PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2014, 41(10): 1075~1084
www.pibb.ac.cn

Immune Cells in Tumor Microenvironment

SONG Nan, LI Tao, ZHANG Xue-Min*
(*State Key Laboratory of Proteomics, Institute of Basic Medical Sciences, National Center of Biomedical Analysis, Beijing* 100850, China)

Abstract Both epidemiological and clinical evidences have indicated a strong association between inflammation and cancers. However, the molecular and genetic relationships between inflammation and tumor just begin to be understood. Accumulating data have established the notion that tumor microenvironment is largely orchestrated by the infiltrated immune cells including T lymphocytes, macrophages, dendritic cells, and mast cells. These cells are recruited to the tumor stroma and co-operate with each other, either to facilitate the initiation, invasion, migration and metastasis of tumor, or to elicit the anti-tumor immunity. Here, we review recent progress on how these immune cells function in tumor microenvironment. Understanding this issue is critical for developing novel strategies of tumor immune therapy.

Key words tumor, Th17, Treg, macrophage, myeloid derived suppressor cells, dendritic cell, mast cell
DOI: 10.3724/SP.J.1206.2014.00245

The tumor microenvironment is the cellular environment that consists of tumor cells, immune cells, microvasculature, fibroblasts, other stroma cells, and the extracellular matrix[1–2]. It has been well established that the inflammatory state in tumor microenvironment plays critical role in the initiation, progression and metastasis of almost all solid tumors[2–5]. The tumor-associated immunity is modulated by the accumulation and interplay of a variety of immune cells including T lymphocytes, B lymphocytes, as well as myeloid cells including macrophages, myeloid-derived suppressor cells, dendritic cells, and mast cells[6–7]. The molecular and cellular mechanisms underlying the interaction between immune cells and tumors have been intensively studied. In this review, we summarize the current knowledge about the function of immune cells in microenvironment that have been demonstrated to significantly affect tumor pathogenicity (Figure 1).

1 T lymphocytes

T lymphocytes play a central role in cell-mediated immunity, and these cells can be classified into several subtypes: $CD4^+$ T cells, cytotoxic T cells (CTLs), memory T cells and natural killer T cells(NKT cells)[8]. Since the pro- and anti-tumor functions of CTLs, memory T cells, NKT cells have been well reviewed elsewhere [9–11], this section concentrates on $CD4^+$ T

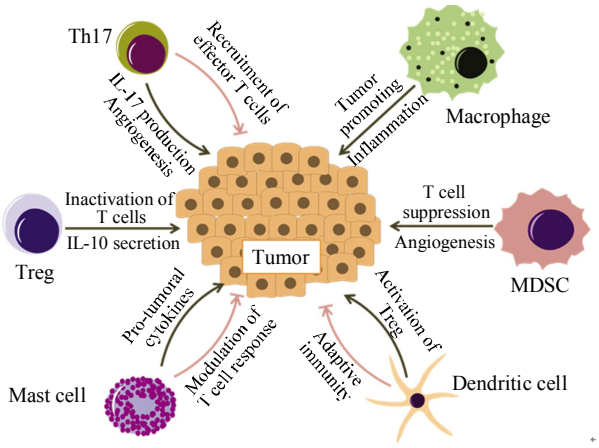

Fig. 1 The different roles of immune cells in tumor microenvironment

Th17 cells are able to eliminate cancer cells by the recruitment of $CD8^+$ effector T cells, while they can also stimulate angiogenesis by the production of IL-17. Tregs, known as suppressor T cells, can inactivate the T cell-mediated tumor immunity by the secretion of IL-10, CTLA-4, *etc*. Tumor-associated macrophages can facilitate the tumor-promoting inflammation by secreting a large amount of cytokines. Myeloid derived suppressor cells (MDSCs) can decrease the activity of antigen-presenting cell (APCs), natural killer (NK) and T cells, and also induce angiogenesis in the hypoxic microenvironment. Dendritic cells (DCs) participate as APCs that can promote the adaptive immunity. However, DCs can favor the tumor progression through mediating tolerance under certain circumstances. Similarly, mast cells, another type of APCs, have also been identified to modulate the anti-tumor immunity, while can generate a series of pro-angiogenic factors to promote tumor progression.

*Corresponding author.
Tel: 86-10-68246161, E-mail: zhangxuemin@cashq.ac.cn
Received: August 25, 2014 Accepted: September 11, 2014

cells, with a particular focus on the Th17 and T regulatory cells (Treg).

$CD4^+$ T cells are essential organizers of cell-mediated immunity, participating in the each stage of immune response[8, 12]. Upon activation, naive $CD4^+$ T cells differentiate into various subsets of T helper cells (Th cells) including Th1, Th2, and Th17 cells[8, 12–14]. Th1 cells are documented to produce interferon-γ (IFN-γ) and functions in immunity against intracellular pathogens[8, 12]. Th2 cells assist B cells for the production of antibodies[8, 12]. Th17, characterized by the production of IL-17, is identified in 2005[13–14]. Both Th1 and Th2 can initiate a cytotoxic T cells (also known as $CD8^+$ T cells)-based anti-tumor response, while the role of Th17 cells in malignancy is currently under debate, as both pro- and anti-tumor activities of Th17 have been reported[15–16]. Regarding the anti-tumor effect, under the stimulation of IL-17 and IFN-γ, Th17 cells can also play a protective role in tumor immunity by promoting the activation of tumor-specific $CD8^+$ T cells, and recruiting of dendritic cells into tumor tissue[17–19]. Drake and his colleagues reported that the portion of Th17 cells in prostate cancer inversely correlated with the stage of tumor progression[20]. In addition, a portion of Th17 cells may be trans-differentiated into Th1-type cells, which also facilitates the anti-tumor immunity[18]. On the other hand, Th17 cells also exhibit pro-tumor functions. Th17-derived IL-17A promotes the melanoma development *via* IL-17 receptor[21–22]. Enhanced Th17 cell infiltration is observed in lung cancer, and these infiltrated Th17 cells trigger the proliferation of the tumor cells[23]. Recently, Ferrara and his colleagues have uncovered that Th17-derived IL-17A induced the expression of granulocyte colony-stimulating factor (G-CSF), leading to the recruitment of immature myeloid-cell into the tumor microenvironment, and promote VEGF inhibition resistance[24–25].

Tregs, also known as suppressor T cells, are characterized by the expression of CD4, CD25 and Foxp3[26]. Tregs represent about 5% of circulating $CD4^+$ T lymphocytes in the peripheral blood, and play an anti-inflammatory role by shutting down immune responses after the invading organisms being eliminated[27–28]. There are three subsets of Tregs including naturally occurring Tregs, antigen-induced Tregs, and Tregs originated from $CD8^+$ T cells[28–29]. The increased Tregs has been observed in a variety of tumors including breast cancer, melanoma, and hepatocellular carcinoma[30–33]. Most of the immune cells in the tumor stroma, such as T cells, B cells, dendritic cells and macrophages, are the targets of Tregs[28, 34]. Thus, Tregs mainly function as a pro-tumor T cell population. Tregs are reported to inhibit the expression of co-stimulatory molecules including CD80, CD83, and CD86, on the surface of dendritic cells, thus inactivate T cells[35]. Tregs also suppresses Th17 activity, which is associated with poor prognosis in several cancers. Ablation of Treg can evoke antitumor responses in colitis-associated colon cancer[36]. Using transplantable tumor models in mice, Stewart *et al*.[37] have reported that the majority of tumor-associated IL-10 was produced by activated Treg population. This Tregs-derived IL-10 production limits Th17 cell numbers in both spleen and tumor, and thus restrains Th17-type inflammation[37]. In addition, after infiltration into tumor microenvironment, Tregs significantly block effector T cells activation and directly suppress the anti-tumor immunity, most if not all, *via* the production of CTLA-4, IL-10[21]. Tregs also severely impair the anti-tumor capacity of $CD8^+$ T cells through inhibiting the proliferation and infiltration of $CD8^+$ T cells in tumor microenvironment. Bauer *et al*.[38] demonstrated that Tregs locally induced a dysfunctional state of infiltrated CTLs by altering the balance of co-stimulatory and co-inhibitory signals within tumor microenvironment. Moreover, Tregs directly suppress B cells proliferation, increase the death of the cells by cell-to-cell connection, and also inhibit immunoglobulin production in B cells[39]. Taken together, the blockade of the infiltration of Tregs might become an effective approach to break the immune tolerance in the context of tumor microenvironment, yet it still needs further investigation to confirm the outcome of Tregs depletion in clinical trials.

2 Tumor-associated macrophages

Macrophages are differentiated from circulating monocytes and reside throughout the body tissues with highly heterogeneous characteristics. During microbial infection or injury, these tissue-specific macrophage subsets produce high amount of pro-inflammatory cytokines, recruit additional macrophages and other immune cells, phagocytose toxic materials, and also regulate the adaptive immunity. Macrophages resident in tumors are commonly termed as tumor-associated macrophages (TAMs)[40–44]. Large numbers of TAMs in tumor microenvironment are often associated with

high malignance and poor prognosis[45–48].

In response to different environmental stimuli, macrophages can be polarized into "M1 macrophages", the classically activated macrophages, or "M2 macrophages", the alternatively activated macrophages [49]. M1 macrophages are activated by IFN-γ and bacterial products, such as LPS. They express high levels pro-inflammatory cytokines, and release reactive oxygen species (ROS) and reactive nitrate species (RNS). It is believed that M1 macrophages possess anti-tumor activity. M2 macrophages are activated by IL-4, IL-10, IL-13 and glucocorticoid hormones, which render these cells anti-inflammatory function, and promote tumor progression [50–51]. Animal model and clinical studies suggest that TAMs are M2-like cells, which inhibit anti-tumor immunity, contribute to immune evasion and facilitate tumor initiation, progression and metastasis[52–53]. However, TAMs have been reported to share the features of both M1 and M2 cells[48]. It is now accepted that in contrast to the binary M1/M2 definition, macrophages can be polarized to a mixed-phenotype state under certain physiological and pathological conditions [54–56]. This conclusion is supported by a recent report that the expression of CUEDC2 is almost undetectable in TAMs, and these macrophages lacking CUEDC2 produce higher amount of pro-inflammatory cytokines to promote colon cancers [57]. A widely accepted model regarding the origin of macrophages is that circulating monocytes in peripherial blood differentiate into macrophages in tissues. However the local self-renewal of tissue-resident macrophages has been reported by several groups [58–60]. Recently, by utilizing parabiosis studies and gene-expression profiling comparison in mammary tumor mouse model, Ming O. Li's group revealed the cellular origin of TAMs[61]. Distinct from tissue macrophages, TAMs are mostly differentiated from circulating inflammatory monocytes.

The causal link between inflammation and tumor initiation is well established [62]. When subject to persistent microbial infection or chronic stimulation, macrophages recognize the foreign materials and activate transcriptional mechanisms that lead to secretion of pro-inflammatory cytokines and chemokines [46, 62]. However, excessively produced cytokines could also sustain a state of chronic inflammation and promote tumor initiation. In established tumors, TAMs facilitate tumor cell migration, invasion, matrix remodeling and angiogenesis, which are required for tumor cells to escape from primary sites into the circulatory system and form metastases. In tumor microenvironments, anti-inflammatory cytokines, such as IL-4, IL-13, IL-10 and M-CSF, induce the transition of TAMs from a pro-inflammatory state to a tumor immunosuppressive phenotype that contributes to sustain tumor progression[53].

3 Myeloid derived suppressor cells

Recently, a cluster of immature myeloid cells has been characterized as myeloid derived suppressor cells (MDSCs), which are constantly accumulated in various cancer tissues and suppressed the immune response in tumor microenvironment [63–64]. MDSCs are a group of unwell-differentiated, dysfunctional progenitor cells that rapidly emerged under a variety of stress conditions especially in cancer development[65–67]. Detailed studies showed the accumulation of MDSCs in the tumor site perturbed the immune response by antagonizing mature immune cells, and thus contributed to the escape of tumor cells from the normal immune surveillance [46, 68–70]. Moreover, proinflammatory molecules secreted by tumor and host cells expand MDSCs and recruit them to facilitate cancer development[71–73].

Based on the expression of myeloid membrane markers, MDSCs can be divided into two major subtypes, monocytic-MDSCs (Mo-MDSCs) and granulocytic-MDSCs (G-MDSCs), which are usually defined as $CD11b^+/CD14^+/CD33^+/HLA^-/DR^-$, and $CD11b^+/CD33^+/CD15^+$, respectively [63, 74–77]. During tumor development, the proliferation of MDSCs are stimulated by tumor-secreted cytokines including VEGFA, stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or granulocyte-CSF (G-CSF) and tumor necrosis factor (TNF) *etc*. [78–81]. Thus, these excessive and malignant stimulators rapidly induce myeloid cell to become immature MDSCs. On the other hand, the C-X-C motif chemokine family (CXCL) also play a key role in the mobilization and homeostasis of MDSCs [82–84]. As reported, the abnormal activity of the JAK-STATs and NF-κB signaling contributed to MDSCs expansion, and the down-regulation of TGF-β signaling promoted the infiltration of MDSCs in tumors[76, 85–89].

The major role of MDSCs is to suppress T cell function and the suppressive activity depends on

cell-to-cell contact. MDSCs exhibited an upregulated intracellular level of arginase, and suppress $CD4^+$ and $CD8^+$ T cells by depleting their surroundings of arginine, which is essential for T cell activation [90-91]. Increased expression of inducible nitric oxide synthase (iNOS) in MDSCs inhibits $CD8^+$ T cells by catalyzing the nitration of the T cell antigen receptor (TCR) and thereby disturbing T cell-peptide-MHC complex [91]. Recent work demonstrated that MDSCs indirectly induced Tregs, which are crucial for shutting down T cell-mediated immunity[92-93]. Except for suppression of T cell function, MDSCs has also been suggested to function as regulators of tumor invasion and angiogenesis [87, 94]. In these processes, hypoxia and hypoxia-inducible factor-1α were reported to be responsible for the upregulation of matrix metalloproteinases (MMPs), arginase and iNOS expression in MDSCs[95-96]. Due to the dual function of MDSCs in cancer development, eliminating MDSCs reduces the risk of tumorigenesis and improves the prognosis of cancer therapy, while a comprehensive understanding of the mechanisms of MDSCs regulation will provide valuable information for more efficient cancer therapeutic strategies.

4 Dendritic cells

Dendritic cells (DCs) are a group of professional antigen-presenting cells (APCs) that share the capability to uptake and process antigens, including tumor antigens, for presentation to naive T cells [97-98]. DCs have been found highly heterogeneous in ontogeny, localization, cytokine profiles, and immunological function. According to the immune surveillance paradigm, DCs sense malignant lesions and present the tumor antigens to adaptive immune cells which eliminate the tumorous cells and prevent the tumor formation. In line with this concept, it has been reported that more infiltrated DCs in certain solid tumors correlated with favorable prognostic features[99]. In growing solid tumors, tumor damage-associated molecular patterns (DAMP) could be recognized by DCs, and trigger innate immunity and then start the priming of the anti-tumor adaptive immunity. The role of Type Ⅰ IFN in this process has been underscored by a series of works [98]. Fuertes *et al.* [100] reported a correlation between a type Ⅰ IFNs transcriptional profile and T cell markers in human metastatic melanoma. They further found that in mice lacking IFN signaling, intratumoral accumulation of $CD8^+$ DCs and tumor-induced T cell priming were almost completely loss. In the meantime, Diamond *et al.* [101] reported that tumor rejection was defective in mice lacking IFNαR1 in DCs, but was grossly normal in mice lacking IFNαR1 in macrophages and granulocytes, suggesting that DCs were the major targets of Type Ⅰ IFNs. According to these findings, new therapeutic strategies were developed targeting the type Ⅰ IFNs in the tumor environment. Yang *et al* [102] armed the therapeutic antibody (Ab) with IFN-β and observed that it is more potent in controlling Ab-resistant tumors. Ab-IFN-β therapy directly and mainly targets intratumoral DCs, increases cross-presentation in the tumor microenvironment, and activates CTL against tumor.

Except for the role in anti-tumor immunity, DCs have also been found to accelerate tumor progression through various mechanisms[98]. Garrett *et al.*[103] found that T-bet deficiency in DC cells elicited uncontrollable MyD88-independent intestinal inflammation, which promoted the development of ulcerative colitis and later progression to colonic dysplasia and rectal adenocarcinoma. Pedroza-Gonzalez found that breast cancer cells could secret TSLP (Thymic stromal lymphopoietin). TSLP induced and maintained the $OX40L^+$ DCs, which further promoted the pro-tumor Th2 inflammation in the breast cancer tissues[104]. Chemotherapy causes massive tumor cell death, releasing a combination of molecules including tumor antigens, DAMPs and other factors that regulate DCs function in the tumor microenvironment. Ma and colleagues [105] found that ATP released by dying cancer cells recruited myeloid cells into tumors, and stimulated the local differentiation of $CD11c^+CD11b^+Ly6C^{hi}$ DCs. These cells engulf tumor antigens *in situ* and presented them to T lymphocytes, thus vaccinated mice against cancer cells. In a different model, Baghdadi *et al.* [106] found that DAMPs released from chemotherapy-damaged tumor cells reduced antigen presentation and impaired CTL responses. They demonstrated that DAMP-induced TIM-4 expression in DCs repressed tumor-specific immunity through directly interacting with AMPKα1 and activating autophagy-mediated degradation of ingested tumors. Since tumors of different tissues and different stages have unique features, DCs function in tumor microenvironment is also spatially and temporally dynamic. In mucosal system, FcRn (neonatal Fc receptor for IgG) on the

DCs has a fundamental role in the anti-tumor immunesurveillance through mediating the cross presentation of IgG-complexed antigens and the secretion of cytotoxicity-promoting cytokines [107]. Using an inducible aggressive ovarian carcinoma, Scarlett and colleagues [108] found that along tumor progression, DCs undergo a phenotypic switch from tumor-preventing to tumor-promoting. Depleting DCs in the early stages accelerates tumor expansion, but DC depletion at advanced stages significantly delays aggressive malignant progression [108]. Taken together, the considerable progress made in the understanding of DC biology in tumor microenvironment has clearly opened avenues for the development of novel anti-tumor therapies. Further investigations on the function and differentiation of DCs may provide more potent strategies to rewire the signaling pathways from "pro-tumor" DCs into "anti-tumor" DCs.

5 Mast cells

Mast cells (MCs) are also tissue-resident sentinel cells. It has been identified that mast cell progenitors are derived from hematopoietic stem cells or differentiated later in the myeloid lineage from the granulocyte monocyte progenitor[109]. The infiltration of mast cells in tumor microenvironment correlates with tumor development thus has been utilized as a novel prognostic marker[110]. For example, increased mast cell count is associated with unfavorable prognosis in follicular lymphoma, Hodgkin lymphoma [111]. In addition, mast cells can also induce the release of pro-angiogenic factors. High MC score together with angiogenesis shows poor clinical outcome, short recurrence free survival in colorectal cancer, lung cancer, and pancreatic cancer[112–117]. Nakayama *et al*.[118] discovered the potential role for mast cell-derived angiopoeitin 1 (Ang-1) in murine myeloma. Both Ang-1 and VEGF-A expression are found in murine mast cells. The pro-tumor effect of mast cells is inhibited by addition of antibodies against Ang-1, VEGF-A or both, suggesting mast cell-derived Ang-1 plays a potent role in promoting angiogenesis in myeloma.

Mast cells are also antigen-presenting cells [109, 119]. They promote the maturation of dendritic cells, interact with both T cells and B cells, and modulate immune responses [119–121]. Indeed, mast cells express antigen presentation molecules including MHC class Ⅱ and CD28, and thus activate T cells to initiate adaptive immunity, and contribute to tumor rejection [122]. Mast cells can also recruit eosinophils and neutrophils and activate anti-tumor adaptive T and B cell responses[123]. In contrast, the presence of mast cells may facilitate tumorigenesis. It has been recognized that the recruitment of Tregs into the tumor microenvironment is partially mediated by mast cell-derived adenosine [124]. Mast cells also interact with Tregs, and this interaction determines the level of inflammation, thus further dictates the tumor progression [124]. Tregs suppress the mast cell differentiation and degranulation *via* the cell-cell contact mediated by the interaction between OX40 from Tregs and OX40L from mast cells. On the other hand, mast cells also block the Treg-derived IL-10 production through the same interaction [123]. Moreover, mast cell-secreted proinflammatory cytokines including IL-6 and IL-23 interrupt the suppressive effect of Tregs [115, 125]. In all, mast cells generate a variety of cytokines that either promote angiogenesis, or regulate the anti-tumor immunity. However, the extent to which mast cells are a relevant source of these cytokines is an unresolved, but important, question.

6 Concluding remarks

By characterizing immune cells in tumor microenvironment with mouse models and human samples, people gain more insights of the diverse immune cells that modulate the initiation and progression of tumors. Based on this understanding, targeting the immune cells in the tumor microenvironment could be a novel approach to treat malignancies. There are still some challenges in this field: since the different orchestration of the immune cells may lead to different clinical outcomes, future studies will need to take a comprehensive view of tumor immune environment as a whole. It is still obscure that how different immune cells cooperate with each other within tumor tissues. Thus the molecular mechanisms that regulate the cell-cell interaction need to be uncovered. Additionally, the composition of the immune cells in the microenvironments of primary tumors and metastases may be different, and immunotherapies that target multiple lesions in one person are required for a better efficacy. Besides, a big data-based mathematical model can certainly improve the precision of prognosis prediction and accelerate the development of anti-tumor immunotherapies.

References

[1] McCarthy N. Tumour microenvironment: the same, but different. Nat Reviews Cancer, 2011, **11**(4): 232

[2] McCarthy N. Tumour microenvironment: more than just a mutagen. Nat Rev Cancer, 2014, **14**(4): 213

[3] Lokody I. Microenvironment: Tumour-promoting tissue mechanics. Nat Rev Cancer, 2014, **14**(5): 296

[4] Seton-Rogers S. Tumour microenvironment: means of resistance. Nat Rev Cancer, 2013, **13**(9): 607

[5] Seton-Rogers S. Tumour microenvironment: teaching old macrophages new tricks. Nat Rev Cancer, 2013, **13**(11): 753

[6] Elinav E, Nowarski R, Thaiss C A, *et al*. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer, 2013, **13**(11): 759−771

[7] Gajewski T F, Meng Y, Blank C, *et al*. Immune resistance orchestrated by the tumor microenvironment. Immunol Rev, 2006, **213**: 131−145

[8] Murphy K M, Reiner S L. The lineage decisions of helper T cells. Nat Rev Immunol, 2002, **2**(12): 933−944

[9] Coulie P G, Van den Eynde B J, van der Bruggen P, *et al*. Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy. Nat Rev Cancer, 2014, **14**(2): 135−146

[10] Vivier E, Ugolini S, Blaise D, *et al*. Targeting natural killer cells and natural killer T cells in cancer. Nat Rev Immunol, 2012, **12**(4): 239−252

[11] Gattinoni L, Klebanoff C A, Restifo N P. Paths to stemness: building the ultimate antitumour T cell. Nat Rev Cancer, 2012, **12**(10): 671−684

[12] Abbas A K, Murphy K M, Sher A. Functional diversity of helper T lymphocytes. Nature, 1996, **383**(6603): 787−793

[13] Park H, Li Z, Yang X O, *et al*. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol, 2005, **6**(11): 1133−1141

[14] Harrington L E, Hatton R D, Mangan P R, *et al*. Interleukin 17-producing $CD4^+$ effector T cells develop *via* a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol, 2005, **6**(11): 1123−1132

[15] Kumar P, Chen K, Kolls J K. Th17 cell based vaccines in mucosal immunity. Curr Opin Immunol, 2013, **25**(3): 373−380

[16] Ji Y, Zhang W. Th17 cells: positive or negative role in tumor?. Cancer Immunol, Immunother, 2010, **59**(7): 979−987

[17] Kryczek I, Wei S, Szeliga W, *et al*. Endogenous IL-17 contributes to reduced tumor growth and metastasis. Blood, 2009, **114** (2): 357−359

[18] Kryczek I, Banerjee M, Cheng P, *et al*. Phenotype, distribution, generation, and functional and clinical relevance of Th17 cells in the human tumor environments. Blood, 2009, **114**(6): 1141−1149

[19] Martin-Orozco N, Muranski P, Chung Y, *et al*. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. Immunity, 2009, **31**(5): 787−798

[20] Sfanos K S, Bruno T C, Maris C H, *et al*. Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing. Clin Cancer Res, 2008, **14**(11): 3254−3261

[21] von Euw E, Chodon T, Attar N, *et al*. CTLA4 blockade increases Th17 cells in patients with metastatic melanoma. J Transl Med, 2009, **7**: 35

[22] Muranski P, Boni A, Antony P A, *et al*. Tumor-specific Th17-polarized cells eradicate large established melanoma. Blood, 2008, **112**(2): 362−373

[23] Chang S H, Mirabolfathinejad S G, Katta H, *et al*. T helper 17 cells play a critical pathogenic role in lung cancer. Proc Natl Acad Sci USA, 2014, **111**(15): 5664−5669

[24] Chung A S, Wu X, Zhuang G, *et al*. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nat Med, 2013, **19**(9): 1114−1123

[25] Shojaei F, Wu X, Qu X, *et al*. G-CSF-initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. Proc Natl Acad Sci USA, 2009, **106**(16): 6742−6747

[26] Fontenot J D, Gavin M A, Rudensky A Y. Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. Nat Immunol, 2003, **4**(4): 330−336

[27] Whiteside T L. What are regulatory T cells (Treg) regulating in cancer and why?. Semin Cancer Biol, 2012, **22**(4): 327−334

[28] Wang Y, Ma Y, Fang Y, *et al*. Regulatory T cell: a protection for tumour cells. J Cell Mol Med, 2012, **16**(3): 425−436

[29] Xue D, Lu M, Gao B, *et al*. Screening for transcription factors and their regulatory small molecules involved in regulating the functions of CL1-5 cancer cells under the effects of macrophage-conditioned medium. Oncol Rep, 2014, **31**(3): 1323−1333

[30] Tosolini M, Kirilovsky A, Mlecnik B, *et al*. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, th2, treg, th17) in patients with colorectal cancer. Cancer Res, 2011, **71**(4): 1263−1271

[31] Fridman W H, Galon J, Pages F, *et al*. Prognostic and predictive impact of intra- and peritumoral immune infiltrates. Cancer Res, 2011, **71**(17): 5601−5605

[32] Bates G J, Fox S B, Han C, *et al*. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol, 2006, **24**(34): 5373−5380

[33] Curiel T J, Coukos G, Zou L, *et al*. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med, 2004, **10**(9): 942−949

[34] Duhen T, Duhen R, Lanzavecchia A, *et al*. Functionally distinct subsets of human $FOXP3^+$ Treg cells that phenotypically mirror effector Th cells. Blood, 2012, **119**(19): 4430−4440

[35] Misra N, Bayry J, Lacroix-Desmazes S, *et al*. Cutting edge: human $CD4^+CD25^+$ T cells restrain the maturation and antigen-presenting function of dendritic cells. J Immunol, 2004, **172**(8): 4676−4680

[36] Pastille E, Bardini K, Fleissner D, *et al*. Transient ablation of regulatory T cells improves antitumor immunity in colitis-associated colon cancer. Cancer Res, 2014, **74**(16): 4258−4269

[37] Stewart C A, Metheny H, Iida N, *et al*. Interferon-dependent IL-10 production by Tregs limits tumor Th17 inflammation. J Clin Invest, 2013, **123**(11): 4859−4874

[38] Bauer C A, Kim E Y, Marangoni F, *et al*. Dynamic Treg interactions with intratumoral APCs promote local CTL dysfunction. J Clin Invest, 2014, **124**(6): 2425−2440

[39] Lim H W, Hillsamer P, Banham A H, *et al*. Cutting edge: direct suppression of B cells by $CD4^+$ $CD25^+$ regulatory T cells. J Immunol, 2005, **175**(7): 4180−4183

[40] Murray P J, Wynn T A. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol, 2011, **11**(11): 723−737

[41] Gordon S, Taylor P R. Monocyte and macrophage heterogeneity. Nat Rev Immunol, 2005, **5**(12): 953−964

[42] Geissmann F, Gordon S, Hume D A, *et al*. Unravelling mononuclear phagocyte heterogeneity. Nat Rev Immunol, 2010, **10**(6): 453−460

[43] Geissmann F, Manz M G, Jung S, *et al*. Development of monocytes, macrophages, and dendritic cells. Science, 2010, **327**(5966): 656−661

[44] Taylor P R, Martinez-Pomares L, Stacey M, *et al*. Macrophage receptors and immune recognition. Annu Rev Immunol, 2005, **23**: 901−944

[45] Biswas S K, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol, 2010, **11**(10): 889−896

[46] Gabrilovich D I, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol, 2012, **12**(4): 253−268

[47] Mantovani A. B cells and macrophages in cancer: yin and yang. Nat Med, 2011, **17**(3): 285−286

[48] Qian B Z, Pollard J W. Macrophage diversity enhances tumor progression and metastasis. Cell, 2010, **141**(1): 39−51

[49] Martinez F O, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol, 2009, **27**: 451−483

[50] Laskin DL, Sunil VR, Gardner CR, *et al*. Macrophages and tissue injury: agents of defense or destruction?. Annu Rev Pharmacol Toxicol, 2011, **51**: 267−288

[51] Odegaard J I, Chawla A. Alternative macrophage activation and metabolism. Annu Rev Pathol, 2011, **6**: 275−297

[52] Mantovani A, Sozzani S, Locati M, *et al*. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol, 2002, **23**(11): 549−555

[53] Wynn T A, Chawla A, Pollard J W. Macrophage biology in development, homeostasis and disease. Nature, 2013, **496**(7446): 445−455

[54] Biswas S K, Sica A, Lewis C E. Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms. J Immunol, 2008, **180**(4): 2011−2017

[55] Sica A, Mantovani A. Macrophage plasticity and polarization: *in vivo* veritas. J Clin Invest, 2012, **122**(3): 787−795

[56] Karnevi E, Andersson R, Rosendahl A H. Tumour-educated macrophages display a mixed polarisation and enhance pancreatic cancer cell invasion. Immunol Cell Biol, 2014, **92**(6): 543−552

[57] Chen Y, Wang S X, Mu R, *et al*. Dysregulation of the miR-324-5p-CUEDC2 axis leads to macrophage dysfunction and is associated with colon cancer. Cell Rep, 2014, **7**(6): 1982−1993

[58] Jenkins S J, Ruckerl D, Cook P C, *et al*. Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. Science, 2011, **332**(6035): 1284−1288

[59] Schulz C, Gomez Perdiguero E, Chorro L, *et al*. A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science, 2012, **336**(6077): 86−90

[60] Hashimoto D, Chow A, Noizat C, *et al*. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity, 2013, **38**(4): 792−804

[61] Franklin R A, Liao W, Sarkar A, *et al*. The cellular and molecular origin of tumor-associated macrophages. Science, 2014, **344**(6186): 921−925

[62] Grivennikov S I, Greten F R, Karin M. Immunity, inflammation, and cancer. Cell, 2010, **140**(6): 883−899

[63] Filipazzi P, Huber V, Rivoltini L. Phenotype, function and clinical implications of myeloid-derived suppressor cells in cancer patients. Cancer Immunol Immunother, 2012, **61**(2): 255−263

[64] Gabrilovich D I, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol, 2009, **9**(3): 162−174

[65] Brys L, Beschin A, Raes G, *et al*. Reactive oxygen species and 12/15-lipoxygenase contribute to the antiproliferative capacity of alternatively activated myeloid cells elicited during helminth infection. J Immunol, 2005, **174**(10): 6095−6104

[66] Makarenkova V P, Bansal V, Matta B M, *et al*. $CD11b^+$/$Gr\text{-}1^+$ myeloid suppressor cells cause T cell dysfunction after traumatic stress. J Immunol, 2006, **176**(4): 2085−2094

[67] Zhu B, Bando Y, Xiao S, *et al*. $CD11b^+$Ly-6C (hi) suppressive monocytes in experimental autoimmune encephalomyelitis. J Immunol, 2007, **179**(8): 5228−5237

[68] Gabrilovich D. Mechanisms and functional significance of tumour-induced dendritic-cell defects. Nat Rev Immunol, 2004, **4**(12): 941−952

[69] Marigo I, Dolcetti L, Serafini P, *et al*. Tumor-induced tolerance and immune suppression by myeloid derived suppressor cells. Immunol Rev, 2008, **222**: 162−179

[70] Marx J. Cancer immunology. Cancer's bulwark against immune attack: MDS cells. Science, 2008, **319**(5860): 154−156

[71] Almand B, Clark J I, Nikitina E, *et al*. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol, 2001, **166**(1): 678−689

[72] Bunt S K, Sinha P, Clements V K, *et al*. Inflammation induces myeloid-derived suppressor cells that facilitate tumor progression. J Immunol, 2006, **176**(1): 284−290

[73] Bunt S K, Yang L, Sinha P, *et al*. Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. Cancer Res,

2007, **67**(20): 10019-10026

[74] Mielcarek M, Martin P J, Torok-Storb B. Suppression of alloantigen-induced T-cell proliferation by $CD14^+$ cells derived from granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells. Blood, 1997, **89**(5): 1629-1634

[75] Okazaki T, Ebihara S, Asada M, *et al*. Granulocyte colony-stimulating factor promotes tumor angiogenesis *via* increasing circulating endothelial progenitor cells and $Gr1^+CD11b^+$ cells in cancer animal models. Int Immunol, 2006, **18**(1): 1-9

[76] Poschke I, Mougiakakos D, Hansson J, *et al*. Immature immunosuppressive $CD14^+$HLA-DR-/low cells in melanoma patients are Stat3hi and overexpress CD80, CD83, and DC-sign. Cancer Res, 2010, **70**(11): 4335-4345

[77] Yang L, DeBusk L M, Fukuda K, *et al*. Expansion of myeloid immune suppressor Gr^+CD11b^+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell, 2004, **6**(4): 409-421

[78] Dolcetti L, Peranzoni E, Ugel S, *et al*. Hierarchy of immunosuppressive strength among myeloid-derived suppressor cell subsets is determined by GM-CSF. Eur J Immunol, 2010, **40**(1): 22-35

[79] Kowanetz M, Wu X, Lee J, *et al*. Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of $Ly6G^+Ly6C^+$ granulocytes. Proc Natl Acad Sci USA, 2010, **107**(50): 21248-21255

[80] Sawanobori Y, Ueha S, Kurachi M, *et al*. Chemokine-mediated rapid turnover of myeloid-derived suppressor cells in tumor-bearing mice. Blood, 2008, **111**(12): 5457-5466

[81] Sica A, Bronte V. Altered macrophage differentiation and immune dysfunction in tumor development. J Clin Invest, 2007, **117**(5): 1155-1166

[82] McQuibban G A, Butler G S, Gong J H, *et al*. Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. J Biol Chem, 2001, **276**(47): 43503-43508

[83] Nagasawa T, Hirota S, Tachibana K, *et al*. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. Nature, 1996, **382**(6592): 635-638

[84] Xu L, Duda D G, di Tomaso E, *et al*. Direct evidence that bevacizumab, an anti-VEGF antibody, up-regulates SDF1alpha, CXCR4, CXCL6, and neuropilin 1 in tumors from patients with rectal cancer. Cancer Res, 2009, **69**(20): 7905-7910

[85] Delano M J, Scumpia P O, Weinstein J S, *et al*. MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. J Exp Med, 2007, **204**(6): 1463-1474

[86] Forrester E, Chytil A, Bierie B, *et al*. Effect of conditional knockout of the type Ⅱ TGF-beta receptor gene in mammary epithelia on mammary gland development and polyomavirus middle T antigen induced tumor formation and metastasis. Cancer Res, 2005, **65**(6): 2296-2302

[87] Li H, Han Y, Guo Q, *et al*. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-beta 1. J Immunol, 2009, **182**(1): 240-249

[88] Yang L, Huang J, Ren X, *et al*. Abrogation of TGF beta signaling in mammary carcinomas recruits $Gr\text{-}1^+CD11b^+$ myeloid cells that promote metastasis. Cancer Cell, 2008, **13**(1): 23-35

[89] Zon L I. Intrinsic and extrinsic control of haematopoietic stem-cell self-renewal. Nature, 2008, **453**(7193): 306-313

[90] Bronte V, Zanovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol, 2005, **5**(8): 641-654

[91] Nagaraj S, Gupta K, Pisarev V, *et al*. Altered recognition of antigen is a mechanism of $CD8^+$ T cell tolerance in cancer. Nat Med, 2007, **13**(7): 828-835

[92] Huang B, Pan P Y, Li Q, *et al*. $Gr\text{-}1^+CD115^+$ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. Cancer Res, 2006, **66**(2): 1123-1131

[93] Serafini P, Mgebroff S, Noonan K, *et al*. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. Cancer Res, 2008, **68**(13): 5439-5449

[94] Asahara T, Murohara T, Sullivan A, *et al*. Isolation of putative progenitor endothelial cells for angiogenesis. Science, 1997, **275**(5302): 964-967

[95] Corzo C A, Condamine T, Lu L, *et al*. HIF-1alpha regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. J Exp Med, 2010, **207**(11): 2439-2453

[96] Du R, Lu K V, Petritsch C, *et al*. HIF1alpha induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. Cancer Cell, 2008, **13**(3): 206-220

[97] Mildner A, Jung S. Development and function of dendritic cell subsets. Immunity, 2014, **40**(5): 642-656

[98] Steinman R M, Banchereau J. Taking dendritic cells into medicine. Nature, 2007, **449**(7161): 419-426

[99] Shurin M R, Potapovich A I, Tyurina Y Y, *et al*. Recognition of live phosphatidylserine-labeled tumor cells by dendritic cells: a novel approach to immunotherapy of skin cancer. Cancer Res, 2009, **69**(6): 2487-2496

[100]Fuertes M B, Kacha A K, Kline J, *et al*. Host type Ⅰ IFN signals are required for antitumor $CD8^+$ T cell responses through CD8 {alpha}+ dendritic cells. J Exp Med, 2011, **208**(10): 2005-2016

[101]Diamond M S, Kinder M, Matsushita H, *et al*. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. J Exp Med, 2011, **208**(10): 1989-2003

[102]Yang X, Zhang X, Fu M L, *et al*. Targeting the tumor microenvironment with interferon-beta bridges innate and adaptive immune responses. Cancer Cell, 2014, **25**(1): 37-48

[103]Garrett W S, Punit S, Gallini C A, *et al*. Colitis-associated colorectal cancer driven by T-bet deficiency in dendritic cells. Cancer Cell, 2009, **16**(3): 208-219

[104]Pedroza-Gonzalez A, Xu K, Wu T C, *et al*. Thymic stromal lymphopoietin fosters human breast tumor growth by promoting type 2 inflammation. J Exp Med, 2011, **208**(3): 479-490

[105]Ma Y, Adjemian S, Mattarollo S R, *et al*. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-

presenting cells. Immunity, 2013, **38**(4): 729−741

[106]Baghdadi M, Yoneda A, Yamashina T, *et al*. TIM-4 glycoprotein-mediated degradation of dying tumor cells by autophagy leads to reduced antigen presentation and increased immune tolerance. Immunity, 2013, **39**(6): 1070−1081

[107]Baker K, Rath T, Flak M B, *et al*. Neonatal Fc receptor expression in dendritic cells mediates protective immunity against colorectal cancer. Immunity, 2013, **39**(6): 1095−1107

[108]Scarlett U K, Rutkowski M R, Rauwerdink A M, *et al*. Ovarian cancer progression is controlled by phenotypic changes in dendritic cells. J Exp Med, 2012, **209**(3): 495−506

[109]Galli S J, Maurer M, Lantz C S. Mast cells as sentinels of innate immunity. Curr Opin Immunol, 1999, **11**(1): 53−59

[110]Galli S J, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nat Rev Immunol, 2008, **8**(6): 478−486

[111]Molin D, Edstrom A, Glimelius I, *et al*. Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. Br J Haematol, 2002, **119**(1): 122−124

[112]Johansson A, Rudolfsson S, Hammarsten P, *et al*. Mast cells are novel independent prognostic markers in prostate cancer and represent a target for therapy. Amer J Pathol, 2010, **177**(2): 1031−1041

[113]Soucek L, Lawlor E R, Soto D, *et al*. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. Nat Med, 2007, **13**(10): 1211−1218

[114]Gulubova M, Vlaykova T. Prognostic significance of mast cell number and microvascular density for the survival of patients with primary colorectal cancer. J Gastroenterol Hepatol, 2009, **24** (7): 1265−1275

[115]Blatner N R, Bonertz A, Beckhove P, *et al*. In colorectal cancer mast cells contribute to systemic regulatory T-cell dysfunction. Proc Natl Acad Sci USA, 2010, **107**(14): 6430−6435

[116]Strouch M J, Cheon E C, Salabat M R, *et al*. Crosstalk between mast cells and pancreatic cancer cells contributes to pancreatic tumor progression. Clin Cancer Res, 2010, **16**(8): 2257−2265

[117]de Souza D A, Jr., Toso V D, Campos M R, *et al*. Expression of mast cell proteases correlates with mast cell maturation and angiogenesis during tumor progression. PloS One, 2012, **7** (7): e40790

[118]Nakayama T, Yao L, Tosato G. Mast cell-derived angiopoietin-1 plays a critical role in the growth of plasma cell tumors. J Clin Invest, 2004, **114**(9): 1317−1325

[119]Shelburne C P, Nakano H, St John A L, *et al*. Mast cells augment adaptive immunity by orchestrating dendritic cell trafficking through infected tissues. Cell Host Microbe, 2009, **6**(4): 331−342

[120]Huang B, Lei Z, Zhang G M, *et al*. SCF-mediated mast cell infiltration and activation exacerbate the inflammation and immunosuppression in tumor microenvironment. Blood, 2008, **112**(4): 1269−1279

[121]Suto H, Nakae S, Kakurai M, *et al*. Mast cell-associated TNF promotes dendritic cell migration. J Immunol, 2006, **176**(7): 4102−4112

[122]Theoharides T C, Kempuraj D, Kourelis T, *et al*. Human mast cells stimulate activated T cells: implications for multiple sclerosis. Ann NY Acad Sci, 2008, **1144**: 74−82

[123]Kennedy Norton S, Barnstein B, Brenzovich J, *et al*. IL-10 suppresses mast cell IgE receptor expression and signaling *in vitro* and *in vivo*. J Immunol, 2008, **180**(5): 2848−2854

[124]Piconese S, Gri G, Tripodo C, *et al*. Mast cells counteract regulatory T-cell suppression through interleukin-6 and OX40/OX40L axis toward Th17-cell differentiation. Blood, 2009, **114**(13): 2639−2648

[125]de Vries V C, Pino-Lagos K, Nowak E C, *et al*. Mast cells condition dendritic cells to mediate allograft tolerance. Immunity, 2011, **35**(4): 550−561

免疫细胞与肿瘤微环境

宋　楠　李　涛　张学敏*

(国家生物医学分析中心，北京 100850)

摘要　肿瘤细胞和免疫细胞间的相互作用一直是肿瘤生物学关注的热点．流行病学与临床研究均表明，炎症反应与肿瘤的发生发展存在密切关联，但是其中的分子作用机理和遗传学机制尚未完全阐明．研究显示，T 淋巴细胞、巨噬细胞、树突状细胞、巨大细胞等多种免疫细胞会浸润到肿瘤微环境中，协同调控肿瘤生长、免疫逃逸和侵袭转移．本文就近年对肿瘤微环境中免疫细胞功能研究的进展进行综述．正确认识这些免疫细胞在肿瘤发生发展中的作用，对于发展更优的肿瘤免疫治疗手段具有十分重要意义．

关键词　肿瘤，辅助性 T 细胞 17，调节性 T 细胞，巨噬细胞，骨髓来源抑制性细胞，树突状细胞，巨大细胞

学科分类号　R73　　**DOI**: 10.3724/SP.J.1206.2014.00245

* 通讯联系人.

Tel: 010-68246161, E-mail: zhangxuemin@cashq.ac.cn

收稿日期：2014-08-25，接受日期：2014-09-11