer. Cancer Discov, 2016,6(3):270-285
15 Seiler T, Dreyling M. Bruton's tyrosine kinase inhibitors in B-cell lymphoma: current experience and future perspectives. Expert Opin Investig Drugs, 2017,26(8):909-915
16 Hamze M, Desmetz C, Guglielmi P. B cell-derived cytokines in disease. Eur Cytokine Netw, 2013,24(1):20-26
17 Schioppa T, Moore R, Thompson RG, *et al*. B regulatory cells and the tumor-promoting actions of TNF-alpha during squamous carcinogenesis. Proc Natl Acad Sci

USA, 2011,108(26):10 662-10 667
18 Inoue S, Leitner WW, Golding B, *et al*. Inhibitory effects of B cells on antitumor immunity. Cancer Res, 2006,66(15):7741-7747
19 Tao H, Lu L, Xia Y, *et al*. Antitumor effector B cells directly kill tumor cells via the Fas/FasL pathway and are regulated by IL-10. Eur J Immunol, 2015,45(4):999-1009
20 Horikawa M, Minard-Colin V, Matsushita T, *et al*. Regulatory B cell production of IL-10 inhibits lymphoma depletion during CD20 immunotherapy in mice. J Clin Invest, 2011,121(11):4268-4280
21 Gorosito Serran M, Fiocca Vernengo F, Beccaria CG, *et al*. The regulatory role of B cells in autoimmunity, infections and cancer: Perspectives beyond IL10 production. FEBS Lett, 2015,589(22):3362-3369
22 Pylayeva-Gupta Y, Das S, Handler JS, *et al*. IL35-Producing B Cells Promote the Development of Pancreatic Neoplasia. Cancer Discov, 2016,6(3):247-255
23 Ou Z, Wang Y, Liu L, *et al*. Tumor microenvironment B cells increase bladder cancer metastasis via modulation of the IL-8/androgen receptor (AR)/MMPs signals. Oncotarget, 2015,6(28):26 065-26 078
24 Lee KE, Spata M, Bayne LJ, *et al*. Hif1a Deletion Reveals Pro-Neoplastic Function of B Cells in Pancreatic Neoplasia. Cancer Discov, 2016,6(3):256-269
25 Seton-Rogers S. Pancreatic cancer: Spotlight on B cells. Nat Rev Cancer, 2016,16(2):67
26 Forte G, Sorrentino R, Montinaro A, *et al*. Inhibition of CD73 improves B cell-mediated anti-tumor immunity in a mouse model of melanoma. J Immunol, 2012,189(5):2226-2233
27 Kemp TJ, Moore JM, Griffith TS. Human B cells express functional TRAIL/Apo-2 ligand after CpG-containing oligodeoxynucleotide stimulation. J Immunol, 2004,173(2):892-899
28 Iglesia MD, Vincent BG, Parker JS, *et al*. Prognostic B-cell signatures using mRNA-seq in patients with subtype-specific breast and ovarian cancer. Clin Cancer Res, 2014,20(14):3818-3829
29 Tadmor T, Zhang Y, Cho HM, *et al*. The absence of B lymphocytes reduces the number and function of T-regulatory cells and enhances the anti-tumor response in a murine tumor model. Cancer Immunol Immunother, 2011,60(5):609-619
30 Zhang Y, Eliav Y, Shin SU, *et al*. B lymphocyte inhibition of anti-tumor response depends on expansion of Treg but is independent of B-cell IL-10 secretion. Cancer Immunol Immunother, 2013,62(1):87-99
31 Shah S, Divekar AA, Hilchey SP, *et al*. Increased rejection of primary tumors in mice lacking B cells: inhibition of anti-tumor CTL and TH1 cytokine responses by B cells. Int J Cancer, 2005,117(4):574-586
32 Guy TV, Terry AM, Bolton HA, *et al*. Pro- and anti-tumour effects of B cells and antibodies in cancer: a comparison of clinical studies and preclinical models. Cancer Immunol Immunother, 2016,65(8):885-896
33 Kim SJ, Caton M, Wang C, *et al*. Increased IL-12 inhibits B cells' differentiation to germinal center cells and promotes differentiation to short-lived plasmablasts. J Exp Med, 2008,205(10):2437-2448
34 Xia Y, Tao H, Hu Y, *et al*. IL-2 augments the therapeutic efficacy of adoptively transferred B cells which directly kill tumor cells via the CXCR4/CXCL12 and perforin pathways. Oncotarget, 2016,7(37):60 461-60 474
35 Li Q, Lao X, Pan Q, *et al*. Adoptive transfer of tumor reactive B cells confers host T-cell immunity and tumor regression. Clin Cancer Res, 2011,17(15):4987-4995
36 Li Q, Grover AC, Donald EJ, *et al*. Simultaneous targeting of CD3 on T cells and CD40 on B or dendritic cells augments the antitumor reactivity of tumor-primed lymph node cells. J Immunol, 2005,175(3):1424-1432
37 Li Q, Teitz-Tennenbaum S, Donald EJ, *et al*. In vivo sensitized and in vitro activated B cells mediate tumor regression in cancer adoptive immunotherapy. J Immunol, 2009,183(5):3195-3203
38 DiLillo DJ, Yanaba K, Tedder TF. B cells are required for optimal CD4+ and CD8+ T cell tumor immunity: therapeutic B cell depletion enhances B16 melanoma growth in mice. J Immunol, 2010,184(7):4006-4016
39 Kim S, Fridlender ZG, Dunn R, *et al*. B-cell depletion using an anti-CD20 antibody augments antitumor immune responses and immunotherapy in nonhematopoetic murine tumor models. J Immunother, 2008,31(5):446-457
40 Schwartz M, Zhang Y, Rosenblatt JD. B cell regulation of the anti-tumor response and role in carcinogenesis. J Immunother Cancer, 2016,4:40
41 Sarvaria A, Madrigal JA, Saudemont A. B cell regulation in cancer and anti-tumor immunity. Cell Mol Immunol, 2017,14(8):662-674
42 Hagn M, Jahrsdorfer B. Why do human B cells secrete granzyme B? Insights into a novel B-cell differentiation pathway. Oncoimmunology, 2012,1(8):1368-1375
43 Bao Y, Cao X. The immune potential and immunopathology of cytokine-producing B cell subsets: a comprehensive review. J Autoimmun, 2014,55:10-23
44 Wennhold K, Weber TM, Klein-Gonzalez N, *et al*. CD40-activated B cells induce anti-tumor immunity in vivo. Oncotarget, 2017,8(17):27 740-27 753
45 Shimabukuro-Vornhagen A, Schlosser HA, Gryschok L, *et al*. Characterization of tumor-associated B-cell subsets in patients with colorectal cancer. Oncotarget, 2014,5(13):4651-4664
46 Wang JZ, Zhang YH, Guo XH, *et al*. The double-edge role of B cells in mediating antitumor T-cell immunity: Pharmacological strategies for cancer immunotherapy. Int Immunopharmacol, 2016,36:73-85
47 Shalapour S, Font-Burgada J, Di Caro G, *et al*. Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature, 2015, 521(7550):94-98

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