ISSN 0006-2979, Biochemistry (Moscow), 2017, Vol. 82, No. 5, pp. 542-555. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © L. A. Tashireva, V. M. Perelmuter, V. N. Manskikh, E. V. Denisov, O. E. Savelieva, E. V. Kaygorodova, M. V. Zavyalova, 2017, published in Biokhimiya, 2017, Vol. 82, No. 5, pp. 732-748.

REVIEW

Types of Immune-Inflammatory Responses as a Reflection of Cell–Cell Interactions under Conditions of Tissue Regeneration and Tumor Growth

L. A. Tashireva[1], V. M. Perelmuter[1], V. N. Manskikh[2], E. V. Denisov[1]*, O. E. Savelieva[1], E. V. Kaygorodova[1], and M. V. Zavyalova[1,3]

[1]Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, 634050 Tomsk, Russia; E-mail: d_evgeniy@oncology.tomsk.ru
[2]Lomonosov Moscow State University, 119991 Moscow, Russia
[3]Siberian State Medical University, 634050 Tomsk, Russia

Received October 7, 2016
Revision received November 24, 2016

Abstract—Inflammatory infiltration of tumor stroma is an integral reflection of reactions that develop in response to any damage to tumor cells including immune responses to antigens or necrosis caused by vascular disorders. In this review, we use the term "immune-inflammatory response" (IIR) that allows us to give an integral assessment of the cellular composition of the tumor microenvironment. Two main types of IIRs are discussed: type 1 and 2 T-helper reactions (Th1 and Th2), as well as their inducers: immunosuppressive responses and reactions mediated by Th22 and Th17 lymphocytes and capable of modifying the main types of IIRs. Cellular and molecular manifestations of each IIR type are analyzed and their general characteristics and roles in tissue regeneration and tumor growth are presented. Since inflammatory responses in a tumor can also be initiated by innate immunity mechanisms, special attention is given to inflammation based on them. We emphasize that processes accompanying tissue regeneration are prototypes of processes underlying cancer progression, and these processes have the same cellular and molecular substrates. We focus on evidence that tumor progression is mainly contributed by processes specific for the second phase of "wound healing" that are based on the Th2-type IIR. We emphasize that the effect of various types of immune and stroma cells on tumor progression is determined by the ability of the cells and their cytokines to promote or prevent the development of Th1- or Th2-type of IIR. Finally, we supposed that the nonspecific influence on the tumor caused by the cytokine context of the Th1- or Th2-type microenvironment should play a decisive role for suppression or stimulation of tumor growth and metastasis.

DOI: 10.1134/S0006297917050029

Keywords: immune-inflammatory response, lymphocyte subpopulations, macrophages, fibroblasts, tissue regeneration, tumor progression

Inflammation plays an important role in the initiation and development of tumors [1, 2]. First, the inflammatory response can be a background for reactive and neoplastic changes in the epithelium. Second, the inflammation is accompanied by production of proinflammatory mediators (cytokines and reactive oxygen and nitrogen species) that can induce genetic instability [3, 4]. Third, the inflammatory response type essentially determines features of the tumor, including its ability for invasion and metastasis [5]. Malignant tumors can grow only under conditions of adequate angiogenesis and formation of connective tissue, i.e. of the tumor stroma. Key events for angiogenesis and stroma formation are hypoxia and secretion by the tumor cells of some cytokines that mobi-

Abbreviations: CCL, C-C motif ligand; CTL, cytotoxic lymphocytes; CXCL, chemokine (C-X-C motif) ligand; DAMP, damage-associated molecular pattern; DC, dendritic cells; EMT, epithelial–mesenchymal transition; GM-CSF, granulocyte-macrophage colony-stimulating factor 2; IFN, interferon; IIR, immune-inflammatory response; IL, interleukin; ILC, innate lymphoid cells; MDSC, myeloid-derived suppressor cells; NK, natural killers; NOS, nitric oxide synthase; PAMP, pathogen-associated molecular pattern; PGE2, prostaglandin E2; TAM, tumor associated macrophages; TCR, T-cell receptor; TGF-β, transforming growth factor β; Th, T helper; TLR, Toll-like receptor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

* To whom correspondence should be addressed.

lize from the bone marrow progenitors of endothelium, fibroblasts, and macrophages into the tumor.

Inflammatory infiltration is a manifestation of a complex of processes caused by mechanisms of the innate and adaptive immune responses. The inflammation is expressed essentially depending on the tumor cell ability to secrete proinflammatory cytokines [6]. Whether the tumor cells maintain the "dormant" state for a long time or become a clinically observable growing tumor due to proliferation significantly depends on events occurring in the stroma and on the type of the inflammatory response.

The ability for formation of inflammatory response was produced during evolution for compensation of infectious or traumatic damage and development of tissue regeneration. This was provided by cellular and molecular mechanisms capable of destroying pathogens, purifying the damaged regions from necrotic tissue elements, and of stimulating fibroblasts for generation of connective tissue and surface epithelium to proliferate and cover the tissue defect [7]. Finally, in the case of damage, the adequacy of the inflammatory response is determined by successful tissue regeneration.

In description of processes in the stroma, tumors are often presented as "wounds that do not heal" [8]. This approach is reasonable because inflammation underlies both tissue regeneration and remodeling of the tumor stroma. Tissue regeneration has three phases: the inflammatory phase, organization phase (production of connective tissue and epithelization of the skin or mucosa damages), and tissue remodeling [9]. The first and second phases of tissue regeneration are manifested by inflammatory responses. The first phase proceeds as acute inflammation during which immune mechanisms, especially phagocytosis, purifies the damaged tissue region from pathogens and dead tissue elements. The second phase of tissue regeneration manifests itself as a productive inflammation and is characterized by generation of granulation tissue (angiogenesis), mature connective tissue, proliferation, and differentiation of the surface epithelium. Numerous growth factors produced by macrophages and lymphocytes during wound healing stimulate the proliferation of epithelial stem cells [10]. The development of tissue regeneration depends on the adequacy of inflammatory responses in the zone of damage. The second and third phases of tissue regeneration can occur only under conditions of well-timed termination of the first inflammation phase [11]. There are many data indicating that in malignant tumors just these processes underlie stroma formation and remodeling and the acquisition by the tumor cells of the ability for invasion and progression. Processes similar to those observed during tissue regeneration ("wound healing") either prevent stroma formation and tumor development due to inhibition of angio- and fibrogenesis or promote tumor progression due to stimulation of fibrosis, angiogenesis, proliferation of epithelial stem cells, and epithelial–mesenchymal transition (EMT). Because these mechanisms are physiologically purposed for involvement in tissue repair, we think that all events that develop during the inflammatory response under various situations, including inflammation during tumorigenesis, should be considered from the point of view of their influence on tissue regeneration. Therefore, in this review we focus our attention on the relation between inflammation and the immune response type, the role of inflammation *in situ* in progression of malignancies, mainly of carcinomas, and on the inflammation similarity to pathophysiological prototypes that manifested themselves during tissue regeneration.

IMMUNE-INFLAMMATORY RESPONSES WITHIN TUMOR STROMA

The presence of inflammatory infiltration in tumors is doubtless. Such infiltration is significantly stronger or weaker in different cases. Inflammation can be induced in tumors by various causes, in particular, by a pathogen. It is known that some tumors can be infected with persisting bacteria or viruses [12, 13]. In such cases the inflammation is underlain by the innate immunity mechanisms and is initiated by interaction of pathogen-associated molecular patterns (PAMPs) with Toll-like receptors (TLRs) of the tumor epithelium and then is enhanced due to their interaction with TLRs of macrophages and neutrophilic leukocytes. The development in the tumor stroma of an infection-unrelated inflammation seems to be more likely. It is known that tumor cells can be under conditions of hypoxia; moreover, a focal necrosis is frequently observed in some tumors. Therefore, the involvement of stress-associated molecular patterns (SAMPs) and of damage-associated molecular patterns (DAMPs) should be considered, which can activate the innate immune response. These mechanisms can explain the presence of innate immunity cells in the inflammatory infiltrate. Moreover, the infiltrate also contains cells responsible for adaptive immunity responses. In some tumors antigens have been found, including those capable of leading to development of adaptive immunogenesis and specific immune responses *in situ* [14]. This is confirmed by morphological data: in addition to diffuse or focal inflammatory infiltration of the tumor stroma, tertiary lymphoid structures (TLS) including T and B zones can be formed within it [15].

Because inflammatory infiltration of the tumor stroma is a manifestation of effector immune responses of innate or adaptive immunogenesis, we think that the term "immune-inflammatory responses" (IIR) can be used. In accordance with the literature data, we think it is reasonable to consider some types of immune-inflammatory effector responses, which seem to be realized also within the tumor stroma. First, these responses can be divided

into innate (antigen-independent) and adaptive (antigen-dependent) IIRs. In each group, we can pick the Th1-like type IIR associated with production of proinflammatory Th1 cytokines (type 1 T-helper) and Th2-like type IIR associated with production of anti-inflammatory Th2 cytokines. These IIR variants can be corrected and supplemented by Th17- and Th22-type responses and by immunosuppressive responses mediated by T-regulatory lymphocytes (Treg) and myeloid-derived suppressor cells (MDSC).

To identify these IIR types, it is reasonable to use the determination of the cellular composition and of molecules that demonstrate the specific activity of these cells. The key cells whose identification within the stroma will help to characterize the type of the immune-inflammatory response are $CD4^+$ T lymphocytes. $CD4^+$ T cells are represented by the following subtypes: Th1, Th2, Th9, Th17, Th22, Treg, and follicular Th cells (Tfh) [16]. Each subtype can be characterized by its ability to produce a certain set of cytokines and by expression of transcriptional factors (table).

The most important IIR participants in the tumor stroma are macrophages (M0, M1, M2, etc.), dendritic cells, fibroblasts, neutrophils, B lymphocytes, natural killers (NK), mesenchymal stem cells, myeloid cells-suppressors, etc. [18].

Thus, based on the presence of various cell types and on their production of specific cytokines, one can determine the IIR type within the tumor stroma and study their role in tumor progression.

INFLAMMATION MEDIATED BY INNATE IMMUNITY MECHANISMS

The innate immune system consists of different cells including dendritic cells, lymphocytes, macrophages, and granulocytes. These cells are involved in the development of inflammation and tissue regeneration and interact with the adaptive immune system [19]. The innate immunity responses are activated mainly by TLRs capable of recognizing PAMP and DAMP ligands and are located on different cells including epitheliocytes. Thus, macrophages and neutrophils are accumulated in places where the corresponding ligands bind with TLRs. The TLR-possessing neutrophils interact with PAMPs and additionally secret proinflammatory cytokines that increase inflammatory infiltration [19]. It should be noted that in the human body monocytes and neutrophilic leukocytes are sources not only of proinflammatory cytokines. It has been shown *in vivo* that interleukin 10 (IL-10) produced by different cells of the innate immune system, including dendritic cells, macrophages, and neutrophils, inhibits secretion of proinflammatory cytokines [20]. M2 and N2 leukocytes can be sources of IL-10 [21].

Innate lymphoid cells (ILC) are important participants in developing inflammation in tissues. These cells consist not only of classical cytotoxic NK cells and lymphoid tissue inducing cells (LTi cells), but also include a recently described population of noncytotoxic ILC. All cells of the ILC family (including the ILC1, ILC2, and ILC3 subpopulations) are characterized by a classic lymphoid morphology and by the absence of expression of surface linear molecules (Lin^-) that are inherent in lymphoid elements involved in adaptive immunogenesis [22]. ILCs are constitutively present in tissues and can be activated under the influence of cytokines and growth factors produced by local epithelial and myeloid cells. Thus, IL-12, IL-15, and IL-18 lead to activation of NK cells and ILC1, whereas IL-2, IL-4, IL-25, IL-33, the thymus stromal lymphopoietin (TSLP), IL-9, and TNFSF15 (tumor necrosis factor ligand superfamily member 15) can activate ILC2. As discriminated from this, IL-1β and IL-23 stimulate the ILC3-mediated response [22]. ILC1

Differentiation signals and markers of $CD4^+$ T lymphocytes

Cell type	Differentiation signal	Transcription factors	Surface markers and marker cytokines
Th1	IL-12, IFN-γ	**Tbet**, STAT1, STAT4 and Runx3	CXCR3, IFN-γ
Th2	IL-4	**GATA-3**, STAT6 and STAT5	IL-33R, IL-4, IL-13 and IL-5
Th9	TGF-β, IL-4	**BATF**, STAT6	IL-9
Th17	IL-6, TGF-β, IL-1β and (IL-23, IL-21)	**RORγt**, STAT3, Batf, Runx1 and RORα	CD161, IL-17A, IL-17F and GM-CSF
Th22	IL-6, IL-13 and TNFα	**AhR**	CCR4, CCR6, CCR10 and IL-22
Tfh	IL-6, IL-21	**Bcl-6**, Ascl2	CXCR5, PD-1 and IL-21
Treg	TGF-β, IL-2	**Foxp3**, STAT5	IL-10, TGF-β

Note: In the table, data of the review by Caza et al. [17] are given. Designations: Tbet, T-box transcription factor; STAT, signal transducer and activator of transcription; Runx, runt-related transcription factor; GATA-3, GATA binding protein 3; BATF, basic leucine zipper transcription factor; ROR, retinoid acid-related orphan receptor; AhR, aryl hydrocarbon receptor; Bcl-6, B-cell lymphoma 6 protein; Ascl2, Achaete-scute homolog 2; PD-1, programmed cell death protein 1; Foxp3, forkhead box P3. Key transcription factors regulating differentiation of T helper subpopulations are printed in bold.

are noncytotoxic Lin^- cells capable of producing interferon gamma (IFN-γ) and tumor necrosis factor (TNF) [23]. As differentiated from ILC1, ILC2 produce cytokines associated with the Th2-immune response (IL-4, IL-5, IL-9, and IL-13) and the epidermal growth factor ligand and promote type-2 inflammation [24]. Depending on stimuli, ILC3 in turn can produce IL-17A, IL-17F, IL-22, granulocyte-macrophage colony-stimulating factor 2 (GM-CSF), and TNF, as well as stimulate chronic inflammation [25]. It should be noted that in the spectra of secreted cytokines and transcription factors, ILC1, ILC2, and ILC3 subpopulations are very similar to the corresponding subpopulations of Th cells. However, unlike the T helper subpopulations, these cells do not need antigenic stimulation for functioning.

In "innate type" inflammation foci, naïve dendritic cells (DC) can be polarized to different type DCs (DC1 and DC2) capable of initiating specific (adaptive) immunity to antigens of pathogens or tumors. In the human body, DC1 can polarize naïve $CD4^+$ T lymphocytes to Th1 lymphocytes, whereas DC2 mediate the polarization of Th2, Th17, and Treg lymphocytes [26]. $CD1c^+$ DCs have been shown to express TLR1-8 and display high plasticity, secreting various sets of cytokines including IL-1α, IL-1β, IL-12p40, IL-12p70, IL-6, IL-7, TNF-α, IL-8, IL-10, and IFN-β [27, 28].

Role in tissue regeneration. It is known that in mice, TLR4 and, to a lesser degree, TLR2 can regulate wound healing indirectly, mediated through expression of transforming growth factor β (TGF-β) and C–C motif ligand 5 (CCL5) [29]. On the contrary, in the human body ILC2 and ILC3 but not ILC1 are involved in tissue regeneration and remodeling [19] mediated through expression of genes such as amphiregulin, decorin, asporin, and dermatopontin [30].

Involvement in tumor growth. It should be noted that tumor epithelial cells possessing TLRs can initiate, similarly to normal cells, the "innate type" inflammation in response to PAMPs of bacteria and viruses that occasionally infect the tumor. DAMPs released during necrosis of tumor elements can be especially significant for development of the "innate type" inflammation. Thus, it is known that TLR3, TLR4, and TLR9 are expressed on tumor cells of patients with breast cancer [31]. Modulation of the microenvironment through TLRs can be a mechanism of tumor cell progression. It has been shown that a signal transmitted through TLRs stimulates the releasing by the tumor cells of cytokines and chemokines associated with the immune response, in particular IL-8 [32].

However, the interaction of PAMP and DAMP ligands with TLRs on tumor cells can not only initiate immune responses, but directly promote the unfavorable course of malignization. Thus, activation of TLR4 promotes the αvβ3-integrin-mediated adhesion and invasion of the MDA-MB-231 tumor cell line [33]. In hepatocellular carcinoma, another mechanism of TLR-induced tumor progression is EMT triggering both directly [34] and with involvement of the stroma cells [35].

It is known that the innate immune system cells (myeloid cells such as tumor-associated macrophages (TAMs), type 2 neutrophils (N2), DCs, and MDSCs) have *in vivo* proangiogenic features and promote progression of malignancies [36]. The activity of $CD8^+$ cells specific to tumor antigens can be inhibited by DCs within the tumor microenvironment [37]. However, it is also thought that DCs within the microenvironment are defective because they cannot provide a full-value immune response to the tumor-associated antigens [38].

Some studies have demonstrated that innate lymphoid cells are involved in tumor growth *in vitro*. Thus, $CCR7^+CD4^-$ ILC3 promoted the proliferation of melanoma cells expressing CCL21 [39]. However, another study revealed the ILC3-mediated regression of B16 melanoma cells due to expression of IL-12 [40].

Data on the contribution of innate immunity cytotoxic responses to tumor development are contradictory. Innate immunity cells, such as T cells expressing the T-cell receptor αβ (TCR), NK cells, γδ T cells, and natural T-cell killers (NKT cells) that are subtypes of the lymphoid population not only influence tumor growth through production of IFN-γ and TNF-α leading to aging of the tumor cells, but also eliminate p53-expressing tumor cells using antigen-nonspecific mechanisms [41]. NK and NKT cells are known to infiltrate the stroma, but there are some data indicating that they do not have contact with the tumor cells [42]. Moreover, it is believed that in some cases NK cells are unable to cause death of tumor cells because of their anergic phenotype arising under the influence of the tumor-derived transforming growth factor (TGF-β) [43]. However, the presence of such cells is a good prognostic marker in various carcinomas (e.g. carcinoma of stomach, colon, lungs, kidneys, and liver) [42].

ROLE OF Th22 LYMPHOCYTES IN DEVELOPMENT OF IIR

General data. In the context of IIR development, special attention should be given to Th22 lymphocytes and IL-22 produced by them. In the human body, Th22 lymphocytes are derived from naïve Th0 lymphocytes under the influence of lymphotoxin α and IL-6 and are characterized by expression of CCR4 and CCR10 chemokine receptors. Similarly to Th1 and Th17 cells, Th22 lymphocytes produce IL-17A, IL-17F, and IL-22 [44, 45]. However, IL-22 is also produced by other lymphocytes of the innate and adaptive immune systems: by Th1 and Th17 lymphocyte subpopulations and by ILCs, NK, NKT, and γδ T cells [44, 46]. Cells not belonging to the hematopoietic system do not produce IL-22 [47].

Therefore, IL-22 is unique because it is produced only by immune cells, which, however, do not have receptors to it [44, 48], but acts only on non-immune cells. IL-22 receptors (IL-22R1 and IL-10R2) are expressed mainly on epithelial cells. IL-22R1 is produced also in tissues forming external barriers [49].

Role in tissue regeneration. IL-22 plays an important role in maintenance of homeostasis in the intestinal, liver, and pulmonary epithelium [49]. Under *in vitro* conditions, IL-22 stimulates the proliferation and migration of keratinocytes but inhibits their differentiation. IL-22R1 and IL-10R2 expression on keratinocytes is stimulated by IFN-γ and TNF that suggests an increase in the effects of IL-22 [50]. In a mouse model of tissue regeneration, the signaling pathway activated by IL-22 was shown to lead to myofibroblastic differentiation of fibroblasts and stimulation of intercellular matrix gene expression [51]. Studies on the expression profile of Th22 lymphocytes revealed the presence of a fibroblast growth factor (FGF1), which is powerful mitogen acting on various types of cells including endothelial cells, and FGF5, which is associated with differentiation of some cells [52]. Moreover, it was supposed that Th22 cells can play a role in remodeling and repair of the epithelial barrier because they can express CCL7 involved in production of fibers [53] and produce CCL15 and CCL23 (splice variant 2) involved in angiogenesis, as shown in the human fibrosarcoma HT1080 cell line [54].

Involvement in tumor growth. It was shown in a mouse model of inflammation and colon cancer that IL-22 promotes tumor development [55]. IL-17 stimulates production of proangiogenic factors [56] supporting tumor development [57]. In the high grade hepatocellular carcinoma, an increased expression of IL-22 was found in patients with poor survival [58].

Th1-TYPE IMMUNE-INFLAMMATORY RESPONSE

General data. Formation of the Th1-immune response is mainly determined by characteristics of the antigen, the type of dendritic cell presenting the antigen, and by the cytokine profile of cells involved in Th0 lymphocyte polarization. Th1 lymphocyte differentiation is mainly induced by IL-12 and IFN-γ. $CD4^+$ Th1 lymphocytes produce IFN-γ, IL-2, and lymphotoxin α, which mediate the "cellular" immunity [59]. In the human body, Th1 lymphocytes can activate monocytes and NK cells by secreting IFN-γ and significantly increase their ability to eliminate intracellular pathogens. The Th1 immune response results in formation of a pool of the antigen-specific $CD8^+$ cytotoxic cells (CTL). These cells recognize specific antigens on the cell surface together with main histocompatibility complex (MHC) class I, are activated, and secrete a set of apoptosis-related cytokines such as perforin, granzyme, lymphotoxin α, IFN-γ, and fragmentin [60].

In addition to lymphocytes, M1 macrophages are key cells of the Th1-type IIR. These "classically activated macrophages" are characterized by a high level of IL-12 secretion and by a low level of IL-10 secretion. The most important function of M1 macrophages is their phagocytic activity. A macrophage acquires the M1 phenotype in response to the Th1 cytokines: IFN-γ, TNF, and of some bacterial components, e.g. lipopolysaccharide (LPS) [61]. In the human body, the C-X-C chemokine receptor 3 (CXCR) plays a key role in macrophage polarization to the M1 type [62]. M1 macrophages are characterized by production of such proinflammatory factors as IL-6, IL-12, IL-23, and TNF. Moreover, M1 macrophages have high expression of the MHC class II molecules that is necessary for antigen presentation [62]. Due to these features, macrophages are a connecting link between the innate and adaptive immune systems. Besides, activated macrophage with M1 phenotype can produce CXCL-10 (chemokine (C-X-C motif) ligand), which is an attractant for $CD8^+$ and $CD4^+$ Th1 cells. An important specific feature of M1 macrophages is their ability to express the inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and to produce IL-12, which activates NK and Th1 cells [62].

In some studies, neutrophils, similarly to Th1/Th2 and M1/M2, are subdivided into N1/N2 subpopulations localized in the stroma of human tumors [21]. The neutrophil subpopulations are characterized by different expression markers, which include cytokines and chemokines. TGF-β inhibition increases the number of hypersegmented neutrophils, their N1 polarization (high expression by neutrophils of TNF, intercellular adhesion molecule (ICAM-1), and CD95), and antitumor activity. Phagocytosis and production of reactive oxygen species are key functions of N1 neutrophils. Moreover, N1 neutrophils in the human body often produce chemoattractants for Th1 cells including CCL3, CXCL9, and CXCL10, and proinflammatory cytokines, such as IL-12, TNF-α, GM-CSF, and vascular endothelial growth factor (VEGF) [63, 64].

Role in tissue regeneration. The Th1-type IIR is specific for the first phase of tissue regeneration. The abnormal function of this IIR and its incompleteness inhibit tissue repair processes. A persisting cellular infiltrate of the proinflammatory Th1-type mainly consisting of neutrophils and M1 macrophages was shown to disturb the healing of chronic ulcers in humans [65]. Deregulation of production of proinflammatory cytokines, such as IL-1β and TNF, prolongs the inflammatory phase of wound healing, whereas Th1 lymphocytes have an antifibrotic action due to formation of IFN-γ [66].

Involvement in tumor growth. It has been shown that in RIP1-Tag2 mice, Th1 cells induce production of antiangiogenic chemokines CXCL9 and CXCL10 via

INF-γ and TNF that results in an inhibition of neoangiogenesis in a tumor [67]. Studies in mouse models have shown that CXCR3 expression promotes recruiting of NK cells, $CD4^+$ Th1 cells, and cytotoxic $CD8^+$ T lymphocytes into the tumor [68]. It has been shown in samples of human breast, pancreas, bladder, stomach, colon, and ovaries carcinomas that a high number of $CD8^+$ T cells in the tumor microenvironment supported by $CD4^+$ Th1 cells correlates with a favorable prognosis [43]. These events can be one of the antitumor mechanisms of Th1 lymphocytes. It is known that in human tumors M1 macrophages and dendritic cells functioning together with Th1 lymphocytes can produce antiangiogenic factors. The M1-dependent polarization of $CD8^+$ T lymphocytes leads to arising of CTLs, which can bind with antigens on the tumor cell surface and then kill this cell due to releasing of granzyme B and perforins [69]. The study by Shen et al. revealed that in human intestinal mucosa, tumor-associated neutrophils N1 (N1 TAN) promote an increase in the antitumor activity of $CD8^+$ T lymphocytes [70].

However, the results of some studies suggest a possible promoting effect of the Th1-type response on tumor growth. Thus, it was observed in different solid tumors that all cytokines secreted by M1 macrophages are associated with unfavorable outcome [2]. Moreover, the adaptive transfer of Th1 lymphocytes was shown to promote relapses in experimental animals [71]. $CD8^+$ T lymphocytes promote formation of neoplasms in the chemically induced skin carcinogenesis in mice [72].

Thus, cooperation of Th1 lymphocytes, M1 macrophages, and N1 neutrophils creates a proinflammatory microenvironment and provides phagocytosis of pathogens and development of the first phase of tissue regeneration. This cooperation can prevent the second phase of tissue regeneration and, in most cases, inhibits the growth and progression of malignant tumors.

Th2-TYPE IMMUNE-INFLAMMATORY RESPONSE

General data. Th2-type IIR is associated with Th2 lymphocytes, B lymphocytes, M2 macrophages, and N2 neutrophils. The development of Th2-type IIR is also supported by fibroblasts. The differentiation of Th2 lymphocytes is mainly induced by IL-4. In the human body, Th2 cells can produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Moreover, Th2 lymphocytes express membrane-bound CD40 ligand (CD40L), which interacts with CD40 receptor (CD40R) on B lymphocytes and activates B cells that is accompanied by synthesis by these cells of cytokines and proliferation with production of antibody-generating plasma cells [59].

In the human body, the differentiation of M2 macrophages is mainly induced by IL-4 produced by Th2 cells, eosinophils, and basophils. M2 macrophages possessing "anti-inflammatory" activity are termed "alternatively activated macrophages" [62]. M2-type macrophages can be subdivided into M2a, M2b, M2c, and M2d subtypes. It has been shown *in vitro* that Th2 cytokines, such as IL-4 and IL-13, can stimulate macrophage transition into M2a, the IL-1R ligand and LPS-containing immune complexes induce polarization of M2b macrophages, whereas IL-10 promotes M2c subtype formation. M2 differentiation can also be induced by parasites, immune complexes, complement, apoptotic cells, macrophage colony-stimulating factor (M-CSF), IL-13, IL-10, and TGF-β [62, 73]. IL-10 secreted by M2 macrophages and Th2 lymphocytes was shown to enhance expression of the programmed cell death-1 receptor ligand (PD-L1) that finally results in reduction of cytotoxicity and suppression of $CD8^+$ cell proliferation in the human body [74].

Role in tissue regeneration. The type-2 IIR is specific for the second phase of tissue regeneration. During the early phase of inflammation, macrophages and neutrophils prevent the development of infection and tissue necrosis, but during transition of the wound healing to the second phase – the proliferation – macrophages acquire the anti-inflammatory M2-phenotype. The growth factors produced by them, e.g. TGF-β, promote the recruiting of fibroblast progenitors into the neighboring tissue, their activation, and transformation to myofibroblasts (activated fibroblasts) expressing α-smooth muscle actin (α-SMA). Myofibroblasts are responsible for the complete closure of the wound. It has been shown in various *in vivo* and *in vitro* models that IL-4, IL-13, platelet-derived growth factor (PDGF), and osteopontin are also involved in fibrogenesis [73]. Moreover, VEGF production mediates the recruitment of endothelial cell progenitors, which are involved in the formation of new vessels [75]. The ability to induce EMT is a key feature of the myofibroblast/activated fibroblast as a key stage of the repair of the injured epidermis and mucosa epithelium [73].

The role of macrophage polarization in tissue regeneration is usually studied *in vitro* in cell cultures and *in vivo* in mouse models. Thus, M2 macrophages are shown to promote wound healing and tissue repair due to synthesis of high levels of anti-inflammatory cytokines IL-10 and TGF-β and of low levels of IL-12, that suppresses the inflammatory response [76].

Involvement in tumor growth. B lymphocytes and antibodies and cytokines produced by them play an ambiguous role in tumorigenesis because of their functional heterogeneity. Some effects of B lymphocytes promote tumor progression. The detection of B cells in the ascitic fluid in human ovary cancer correlates with poor prognosis, and the number of these cells decreases in chemotherapy [77]. It has been shown in 4T1 carcinoma of the breast that B lymphocytes synthesizing TGF-β and

IL-10 can promote differentiation and recruiting of Tregs, which strengthens the immunosuppressive microenvironment of the tumor [78]. In patients with colorectal cancer, B cells inhibit the cytotoxic response of T cells. Antitumor antibodies activating granulocytes and macrophages can promote the tumor invasive growth through modification of the intercellular matrix and stimulation of angiogenesis [79].

However, antitumor effects of a B lymphocyte subpopulation with the CD27 phenotype of memory cells were also observed. The infiltration of human ovary cancer stroma by these cells combined with $CD8^+$ T cells is a favorable prognostic factor [80]. An increase in peritumoral infiltration of B lymphocytes after the injection of IL-12 into the tumor correlates with increased survival of patients with head and neck cancer [81]. It is believed that the presence of B lymphocytes in the tumor is associated with more favorable prognosis of the disease if these cells are structural components of the tertiary lymphoid structures [82, 83].

Hypoxia or necrosis can cause accumulation in the tumor of tumor-associated macrophages (TAMs) due to such hypoxia-induced factors as VEGF and endothelial monocyte-activating polypeptide II (EMAP2) [84]. TAMs have the M2 phenotype and belong to the M2d subtype [62]. In the human body, TAMs with the M2 phenotype have low ability to present antigens and can suppress the "cellular" Th1 response, releasing such immunosuppressive factors as TGF-β, IL-10, and prostaglandin E2 (PGE2). They are also capable of secreting growth factors (epidermal growth factor (EGF) and IL-6) and angiogenesis factors (VEGF and TGF-α) and of producing matrix metalloproteinases (MMPs), which destroy the extracellular matrix (ECM), and chemokines, which can attract cells participating in inflammation (CCL17, CXCL8, CCL18, or CCL22) [62].

Different chemokines and their receptors, e.g. CCR2/CCL2, CCR5/CCL5, CXCR2/CXCL5, and CXCR4/CXCL12, can promote tumor progression through increasing the formation, recruiting, and suppressive activity of TAMs and MDSC. Thus, CCL5 shifts the balance between various types of cells increasing the presence of TAMs, which secrete proangiogenic factors, suppress the antitumor response, and inhibit the antitumor activity of T cells [85].

The stimulation of polymorphonuclears (PMN) by TGF-β polarizes them to the N2 phenotype (N2 TAN) with an increased expression of arginase and CCL2 and CCL5 chemokines. N2 TANs suppress the cytotoxic reaction of the $CD8^+$ T lymphocytes that allows the tumor cells to escape immune supervision. Thus, N2 neutrophils demonstrate their pro-tumor features. It has been shown in *in vivo* models that MMP-9, oncostatin M, CXCL8 (IL-8), and Bv8 produced by neutrophils are associated with the promotion of angiogenesis [86].

There are data indicating the ability of tumor-associated fibroblasts to maintain tumor growth and metastasis through recruiting immune cells, such as TAMs, myeloid suppressor cells, and Treg lymphocytes. Experiments *in vivo* in mouse 4T1 breast carcinoma have shown that the removal of TAMs from the microenvironment leads to immune response polarization towards Th1 [87]. An increase in the TAM density is observed on the invasive front of human cholangiocarcinoma [88].

Thus, the main effects of the Th2-type immune-inflammatory response promote the development of the productive phase of the inflammatory response, termination of the tissue regeneration, and under conditions of tumorigenesis lead to formation of a microenvironment that mainly maintains tumor growth and progression.

IMMUNOSUPPRESSIVE RESPONSES MEDIATED BY Tregs, MDSCs, AND DCs

General data. Under certain conditions, the development of immune-inflammatory responses is modified by participation of Tregs, MDSCs, and DCs. Tregs express the transcription factor Foxp3 and are a subtype of T cells necessary for maintenance of the human immune system homeostasis. It is believed that under normal conditions these cells prevent the immune system response against self-antigens; moreover, that these cells can suppress the activity of the myeloid cell subpopulation [89].

The Treg population includes cells different in phenotype, profile of secreted cytokines, and suppression mechanisms. In the human body, such populations of Tregs as $CD8^+$ Tregs, $CD4^+$ Tregs, and γδ Tregs have been described. Under the influence of TGF-β combined with the TCR-mediated stimulation, naïve $CD4^+$ T cells can differentiate into Tregs [89]. Using some mechanisms, Tregs can suppress the proliferation and effector functions of many cells of the immunity system: CD4, CD8, NKs, NKTs, DCs, macrophages, and B cells. First, $Foxp3^+$ Tregs can suppress effector T cells due to secretion of inhibitory cytokines, such as IL-10 and TGF-β1. Second, $CD25^{high}$ Foxp3-positive regulatory T lymphocytes competitively bind IL-2 and thus deprive the Foxp3-negative T cells of the proliferative stimulus. Finally, Tregs can directly eliminate the effector T cells via the perforin/granzyme-dependent pathway [90]. In *in vitro* experiments, the suppressive effect of Tregs depended on the presence of intercellular contact at a short distance [91].

Tregs can suppress effector functions of Th17 lymphocytes. $CD45RA^+$ and $CD45RA^-$ Tregs suppress the proliferative activity of Th17 cells and production of IL-17, IL-22, and CXCL8. $CD45RA^+$ Tregs also suppress antifibrotic effects of Th17 lymphocytes [92].

Thus, the Treg population is heterogenous. First, Tregs are different in suppressive effects on $CD8^+$ lym-

phocytes and other effector T cells. Second, there are Tregs either associated or unassociated with antigen recognition. Third, Tregs are subdivided into suppressors and non-suppressors.

Role in tissue regeneration. It has been shown in Rag1-deficient mice that the regulatory $CD4^+CD25^+$ T cells promote tissue regeneration, suppressing inflammation *in situ* [93]. It seems that the main functions of Tregs are termination of the acute phase of inflammation arising in tissue damage and transition to the second phase – tissue regeneration. This function is based on the *in vivo* ability of TGF-β to initiate the differentiation of $CD4^+CD25^+Foxp3^+$ Tregs, which, in turn, secrete the "anti-inflammatory" Th2 cytokines IL-10 and TGF-β that can promote fibrosis [89].

Involvement in tumor growth. Tumor cells of various human carcinomas were shown to attract $CD4^+CD25^+Foxp3^+$ T lymphocytes due to such chemokines as CCL22, CCL5, CCL28, and CXCL12 and to stimulate secretion of cytokines by Tregs [94]. It was also shown in the mouse breast carcinoma D2F2 cell line that injection into the tumor of flagellin interacting with TLR5 accelerates the tumor growth, which was associated with a decrease in IFN-γ production and increase in the number of Tregs [95]. Increased number of Tregs in the tumor microenvironment and in peripheral blood is related to tumor progression particularly metastasis and considered as a poor prognostic factor [89].

In tumorigenesis, the role of Tregs is ambiguous. Tregs infiltrating the tumor stroma in patients with hepatocellular carcinoma inhibit the $CD8^+$ T cellular response [96]. In patients with breast cancer, Tregs actively suppress such effector immune cells as NKs, CD8, and $CD4^+CD25^-$ T cells [89, 97]. In the tumor, Foxp3 cells can be subdivided into suppressor and non-suppressor populations based on the expression level of CD39, which is responsible for the suppressive activity of the cells. Non-suppressor $Foxp3^+$ Tregs can secrete proinflammatory cytokines and are associated with more favorable prognosis in the case of human colorectal cancer [98]. Synergism of some effects of the "proinflammatory" Th2-type stromal microenvironment of the tumor and the presence of Tregs in the stroma explains the unfavorable prognostic significance of these cells in the cancer.

Another subpopulation of suppressor cells, which is termed myeloid suppressor cells, is a heterogeneous population including macrophages, progenitors of myeloid cells, immature granulocytes, and dendritic cells. MDSCs inhibit T-cellular responses and functions of NK cells via the NKp30 receptor. In patients with hepatocellular carcinoma, MDSCs induce an immunosuppressive effect due to induction of regulatory T cells and suppression of functions of NK cells [99].

Role in tissue regeneration. *MDSCs* are known to display not only suppressive but also pronounced proangiogenic effects. The angiogenesis and immune suppression are significantly determined by participation of the same molecular and cellular mediators [100]. Among blood monocytes, inflammatory/classic ($CCR2^+$ $Ly6C^{high}$) and resident/non-classic (CCR2 $Ly6C^{low}$) monocytes are distinguished. VEGF-A expressed by the inflammatory subpopulation of monocytes, which are recruited through CCR2, plays a decisive role in the early formation of vessels *in vivo*, whereas VEGF-A of epidermal origin mediates vascularization during the late phase of wound healing [101].

Involvement of tumor growth. Myeloid suppressor cells can mediate the immune suppression in tumors. Thus, MDSCs can induce the development of Tregs and polarization of macrophages to the TAM-like phenotype both *in vitro* and *in vivo* [102]. It is thought that the main effect of the tumor-associated myeloid cells in the primary tumor and, possibly, in metastatic tumors is just the immune suppression and defense of the tumor cells from the immune response. In the human body, $Gr1^+CD11b^+$ myeloid cells produce TGF-β, which suppresses functioning of cytotoxic $CD8^+$ T lymphocytes and inhibits the natural cytotoxicity cells, B lymphocytes, and dendritic cells [103]. MDSCs inhibit the activity of $CD8^+$ T cells also through the expression of NOS and arginase [104].

DCs. There are numerous data on plasticity of DCs, which can acquire tolerogenic or immunogenic phenotypes depending on the microenvironment signals [105]. Subpopulations of immature DCs that do not have costimulating molecules and cytokine signals induce tolerance of the antigen-specific $CD4^+$ and $CD8^+$ T lymphocytes. However, it has also been shown that in human, myeloid and plasmacytoid DCs can synergically induce the cytotoxicity of NK cells [106].

Thus, immunosuppressive Tregs, similarly to the MDSCs and DCs within the tumor stroma, can promote survival of the tumor cells and their growth and progression.

ROLE OF Th17 LYMPHOCYTES IN IMMUNE-INFLAMMATORY RESPONSES

General data. In the human body, Th17 lymphocytes are differentiated from the naïve $CD4^+$ T cells under the influence of TGF-β and IL-6 and for a long time exist in the presence of IL-21 and IL-23 [107]. Some observations have indicated that under certain conditions the activation by PAMPs of signaling pathways through TLRs results in differentiation of Th17 lymphocytes. Thus, initiation of the signaling pathway in naïve human $CD4^+$ T lymphocytes through TLR2, TLR3, TLR4, and TLR9 promotes the Th17 response [108, 109]. Under natural conditions, the Th17 lymphocyte subpopulation is the main source of IL-17A [108].

In addition to IL-17, Th17 lymphocytes produce TNF, IL-6, IL-22, IL-21, and IL-26, but they do not

secrete IFN-γ or IL-4 [108]. Due to the action of IL-17 on tissues, the production by human endothelial cells of cyclooxygenase-2 (COX-2)/PGE2 and iNOS can be increased [110]. Note that PGE2 acts on naïve T cells through the signaling pathways mediated by PGE2 receptors (EP2 and EP4) that lead to stimulation of the IL-23 and IL-1 expression [108].

Th17 lymphocytes produce the CCL20 chemokine, which causes recruitment of neutrophils and monocytes into sites of T cell activation. Proinflammatory Th17 lymphocytes are involved in protection against extracellular bacteria [108].

Role in tissue regeneration. It was shown in the model of skin wound healing in C57BL/6 mice and in experiments on human tissues *in vitro* that Th17 cytokines (IL-22, IL-17A, and IL-17F) decelerated wound healing [111]. In another study, Th17 lymphocytes were shown to prevent fibrosis development in humans, similarly to Th1 cells [92].

Involvement in tumor growth. It has been shown that Th17 lymphocytes can both promote and prevent tumor growth. Some studies demonstrated an increase in the number of lymphocytes with the Th17 phenotype in the tumor microenvironment, as well as the ability of IL-17 to stimulate the production of proinflammatory cytokines and proangiogenic factors maintaining the tumor development [112]. On the other hand, it has been observed in experiments that the adaptive transfer of Th17 lymphocytes leads to regression of melanoma [71].

A high degree of tumor infiltration with Th17 lymphocytes in patients with colon and pancreatic cancer correlates with unfavorable prognosis [112]. In patients with high grade hepatocellular carcinoma and poor survival, the number of Th17 lymphocytes in the tumor was increased and their expression of IL-22 was strengthened [58]. On the contrary, a decrease in the number of Th17 lymphocytes in ovarian tumor was associated with better survival of the patients [112]. Moreover, Th17 lymphocytes are known to be involved in formation of TLSs [113], whose appearance is associated with more favorable course of various carcinomas [15]. In esophageal cancer, the presence of Th17 lymphocytes in the microenvironment is associated with favorable prognosis [114].

Some action mechanisms of Th17 lymphocytes have been described that can mediate the tumor progression. Thus, the secretion of IL-17 leads to stimulation of angiogenesis in colorectal cancer due to production of VEGF by the tumor cells [115]. Moreover, IL-17 can promote tumor growth of B16 melanoma cell lines and of MB49 bladder carcinoma through the IL-6-Stat3-signaling pathway [116]. The antitumor influence of Th17 lymphocytes can be realized through the activation of cytotoxic T lymphocytes in the tumor, production of IFN-γ and TNF, IL-21 and IL-12 and of GM-CSF [117]. The ambivalence of Th17 lymphocytes can be based on differences in the phenotypes of these cells, which are regulated on the level of activation of signaling pathways of protein kinase B (PKB) and protein kinase called mammalian target of rapamycin (mTOR) [118].

The stroma of most malignant tumors is unequally infiltrated with different leukocyte forms. From the standpoint of pathology, it is a persistent chronic inflammation. Tissue regeneration ("wound healing") is a pathophysiological prototype revealing the essence of immune-inflammatory responses occurring within the tumor stroma. That is why the tumor is called an "open wound". The second phase of "healing" characterized by angiogenesis, fibrogenesis, and formation of the extracellular matrix occurs with involvement of M2 macrophages, activated fibroblasts, and on damage of the epithelium – with development of EMT under the influence of TGF-β. All these events are specific for the Th2-type of the immune-inflammatory response. The second phase of repair can be successfully realized only upon termination of the first "inflammatory" phase of "healing", which is characterized by phagocytosis of pathogens and necrotic debris by M1 macrophages and N1 neutrophils and by synthesis of IFN-γ promoting the completion of phagocytosis. These processes characterize the Th1-type immune-inflammatory response. In the case of a successful "wound healing", the Th1- and Th2-type immune-inflammatory response phases change regularly. It seems that under these conditions one of the main mechanisms responsible for the change of rather antagonistic forms of immune-inflammatory responses is the macrophage plasticity, particularly M1 transformation into M2. The ability of macrophages for autocrine regulation mediated by IL-10 synthesis seems to be a mechanism for switching the Th1 immune-inflammatory response to the Th2-type.

Some studies have shown that the local Th1 response is favorable for the cancer outcome, whereas the Th2 response and presence in the peritumoral infiltrate of T regulatory lymphocytes is associated with poor prognosis. The identity is obvious of the events specific for the first phase of "wound healing" and inhibition of the tumor progression, on one hand, and of those specific for the second phase and stimulation of tumor invasion and metastasizing, on the other hand. Moreover, the more sufficient are responses of the innate and adaptive immune systems, the more likely the Th1-type response within the tissue regeneration will be replaced by the Th2-type with the corresponding unfavorable consequences if these processes are developed in the tumor stroma as a result of its damage due to any cause.

Speaking to the point, stroma infiltration is an integral reflection of adaptive immune effector responses to antigens of the tumor and of the inflammation initiated by the innate immunity mechanisms. The inflammatory infiltrate cells are the most important component of the tumor microenvironment. The immune-inflammatory response initiated by the innate immunity mechanisms is

triggered by DAMPs of the necrotic tumor tissue. This necrosis can be caused by an abnormal angiogenesis, vascular thrombosis, immune destruction, and cell death caused by radio- or chemotherapy. RAMPs of microorganisms occasionally infecting the tumor can be another cause.

On consideration of different aspects of the immune system and inflammation roles in the progression of malignant tumors, attention is usually focused on subpopulations of lymphocytes, macrophages, neutrophils, and fibroblasts, as well as on cytokines, chemokines, adhesion molecules, etc. In connection with such approach, definite molecules are chosen as therapeutic targets and prognostic and predictive markers. Although it is implied that molecular and cellular events occur within definite variants of immunogenesis or inflammation, such approach extremely lacks the generalizations. However, it seems that diagnosis of the immune-inflammatory response type, as a whole would be more productive. Since at different times the immune-inflammatory response can be represented by different cells and molecules, at a certain moment "diagnostic" cells and molecules can be temporarily absent that can be falsely interpreted as "unfavorable" or "favorable" factors. Therefore, the consideration of the immune-inflammatory response type as a target for the therapy or as a prognostic factor can significantly reduce errors on the assessment of significance of the stromal immune-inflammatory responses.

Most researchers believe that favorable effect is mediated by developing specific cytotoxic immune responses. This idea is supported by numerous data on the presence in tumors of antigens capable of inducing the immune response. However, it is well known that more often spontaneous immune responses are not sufficiently effective. Therefore, we think that the favorable effect is more likely associated with the Th1-type "proinflammatory" immune response in the microenvironment independently of the presence or absence of specific immune responses to the tumor antigens. It seems that the set of cytokines secreted by the cells involved in the Th1-type immune-inflammatory response leads to antagonistic suppression of the Th2-type immune response with participation of M2 macrophages, N2 neutrophils, and the tumor-associated fibroblasts. The Th2-type anti-inflammatory phenotype of immune-inflammatory response, which promotes the tumor progression, creates in the tumor favorable conditions for development of tissue repair and epithelial–mesenchymal transition that is necessary for invasion and metastasis of the tumor cells. Effects of Th17 and Treg cells, unlike effects of Th1 and Th2 lymphocytes, are ambiguous and depend on their ability to promote or to prevent the development of these variants of immune-inflammatory responses.

Thus, it is very likely that the observed favorable effect of the tumor microenvironment with the Th1-type immune-inflammatory response is mainly based on nonspecific mechanisms unrelated with recognition of the tumor antigens and is manifested in the antagonistic influence on the development of the Th2-type immune-inflammatory response.

Acknowledgments

The work was supported by the Russian Science Foundation (project No. 16-15-10221).

REFERENCES

1. Coussens, L. M., and Werb, Z. (2002) Inflammation and cancer, *Nature*, **420**, 860-867.
2. Grivennikov, S. I., Greten, F. R., and Karin, M. (2010) Immunity, inflammation, and cancer, *Cell*, **140**, 883-899.
3. Burgio, E., and Migliore, L. (2015) Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics, *Mol. Biol. Rep.*, **42**, 777-790.
4. Khansari, N., Shakiba, Y., and Mahmoudi, M. (2009) Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer, *Recent Pat. Inflamm. Allergy Drug Discov.*, **3**, 73-80.
5. Khan, S., Jain, M., Mathur, V., and Feroz, S. M. (2016) Chronic inflammation and cancer: paradigm on tumor progression, metastasis and therapeutic intervention, *Gulf J. Oncol.*, **1**, 86-93.
6. Bondar, T., and Medzhitov, R. (2013) The origins of tumor-promoting inflammation, *Cancer Cell*, **24**, 143-144.
7. Rakoff-Nahoum, S., and Medzhitov, R. (2008) Role of toll-like receptors in tissue repair and tumorigenesis, *Biochemistry (Moscow)*, **73**, 555-561.
8. Dvorak, H. F. (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing, *N. Engl. J. Med.*, **315**, 1650-1659.
9. Eming, S. A., Krieg, T., and Davidson, J. M. (2007) Inflammation in wound repair: molecular and cellular mechanisms, *J. Invest. Dermatol.*, **127**, 514-525.
10. Blanpain, C., and Fuchs, E. (2014) Stem cell plasticity. Plasticity of epithelial stem cells in tissue regeneration, *Science*, **344**, 1242281.
11. Arnold, K. M., Opdenaker, L. M., Flynn, D., and Sims-Mourtada, J. (2015) Wound healing and cancer stem cells: inflammation as a driver of treatment resistance in breast cancer, *Cancer Growth Metast.*, **8**, 1-13.
12. Arbach, H., Viglasky, V., Lefeu, F., Guinebretiere, J.-M., Ramirez, V., Bride, N., Boualaga, N., Bauchet, T., Peyrat, J.-P., Mathieu, M.-C., Mourah, S., Podgorniak, M.-P., Seignerin, J.-M., Takada, K., and Joab, I. (2006) Epstein–Barr virus (EBV) genome and expression in breast cancer tissue: effect of EBV infection of breast cancer cells on resistance to paclitaxel (Taxol), *J. Virol.*, **80**, 845-853.
13. Li, Y. Y., Ge, Q. X., Cao, J., Zhou, Y. J., Du, Y. L., Shen, B., Wan, Y. J., and Nie, Y. Q. (2016) Association of *Fusobacterium nucleatum* infection with colorectal cancer in Chinese patients, *World J. Gastroenterol.*, **22**, 3227-3233.
14. Zhang, Q., Jia, Q., Deng, T., Song, B., and Li, L. (2015) Heterogeneous expansion of $CD4^+$ tumor-infiltrating T-

lymphocytes in clear cell renal cell carcinomas, *Biochem. Biophys. Res. Commun.*, **458**, 70-76.
15. Dieu-Nosjean, M. C., Goc, J., Giraldo, N. A., Sautes-Fridman, C., and Fridman, W. H. (2014) Tertiary lymphoid structures in cancer and beyond, *Trends Immunol.*, **35**, 571-580.
16. Brucklacher-Waldert, V., Carr, E. J., Linterman, M. A., and Veldhoen, M. (2014) Cellular plasticity of $CD4^+$ T cells in the intestine, *Front. Immunol.*, **5**, 488-499.
17. Caza, T., and Landas, S. (2015) Functional and phenotypic plasticity of $CD4^+$ T cell subsets, *Biomed Res. Int.*, 521957.
18. Werb, Z., and Lu, P. (2015) The role of stroma in tumor development, *Cancer J.*, **21**, 250-253.
19. Portou, M. J., Baker, D., Abraham, D., and Tsui, J. (2015) The innate immune system, Toll-like receptors and dermal wound healing: a review, *Vascul. Pharmacol.*, **71**, 31-36.
20. Moore, K. W., De Waal Malefyt, R., Coffman, R. L., and O'Garra, A. (2001) Interleukin-10 and the interleukin-10 receptor, *Annu. Rev. Immunol.*, **19**, 683-765.
21. Sionov, R. V., Fridlender, Z. G., and Granot, Z. (2015) The multifaceted roles neutrophils play in the tumor microenvironment, *Cancer Microenviron.*, **8**, 125-158.
22. Artis, D., and Spits, H. (2015) The biology of innate lymphoid cells, *Nature*, **517**, 293-301.
23. Bernink, J. H., Peters, C. P., Munneke, M., te Velde, A. A., Meijer, S. L., Weijer, K., Hreggvidsdottir, H. S., Heinsbroek, S. E., Legrand, N., Buskens, C. J., Bemelman, W. A., Mjosberg, J. M., and Spits, H. (2013) Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues, *Nat. Immunol.*, **14**, 221-229.
24. Neill, D. R., Wong, S. H., Bellosi, A., Flynn, R. J., Daly, M., Langford, T. K., Bucks, C., Kane, C. M., Fallon, P. G., Pannell, R., Jolin, H. E., and McKenzie, A. N. (2010) Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity, *Nature*, **464**, 1367-1370.
25. Buonocore, S., Ahern, P. P., Uhlig, H. H., Ivanov, I. I., Littman, D. R., Maloy, K. J., and Powrie, F. (2010) Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology, *Nature*, **464**, 1371-1375.
26. Vremec, D., and Shortman, K. (2015) What's in a name? Some early and current issues in dendritic cell nomenclature, *Front. Immunol.*, **6**, 267.
27. Nizzoli, G., Krietsch, J., Weick, A., Steinfelder, S., Facciotti, F., Gruarin, P., Bianco, A., Steckel, B., Moro, M., Crosti, M., Romagnani, C., Stolzel, K., Torretta, S., Pignataro, L., Scheibenbogen, C., Neddermann, P., De Francesco, R., Abrignani, S., and Geginat, J. (2013) Human $CD1c^+$ dendritic cells secrete high levels of IL-12 and potently prime cytotoxic T-cell responses, *Blood*, **122**, 932-942.
28. Hemont, C., Neel, A., Heslan, M., Braudeau, C., and Josien, R. (2013) Human blood mDC subsets exhibit distinct TLR repertoire and responsiveness, *J. Leukoc. Biol.*, **93**, 599-609.
29. Suga, H., Sugaya, M., Fujita, H., Asano, Y., Tada, Y., Kadono, T., and Sato, S. (2014) TLR4, rather than TLR2, regulates wound healing through TGF-β and CCL5 expression, *J. Dermatol. Sci.*, **73**, 117-124.
30. Spits, H., and Di Santo, J. P. (2011) The expanding family of innate lymphoid cells: regulators and effectors of immunity and tissue remodeling, *Nat. Immunol.*, **12**, 21-27.
31. Gonzalez-Reyes, S., Marin, L., Gonzalez, L., Gonzalez, L. O., del Casar, J. M., Lamelas, M. L., Gonzalez-Quintana, J. M., and Vizoso, F. J. (2010) Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis, *BMC Cancer*, **10**, 665.
32. Voelcker, V., Gebhardt, C., Averbeck, M., Saalbach, A., Wolf, V., Weih, F., Sleeman, J., Anderegg, U., and Simon, J. (2008) Hyaluronan fragments induce cytokine and metalloprotease upregulation in human melanoma cells in part by signaling via TLR4, *Exp. Dermatol.*, **17**, 100-107.
33. Liao, S. J., Zhou, Y. H., Yuan, Y., Li D., Wu, F. H., Wang, Q., Zhu, J. H., Yan, B., Wei, J. J., Zhang, G. M., and Feng Z. H. (2012) Triggering of Toll-like receptor 4 on metastatic breast cancer cells promotes αvβ3-mediated adhesion and invasive migration, *Breast Cancer Res. Treat.*, **133**, 853-863.
34. Jing, Y. Y., Han, Z. P., Sun, K., Zhang, S. S., Hou, J., Liu, Y., Li, R., Gao, L., Zhao, X., Zhao, Q. D., Wu, M. C., and Wei, L. X. (2012) Toll-like receptor 4 signaling promotes epithelial-mesenchymal transition in human hepatocellular carcinoma induced by lipopolysaccharide, *BMC Med.*, **10**, 98.
35. Liu, C. Y., Xu, J. Y., Shi, X. Y., Huang, W., Ruan, T. Y., Xie, P., and Ding, J. L. (2013) M2-polarized tumor-associated macrophages promoted epithelial-mesenchymal transition in pancreatic cancer cells, partially through TLR4/IL-10 signaling pathway, *Lab. Invest.*, **93**, 844-854.
36. Elinav, E., Nowarski, R., Thaiss, C. A., Hu, B., Jin, C., and Flavell, R. A. (2013) Inflammation-induced cancer: crosstalk between tumors, immune cells and microorganisms, *Nat. Rev. Cancer*, **13**, 759-771.
37. Gajewski, F., Schreiber, H., and Fu, Y.-X. (2013) Innate and adaptive immune cells in the tumor microenvironment, *Nat. Immunol.*, **14**, 1014-1022.
38. Balkwill, F. R., Capasso, M., and Hagemann, T. (2012) The tumor microenvironment at a glance, *J. Cell Sci.*, **125**, 5591-5596.
39. Shields, J. D., Kourtis, I. C., Tomei, A. A., Roberts, J. M., and Swartz, M. A. (2010) Induction of lymphoid-like stroma and immune escape by tumors that express the chemokine CCL21, *Science*, **328**, 749-752.
40. Eisenring, M., vom Berg, J., Kristiansen, G., Saller, E., and Becher, B. (2010) IL-12 initiates tumor rejection via lymphoid tissue-inducer cells bearing the natural cytotoxicity receptor NKp46, *Nat. Immunol.*, **11**, 1030-1038.
41. Braumuller, H., Wieder, T., Brenner, E., Abmann, S., Hahn, M., Alkhaled, M., Schilbach, K., Essmann, F., Kneilling, M., Griessinger, C., Ranta, F., Ullrich, S., Mocikat, R., Braungart, K., Mehra, T., Fehrenbacher, B., Berdel, J., Niessner, H., Meier, F., van den Broek, M., Haring, H. U., Handgretinger, R., Quintanilla-Martinez, L., Fend, F., Pesic, M., Bauer, J., Zender, L., Schaller, M., Schulze-Osthoff, K., and Rocken, M. (2013) T-helper-1-cell cytokines drive cancer into senescence, *Nature*, **494**, 361-365.
42. Tachibana, T., Onodera, H., Tsuruyama, T., Mori, A., Nagayama, S., Hiai, H., and Imamura, M. (2005) Increased intratumor Valpha24-positive natural killer T cells: a prognostic factor for primary colorectal carcinomas, *Clin. Cancer Res.*, **11**, 7322-7327.
43. Fridman, W. H., Pages, F., Sautes-Fridman, C., and Galon, J. (2012) The immune contexture in human

tumors: impact on clinical outcome, *Nat. Rev. Cancer*, **12**, 298-306.
44. Jia, L, and Wu, C. (2014) The biology and functions of Th22 cells, *Adv. Exp. Med. Biol.*, **841**, 209-230.
45. Fujita, H., Nograles, K. E., Kikuchi, T., Gonzalez, J., Carucci, J. A., and Krueger, J. G. (2009) Human Langerhans cells induce distinct IL-22-producing $CD4^+$ T cells lacking IL-17 production, *Proc. Natl. Acad. Sci. USA*, **106**, 21795-21800.
46. Simonian, P. L., Wehrmann, F., Roark, C. L., Born, W. K., O'Brien, R. L., and Fontenot, A. P. (2010) γδ T cells protect against lung fibrosis via IL-22, *J. Exp. Med.*, **207**, 2239-2253.
47. Wolk, K., Kunz, S., Asadullah, K., and Sabat, R. (2002) Cutting edge: immune cells as sources and targets of the IL-10 family members? *J. Immunol.*, **168**, 5397-5402.
48. Sabat, R., Witte, E., Witte, K., and Wolk, K. (2013) in *IL-17, IL-22 and Their Producing Cells: Role in Inflammation and Autoimmunity*, Springer, Basel, pp. 3-131.
49. Wolk, K., Witte, E., Witte, K., Warszawska, K., and Sabat, R. (2010) Biology of interleukin-22, *Semin. Immunopathol.*, **32**, 17-31.
50. Eyerich, S., Eyerich, K., Pennino, D., Carbone, T., Nasorri, F., Pallotta, S., Cianfarani, F., Odorisio, T., Traidl-Hoffmann, C., Behrendt, H., Durham, S. R., Schmidt-Weber, C. B., and Cavani, A. (2009) Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling, *J. Clin. Invest.*, **119**, 3573-3585.
51. McGee, H. M., Schmidt, B. A., Booth, C. J., Yancopoulos, G. D., Valenzuela, D. M., Murphy, A. J., Stevens, S., Flavell, R. A., and Horsley, V. (2013) IL-22 promotes fibroblast-mediated wound repair in the skin, *J. Invest. Dermatol.*, **133**, 1321-1329.
52. Reuss, B., Dono, R., and Unsicker, K. (2003) Functions of fibroblast growth factor (FGF)-2 and FGF-5 in astroglial differentiation and blood-brain barrier permeability: evidence from mouse mutants, *J. Neurosci.*, **23**, 6404-6412.
53. Varga, J., and Abraham, D. (2007) Systemic sclerosis: a prototypic multisystem fibrotic disorder, *J. Clin. Invest.*, **117**, 557-567.
54. Hwang, J., Son, K. N., Kim, C. W., Ko, J., Na, D. S., Kwon, B. S., Gho, Y. S., and Kim, J. (2005) Human CC chemokine CCL23, a ligand for CCR1, induces endothelial cell migration and promotes angiogenesis, *Cytokine*, **30**, 254-263.
55. Kirchberger, S., Royston, D. J., Boulard, O., Thornton, E., Franchini, F., Szabady, R. L., Harrison, O., and Powrie, F. (2013) Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model, *J. Exp. Med.*, **210**, 917-931.
56. Takahashi, H., Numasaki, M., Lotze, M. T., and Sasaki, H. (2005) Interleukin-17 enhances bFGF, HGF- and VEGF-induced growth of vascular endothelial cells, *Immunol. Lett.*, **98**, 189-193.
57. Numasaki, M., Fukushi, J., Ono, M., Narula, S. K., Zavodny, P. J., Kudo, T., Robbins, P. D., Tahara, H., and Lotze, M. T. (2003) Interleukin-17 promotes angiogenesis and tumor growth, *Blood*, **101**, 2620-2627.
58. Liao, Y., Wang, B., Huang, Z. L., Shi, M., Yu, X. J., Zheng, L., Li, S., and Li, L. (2013) Increased circulating Th17 cells after transarterial chemoembolization correlate with improved survival in stage III hepatocellular carcinoma: a prospective study, *PLoS One*, **8**, e60444.
59. Zhu, J., and Paul, W. E. (2008) CD4 T cells: fates, functions, and faults, *Blood*, **112**, 1557.
60. Zhang, Y., Zhang, Y., Gu, W., He, L., and Sun, B. (2014) Th1/Th2 cell's function in immune system, *Adv. Exp. Med. Biol.*, **841**, 45.
61. Sica, A., and Mantovani, A. (2012) Macrophage plasticity and polarization: *in vivo* veritas, *J. Clin. Invest.*, **122**, 787-795.
62. Martinez, F. O., and Gordon, S. (2014) The M1 and M2 paradigm of macrophage activation: time for reassessment, *F1000Prime Rep.*, **6**, 13.
63. Scapini, P., Lapinet-Vera, J. A., Gasperini, S., Calzetti, F., Bazzoni, F., and Cassatella, M. A. (2000) The neutrophil as a cellular source of chemokines, *Immunol. Rev.*, **177**, 195-203.
64. Fridlender, Z. G., Sun, J., Kim, S., Kapoor, V., Cheng, G., Ling, L., Worthen, G. S., and Albelda, S. M. (2009) Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN, *Cancer Cell*, **16**, 183-194.
65. Sindrilaru, A., Peters, T., Wieschalka, S., Baican, C., Baican, A., Peter, H., Hainzl, A., Schatz, S., Qi, Y., Schlecht, A., Weiss, J. M., Wlaschek, M., Sunderkotter, C., and Scharffetter-Kochanek, K. (2011) An unrestrained proinflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice, *J. Clin. Invest.*, **121**, 985-997.
66. Barrientos, S., Stojadinovic, O., Golinko, M. S., Brem, H., and Tomic-Canic, M. (2008) Growth factors and cytokines in wound healing, *Wound Rep. Regen.*, **16**, 585-601.
67. Wieder, T., Braumuller, H., Kneilling, M., Pichler, B., and Rocken, M. (2008) T cell-mediated help against tumors, *Cell Cycle*, **7**, 2974-2977.
68. Hensbergen, P. J., Wijnands, P. G. B., Schreurs, M. W., Scheper, R. J., Willemze, R., and Tensen, C. P. (2005) The CXCR3 targeting chemokine CXCL11 has potent antitumor activity *in vivo* involving attraction of $CD8^+$ T lymphocytes but not inhibition of angiogenesis, *J. Immunother.*, **28**, 343-351.
69. Morishima, N., Owaki, T., Asakawa, M., Kamiya, S., Mizuguchi, J., and Yoshimoto, T. (2005) Augmentation of effector $CD8^+$ T cell generation with enhanced granzyme B expression by IL-27, *J. Immunol.*, **175**, 1686-1693.
70. Shen, M., Hu, P., Donskov, F., Wang, G., Liu, Q., and Du, J. (2014) Tumor-associated neutrophils as a new prognostic factor in cancer: a systematic review and meta-analysis, *PLoS One*, **9**, e98259.
71. Muranski, P., Boni, A., Antony, P. A., Cassard, L., Irvine, K. R., Kaiser, A., Paulos, C. M., Palmer, D. C., Touloukian, C. E., Ptak, K., Gattinoni, L., Wrzesinski, C., Hinrichs, C. S., Kerstann, K. W., Feigenbaum, L., Chan, C. C., and Restifo, N. P. (2008) Tumor-specific Th17-polarized cells eradicate large established melanoma, *Blood*, **112**, 362-373.
72. Roberts, S. J., Ng, B. Y., Filler, R. B., Lewis, J., Glusac, E. J., Hayday, A. C., Tigelaar, R. E., and Girardi, M. (2007) Characterizing tumor-promoting T cells in chemically induced cutaneous carcinogenesis, *Proc. Natl. Acad. Sci. USA*, **104**, 6770-6775.
73. Duffield, J. S., Lupher, M., Thannickal, V. J., and Wynn, T. A. (2013) Host responses in tissue repair and fibrosis, *Annu. Rev. Pathol.*, **8**, 241-276.

74. Kuang, D. M., Zhao, Q., Peng, C., Xu, J., Zhang, J. P., Wu, C., and Zheng, L. (2009) Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1, *J. Exp. Med.*, **206**, 1327-1337.
75. Eming, S. A., Martin, P., and Tomic-Canic, M. (2014) Wound repair and regeneration: mechanisms, signaling, and translation, *Sci. Transl. Med.*, **6**, 265.
76. Ferrante, C. J., and Leibovich, S. J. (2012) Regulation of macrophage polarization and wound healing, *Adv. Wound Care (New Rochelle)*, **1**, 10-16.
77. Dong, H. P., Elstrand, M. B., Holth, A., Silins, I., Berner, A., Trope, C. G., Davidson, B., and Risberg, B. (2006) NK- and B-cell infiltration correlates with worse outcome in metastatic ovarian carcinoma, *Am. J. Clin. Pathol.*, **125**, 451-458.
78. Olkhanud, P. B., Damdinsuren, B., Bodogai, M., Gress, R. E., Sen, R., Wejksza, K., Malchinkhuu, E., Wersto, R. P., and Biragyn, A. (2011) Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting $CD4^+$ T cells to T-regulatory cells, *Cancer Res.*, **71**, 3505-3515.
79. Barbera-Guillem, E., Nelson M. B., Barr, B., Nyhus, J. K., May, K. F., Jr., Feng, L., and Sampsel, J. W. (2000) B lymphocyte pathology in human colorectal cancer. Experimental and clinical therapeutic effects of partial B cell depletion, *Cancer Immunol. Immunother.*, **48**, 541-549.
80. Nielsen, J. S., Sahota, R. A., Milne, K., Kost, S. E., Nesslinger, N. J., Watson, P. H., and Nelson, B. H. (2012) $CD20^+$ tumor-infiltrating lymphocytes have an atypical $CD27^-$ memory phenotype and together with $CD8^+$ T cells promote favorable prognosis in ovarian cancer, *Clin. Cancer Res.*, **18**, 3281-3292.
81. Van Herpen, C. M., Van der Voort, R., Van der Laak, J. A., Klasen, I. S., De Graaf, A. O., Van Kempen, L. C., De Vries, I. J., Boer, T. D., Dolstra, H., and Torensma, R. (2008) Intratumoral rhIL-12 administration in head and neck squamous cell carcinoma patients induces B cell activation, *Int. J. Cancer*, **123**, 2354-2361.
82. Germain, C., Gnjatic, S., Tamzalit, F., Knockaert, S., Remark, R., Goc, J., Lepelley, A., Becht, E., Katsahian, S., and Bizouard, G. (2014) Presence of B cells in tertiary lymphoid structures is associated with a protective immunity in patients with lung cancer, *Am. J. Respir. Crit. Care Med.*, **189**, 832-844.
83. Germain, C., Gnjatic, S., and Dieu-Nosjean, M.-C. (2015) Tertiary lymphoid structure-associated B cells are key players in anti-tumor immunity, *Front. Immunol.*, **6**, 67.
84. Murdoch, C., Giannoudis, A., and Lewis, C. E. (2004) Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues, *Blood*, **104**, 2224-2234.
85. Mantovani, A., Sica, A., Sozzani, S., Allavena, P., Vecchi, A., and Locati, M. (2004) The chemokine system in diverse forms of macrophage activation and polarization, *Trends Immunol.*, **25**, 677-686.
86. Gregory, A. D., and Houghton, A. M. (2011) Tumor-associated neutrophils: new targets for cancer therapy, *Cancer Res.*, **71**, 2411-2416.
87. Liao, D., Luo, Y., Markowitz, D., Xiang, R., and Reisfeld, R. A. (2009) Cancer associated fibroblasts promote tumor growth and metastasis by modulating the tumor immune microenvironment in a 4T1 murine breast cancer model, *PLoS One*, **4**, e7965.
88. Atanasov, G., Hau, H. M., Dietel, C., Benzing, C., Krenzien, F., Brandl, A., Wiltberger, G., Matia, I., Prager, I., Schierle, K., Robson, S. C., Reutzel-Selke, A., Pratschke, J., Schmelzle, M., and Jonas, S. (2015) Prognostic significance of macrophage invasion in hilar cholangiocarcinoma, *BMC Cancer*, **15**, 790.
89. Beyer, M., and Schultze, J. L. (2006) Regulatory T cells in cancer, *Blood*, **108**, 804-811.
90. Bilate, A. M., and Lafaille, J. J. (2012) Induced $CD4^+Foxp3^+$ regulatory T cells in immune tolerance, *Annu. Rev. Immunol.*, **30**, 733-758.
91. Thornton, A. M., and Shevach, E. M. (1998) $CD4^+CD25^+$ immunoregulatory T cells suppress polyclonal T cell activation *in vitro* by inhibiting interleukin 2 production, *J. Exp. Med.*, **188**, 287-296.
92. Crome, S. Q., Clive, B., Wang, A. Y., Kang, C. Y., Chow, V., Yu, J., Lai, A., Ghahary, A., Broady, R., and Levings, M. K. (2010) Inflammatory effects of *ex vivo* human Th17 cells are suppressed by regulatory T cells, *J. Immunol.*, **185**, 3199-3208.
93. Murphy, T. J., Choileain, N. Ni., Zang, Y., Mannick, J. A., and Lederer, J. A. (2005) $CD4^+CD25^+$ regulatory T cells control innate immune reactivity after injury, *J. Immunol.*, **174**, 2957-2963.
94. Mailloux, A. W., and Young, M. R. (2010) Regulatory T-cell trafficking: from thymic development to tumor-induced immune suppression, *Crit. Rev. Immunol.*, **30**, 435-447.
95. Sfondrini, L., Rossini, A., Besusso, D., Merlo, A., Tagliabue, E., Menard, S., and Balsari, A. (2006) Antitumor activity of the TLR-5 ligand flagellin in mouse models of cancer, *J. Immunol.*, **176**, 6624-6630.
96. Huang, Y., Wang, F. M., Wang, T., Wang, Y. J., Zhu, Z. Y., Gao, Y. T., and Du, Z. (2012) Tumor-infiltrating $FoxP3^+$ Tregs and $CD8^+$ T cells affect the prognosis of hepatocellular carcinoma patients, *Digestion*, **86**, 329-337.
97. Leong, P. P., Mohammad, R., Ibrahim, N., Ithnin, H., Abdullah, M., Davis, W. C., and Seow, H. F. (2006) Phenotyping of lymphocytes expressing regulatory and effector markers in infiltrating ductal carcinoma of the breast, *Immunol. Lett.*, **102**, 229-236.
98. Lin, Y. C., Mahalingam, J., Chiang, J. M., Su, P. J., Chu, Y. Y., Lai, H. Y., Fang, J. H., Huang, C. T., Chiu, C. T., and Lin, C. Y. (2013) Activated but not resting regulatory T cells accumulated in tumor microenvironment and correlated with tumor progression in patients with colorectal cancer, *Int. J. Cancer*, **132**, 1341-1350.
99. Hoechst, B., Voigtlaender, T., Ormandy, L., Gamrekelashvili, J., Zhao, F., Wedemeyer, H., Lehner, F., Manns, M. P., Greten, T. F., and Korangy, F. (2009) Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor, *Hepatology*, **50**, 799-807.
100. Motz, G. T., and Coukos, G. (2011) The parallel lives of angiogenesis and immunosuppression: cancer and other tales, *Nat. Rev. Immunol.*, **11**, 702-711.
101. Willenborg, S., Lucas, T., van Loo, G., Knipper, J. A., Krieg, T., Haase, I., Brachvogel, B., Hammerschmidt, M., Nagy, A., Ferrara, N., Pasparakis, M., and Eming, S. A. (2012) CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair, *Blood*, **120**, 613-625.

102. Huang, B., Pan, P. Y., Li, Q., Sato, A. I., Levy, D. E., Bromberg, J., Divino, C. M., and Chen, S. H. (2006) Gr-1^{+}CD115^{+} immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell energy in tumor-bearing host, *Cancer Res.*, **66**, 1123-1131.
103. Yang, L., and Moses, H. L. (2008) Transforming growth factor beta: tumor suppressor or promoter? Are host immune cells the answer? *Cancer Res.*, **68**, 9107-9111.
104. Bronte, V., Serafini, P., Mazzoni, A., Segal, D. M., and Zanovello, P. (2003) L-arginine metabolism in myeloid cells controls T-lymphocyte functions, *Trends Immunol.*, **24**, 301-305.
105. Hurwitz, A. A., and Watkins, S. K. (2012) Immune suppression in the tumor microenvironment: a role for dendritic cell-mediated tolerization of T cells, *Cancer Immunol. Immunother.*, **61**, 289-93.
106. Van Beek, J. J., Gorris, M. A., Skold, A. E., Hatipoglu, I., Van Acker, H. H., Smits, E. L., De Vries, I. J., and Bakdash, G. (2016) Human blood myeloid and plasmacytoid dendritic cells cross activate each other and synergize in inducing NK cell cytotoxicity, *Oncoimmunology*, **5**, e1227902.
107. Miossec, P., and Kolls, J. K. (2012) Targeting IL-17 and TH17 cells in chronic inflammation, *Nat. Rev. Drug Discov.*, **11**, 763-776.
108. Nyirenda, M. H., Sanvito, L., Darlington, P. J., O'Brien, K., Zhang, G. X., Constantinescu, C. S., Bar-Or, A., and Gran, B. (2011) TLR2 stimulation drives human naive and effector regulatory T cells into a Th17-like phenotype with reduced suppressive function, *J. Immunol.*, **187**, 2278-2290.
109. Veldhoen, M., Hocking, R. J., Atkins, C. J., Locksley, R. M., and Stockinger, B. (2006) TGFbeta in the context of an inflammatory cytokine milieu supports *de novo* differentiation of IL-17-producing T cells, *Immunity*, **24**, 179-189.
110. Miljkovic, D., Cvetkovic, I., Vuckovic, O., Stosic-Grujicic, S., Mostarica Stojkovic, M., and Trajkovic, V. (2003) The role of interleukin-17 in inducible nitric oxide synthase-mediated nitric oxide production in endothelial cells, *Cell Mol. Life Sci.*, **60**, 518-525.
111. Paris, I., Charreau, S., Guignouard, E., Garnier, M., Favot-Laforge, L., Huguier, V., Bernard, F.-X., Morel, F., and Lecron, J.-C. (2012) Critical role of Th17 pro-inflammatory cytokines to delay skin wound healing, *Cytokine*, **59**, 503.
112. Bailey, S. R., Nelson, M. H., Himes, R. A., Li, Z., Mehrotra, S., and Paulos, C. M. (2014) Th17 cells in cancer: the ultimate identity crisis, *Front. Immunol.*, **5**, 276.
113. Sallusto, F., and Lanzavecchia, A. (2009) Human Th17 cells in infection and autoimmunity, *Microbes Infect.*, **11**, 620-624.
114. Lv, L., Pan, K., Li, X. D., She, K. L., Zhao, J. J., Wang, W., Chen, J. G., Chen, Y. B., Yun, J. P., and Xia, J. C. (2011) The accumulation and prognosis value of tumor infiltrating IL-17 producing cells in esophageal squamous cell carcinoma, *PLoS One*, **6**, e18219.
115. Liu, J., Duan, Y., Cheng, X., Chen, X., Xie, W., Long, H., Lin, Z., and Zhu, B. (2011) IL-17 is associated with poor prognosis and promotes angiogenesis via stimulating VEGF production of cancer cells in colorectal carcinoma, *Biochem. Biophys. Res. Commun.*, **407**, 348-354.
116. Wang, L., Yi, T., Kortylewski, M., Pardoll, D. M., Zeng, D., and Yu, H. (2009) IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway, *J. Exp. Med.*, **206**, 1457-1464.
117. Guery, L., and Hugues, S. (2015) Th17 cell plasticity and functions in cancer immunity, *Biomed. Res. Int.*, **2015**, 314620.
118. Kim, J. S., Sklarz, T., Banks, L. B., Gohil, M., Waickman, A. T., Skuli, N., Krock, B. L., Luo, C. T., Hu, W., Pollizzi, K. N., Li, M. O., Rathmell, J. C., Birnbaum, M. J., Powell, J. D., Jordan, M. S., and Koretzky, G. A. (2013) Natural and inducible TH17 cells are regulated differently by Akt and mTOR pathways, *Nat. Immunol.*, **14**, 611-618.