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Heterogeneity and Plasticity of Immune Inflammatory Responses in the Tumor Microenvironment: Their Role in the Antitumor Effect and Tumor Aggressiveness

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Abstract—This review considers the role that immune inflammatory responses (IIRs) play in tumor development and progression. Intratumoral IIR heterogeneity is presumably due to simultaneous differentiation and activation of certain T helper (Th) subpopulations and macrophages in various loci of the tumor, their phenotypic plasticity, and their antagonism of Th1 and Th2 responses. Evidence is provided to demonstrate that the IIR type in the tumor microenvironment determines the probability of the epithelial–mesenchymal transition (EMT), the emergence of invasive properties in tumor cells, the formation of tumor and premetastatic niches, and chemosensitivity. It is hypothesized that the effect of IIRs on tumor cells depends on the IIR type, which determines the cell and cytokine spectrum in the tumor microenvironment, rather than on the efficiency of specific immune responses to tumor antigens. Lastly, it is assumed that more efficient targets for IIR guidance are not provided by single molecules, but rather by the signaling pathways that can permanently prevent the Th2-type IIRs or suppress inflammatory reactions in the tumor.

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INTRODUCTION

Inflammatory infiltration of the stroma is an important component of the microenvironment of a malignant tumor. Many attempts were made to identify its role in the acquisition of invasive and metastatic properties by tumor cells and to use the findings to predict disease outcome and to optimize treatment. A certain amount of progress has been made in the field. The extent of lymphoid infiltration in breast cancer and the formation of tertiary lymphoid structures in breast and lung cancers were shown to be significant for prognosis. The immune phenotypes of cells involved in inflammatory infiltration and the proportions of various T cell subpopulations and macrophages were proposed for use as prognostic markers in cancers of various localizations.

There is ample evidence characterizing the roles of various inflammatory cells, as well as the cytokines and growth factors they produce in the epithelial–mesenchymal transition (EMT) and the acquisition of invasive properties and metastatic potential by tumor cells. According to current views, the multicomponent responses of the T helper 1 (Th1) and Th2 types, which develop together with innate-type inflammation, are the most important components of the diverse set of cellular and molecular events that took place during immune inflammatory responses (IIRs) in the tumor microenvironment (Fig. 1). IIRs are thought to develop as follows in the tumor. Toll ligands (damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs)) originate from dying tumor cells or, less often, pathogens and interact with Toll-like receptors (TLRs) on tumor cells, thus triggering a signaling cascade leading to NF-κB activation. In turn, this potentiates the production of proinflammatory cytokines (interleukin-1 (IL-1), tumor necrosis factor α (TNF-α), and IL-6) in tumor cells, and the cytokines stimulate the synthesis of cyclooxygenase 2 (COX-2) and IL-8. COX-2 increases the level of prostaglandins (PGs), which increase the vascular permeability and exudation. IL-8 acts as a chemokine and forces monocytes and granulocytes to leave circulation, leading to inflammatory infiltration. Infiltration cells also possess TLRs and synthesize IL-1, TNF-α, and IL-6 in response to PAMPs and DAMPs, thus enhancing and maintaining nonspecific inflammation in the tumor. The phenom-

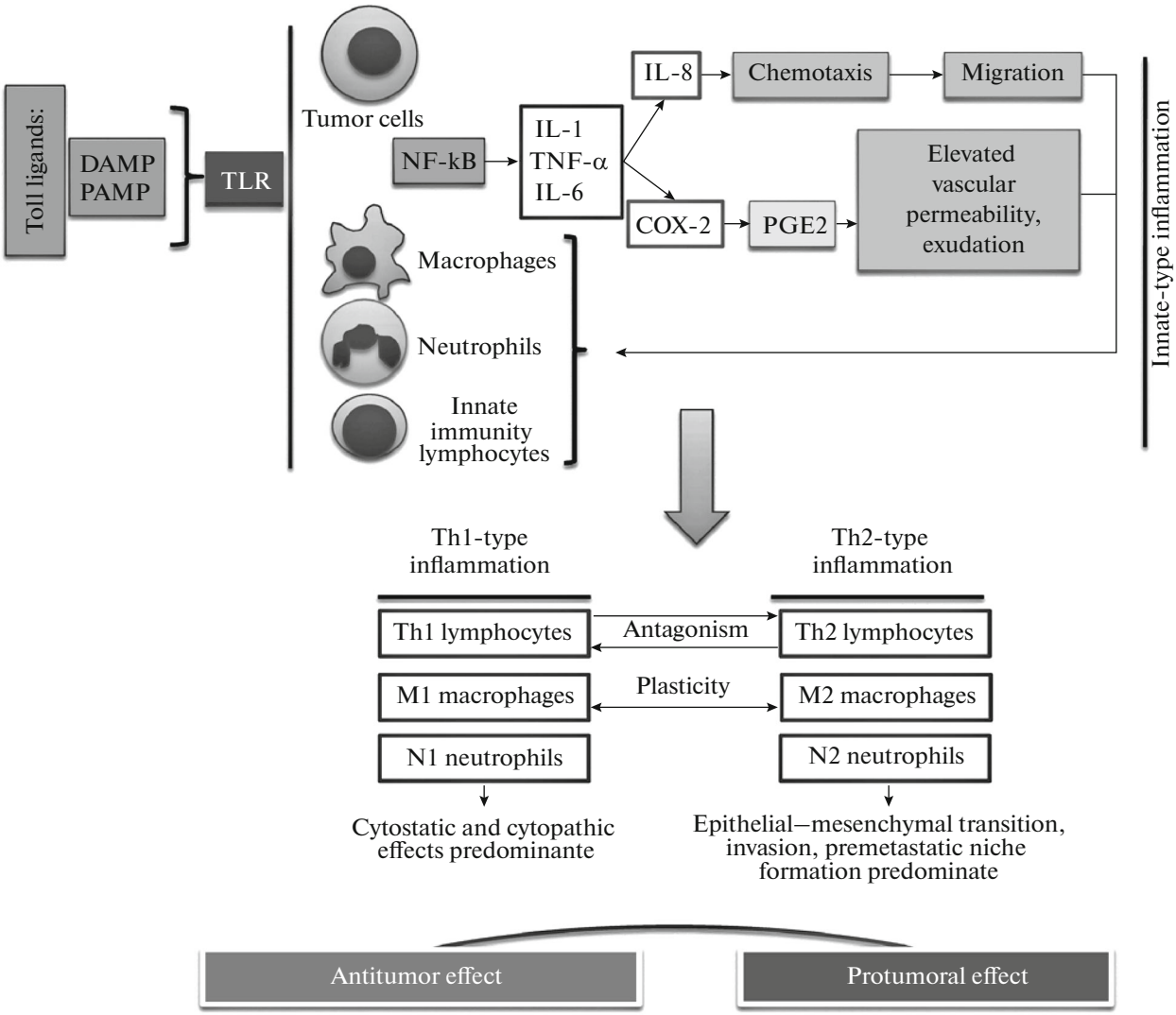

Fig. 1. Development of IIRs in the tumor microenvironment.

enon is essentially a manifestation of an innate inflammation response. This inflammatory response provides a basis for the development of specific IIRs. Dendritic cells are polarized depending on the types of antigens and Toll ligands. Entering a regional lymph node, dendritic cells act together with cytokines, which are different for each particular Th variant, to ensure polarization of Th0 cells to Th1, Th2, Th17, or regulatory T cells (Treg). In addition to the Th1 and Th2 classical polarization variants, Th polarization may be induced by cytokines of an antagonistic Th type. For example, IL-1 was shown to play a role not only in Th1 polarization (Ben-Sasson et al., 2009) but also in Th2 polarization (Bruchard et al., 2015). Secretion of IL-1b and TNF-α is possible in both M1 and M2 macrophages (Martinez and Gordon, 2014). IL-6, which is produced in macrophages, is involved in Th2 polarization and inhibits Th1 polarization (Diehl and Rinson, 2002). Th1 responses are most likely favorable, being capable of suppressing tumor growth and metastasis, while Th2 responses exert an adverse effect, stimulating cancer progression (Tashireva et al., 2017).

The above IIR types are modified by cytokines produced by other immune cells, including Treg, Th17, and myeloid-derived suppressor cells (MDSCs). The mechanism of such effects can be better understood by analogy with regeneration of connective tissue after damage. Th1 reactions with their proinflammatory potential facilitate the first phase of regeneration. Th2 reactions, which terminate inflammation, underlie the second regeneration phase, which is characterized by activated angiogenesis, connective tissue formation, and stimulated cell locomotion and proliferation in epithelial regions adjacent to the damage site (Tashireva et al., 2017). As a result, second-phase

regeneration processes restore connective tissue and the epithelial layer at the damage site (e.g., when the skin or gastric mucosa is damaged).

There is evidence that immune processes affect the outcome of chemotherapy. Relevant data were used to design antitumor immunotherapies, but their efficacy is limited to particular cancer types. Prognostic criteria proposed as a result lack sufficient sensitivity and specificity. The difficulties are probably objective in nature. First, intratumoral heterogeneity and phenotypic plasticity of certain Th subpopulations and macrophages make it difficult to interpret the results of studying inflammatory infiltration of the tumor stroma. It should be noted that both phenomena, especially the heterogeneity of inflammatory responses within the tumor, are still not fully understood.

This review considers the above issues and discusses possible strategies aimed at controlling spontaneous inflammatory responses in the carcinoma microenvironment.

HETEROGENEITY OF IMMUNE INFLAMMATORY RESPONSES IN THE TUMOR STROMA

The intratumoral heterogeneity, particularly substantial differences in tumor cell subpopulations, is well known and is the subject of intense research, while scarce data are available for the heterogeneity of inflammatory responses controlled by the surrounding non-tumor cells, as well as its biological and clinical significance. However, an integral evaluation of the tumor is of low efficiency without consideration of the heterogeneity of inflammatory responses in the tumor stroma, because many scenarios are possible for the parenchyma–stroma interplay and may include variants that are optimal for invasive growth and metastasis and those that inhibit these processes. IIR heterogeneity has been indirectly reported in many studies. In particular, it is manifested by the simultaneous harboring of several subpopulations of lymphocytes and macrophages, e.g., Th1 and Th2 or M1 and M2, in the tumor (Kohrt et al., 2005; West et al., 2011; Zhang et al., 2015; Tashireva et al., 2017).

The significance of IIR heterogeneity in the tumor stroma is supported by the prognostic value of several quantitative ratios, such as $CD4^+/CD8^+$, Th2/Th1 (Kohrt et al., 2005), and $CD68^+$ macrophages/$CD3^+CD20^+$ lymphocytes (Galon et al., 2014; Eiró et al., 2012).

The phenotypic differences among immune cells in the stroma of the primary tumor are possibly a manifestation of intratumoral heterogeneity. Our findings indicate that intratumoral morphological heterogeneity in invasive breast carcinoma of no special type (IC NST) is represented by different morphological structures: tubular, solid, trabecular, alveolar structures, and discrete groups of tumor cells and is associated with tumor progression (Zavyalova et al., 2006; Gerashchenko et al., 2013). In particular, breast tumors that contain alveolar structures show higher risk of lymph node metastasis (Zavyalova et al., 2013).

A decrease in $CD8^+$ T cells around discrete groups of tumor cells and in microenvironment distant from any tumor structures was found to be an important prognostic factor in predicting distant, but not lymph node, metastasis and tumor relapse (Tashireva et al., 2015).

The heterogeneity of inflammatory responses was associated with the relapse rate in breast carcinoma (Perelmuter et al., 2010). Our earlier study showed that small lymphocytes and histiocytes decrease in number when the plasmocyte response increases around trabecular structures and that the changes are associated with a higher rate of lymph node metastasis in breast cancer (Perelmuter et al., 1997).

Antagonism of Th1 and Th2 IIRs

Cell polarization to Th1 or Th2 phenotypes is regulated at the cytokine level. The proinflammatory cytokines IL-1, TNF-α, IL-12, and interferon γ (IFN-γ), which are produced predominantly by M1 macrophages, potentiate Th0 cell polarization to Th1 and suppress the Th2 response. In contrast, the anti-inflammatory cytokines IL-10, IL-4, and IL-13, which are produced predominantly by M2 macrophages, shift Th0 cell differentiation towards Th2 and inhibit Th1 polarization (Murphy and Reiner, 2002).

Macrophages act not only as a source of IL-10 but also as its target. IL-10 inhibits the production of the proinflammatory cytokines IL-6, IL-8, and TNF in response to monocyte stimulation with endotoxin or IFN-γ. In addition, IL-10 suppresses the macrophage ability to present antigens to T cells (Lu et al., 2014). A macrophage-dependent autocrine regulation of IL-10 probably underlies one of the mechanisms responsible for the IIR switch from Th1 to Th2.

Certain cytokines are capable of changing the course of Th1 and Th2 IIRs. For example, IL-17A decreases the production of the chemokine C–C motif ligand 17 (CCL17) in dendritic cells and thereby prevents Th2 recruitment to an inflammation focus (Schnyder-Candrian et al., 2006). IL-4 is capable of inducing the growth factor-independent 1 (Gfi-1) transcriptional repressor, thus optimizing the differentiation conditions for Th2 cells (Zhu et al., 2002) and suppressing differentiation of Th17 and Treg-induced cells (Zhu et al., 2009). Secretion of Th2 cytokines by $CD4^+$ natural killer T (NKT) cells inhibits infiltration by $CD8^+$ T cells (effector cells of the Th1 immune response) in hepatocellular carcinoma (Bricard et al., 2009).

Thus, Th1 and Th2 IIRs are antagonistic at the levels of both gene and cytokine expression. It should also

be noted that proinflammatory cytokines are secreted not only by M1 macrophages, which are involved in Th1 IIRs, but also by M2 macrophages; i.e., the latter synthesize both anti-inflammatory and proinflammatory cytokines. We think that proinflammatory cytokines are synthesized in M2 macrophages as well, because the migration of effector cells into the inflammation focus has to be sustained in inflammatory reactions of any type.

Phenotypic Plasticity of T Cells

The phenomenon of T-cell phenotypic plasticity is probably of importance in chronic inflammation, providing a mechanism of IIR-type switching. However, relevant data are scarce, and transformations were demonstrated only for Th17 into Th1 (but not the reverse) and Th2 into IL-9-producing cells (Bluestone et al., 2009). Direct transformations of Th1 into Th2 or Th2 into Th1 seem to be prohibited (Grivennikov et al., 2010).

The variable Treg capability of suppressor functions can be considered a special form of T-cell plasticity. The interaction of PAMPs and DAMPs with TLRs on the Treg surface substantially changes the function of Treg cells to decrease or increase their suppressor activity. The secretion of IL-6 and IL-1 by dendritic cells after TLR stimulation blocks the suppressor functions of Treg (Bettelli et al., 2006). A TLR8 ligand may totally abolish the Treg suppressor function in humans. The effect is independent of dendritic cells but requires that the TLR8–MyD88I–RAK4 signaling pathway be active in Treg cells (Peng et al., 2005). Flagellin (a protein of bacterial flagella) acts via TLR5 to stimulate suppressor activity of Treg cells; the effect is accompanied by upregulation of Foxp3, which is a key transcription factor of Treg cells (Crellin et al., 2005). Lipopolysaccharide (LPS) abolishes Treg activity in certain cases (Yang et al., 2004). However, the effects of LPS may vary. There are observations that TLR4 stimulation with LPS causes proliferation and increases activity of Treg cells (Caramalho et al., 2003).

Experiments showed that Treg cells with low-level IL-2Rα expression become unstable and lose Foxp3 expression when exposed to IL-2 deficiency (Komatsu et al., 2009). The central proinflammatory cytokine TNF-α is capable of activating mouse Treg cells by stimulating their TNFR2 (Chen et al., 2007). Glucocorticoids increase the $Foxp3^+CD4^+CD25^+$ cell count in mice in vivo (Chen et al., 2006), thus suppressing the immune response. A similar Treg reaction is possible to occur in long-term severe stress provoked by oncological disease or chemotherapy and radiotherapy. Some of the $Foxp3^+$ Treg cells are capable of losing Foxp3 expression and acquiring the phenotype of effector memory T cells producing TNF-γ (Zhou et al., 2009).

Plasticity of Treg cells is evident from their capabilities of losing the suppressor function and being reprogrammed into Th17 in the presence of TGF-β and IL-6 (or IL-1 and IL-23) (Yang et al., 2008). Treg cells reprogrammed into Th17 start to express two transcription factors (FoxP3 and ROR-gt) simultaneously and become capable of producing IL-17, which is a key cytokine of Th17 cells. In addition, human $CD4^+FoxP3^+CCR6^+$ Treg cells can differentiate into cells that secrete IL-17 in response to T-cell receptor (TCR) stimulation in the presence of IL-1b, IL-2, IL-21, IL-23, and human serum (Peng et al., 2005).

Activated Treg cells that display low-level FoxP3 expression, lack the suppressor function, and produce IL-17 in greater amounts than any other $CD4^+$ T-cell population were observed in humans (Miyara et al., 2009). Natural Treg cells can be stimulated to secrete IL-17 and to downregulate FoxP3 expression on exposure to IL-6/IL-1/IL-23 (Yang et al., 2008).

Functional Plasticity of Macrophages

There is ample evidence that the M1 and M2 macrophage subtypes are not stable, but their phenotype depends on the combination of factors present in particular tissues. Thereby, macrophages can show complex phenotypes (Martinez and Gordon, 2014). The ability to transform from M1 to M2 seems to be of importance for the transition from a proinflammatory Th1 IIR to an antagonistic anti-inflammatory Th2 IIR. This mechanism possibly underlies the transition from the inflammatory phase of tissue repair to the second, productive phase, in which connective tissue is generated and tissue defects are epithelized.

The plasticity that macrophages display on activation with various cytokines is so high that a common nomenclature of various functional cell types is still lacking (Martinez and Gordon, 2014). The in vitro data on macrophage plasticity require verification in vivo. LPS and IL-21 were shown to induce changes from the M2 to the M1 macrophage phenotype (Zheng et al., 2013; Das et al., 2015). The opposite macrophage polarization from the proinflammatory M1 to the anti-inflammatory M2 phenotype was also described and is mediated by many factors, such as the presence of apoptotic cells in the inflammation focus, cytokines, and activation of kinases (JNK, JAK, and PI3K). MicroRNAs and long noncoding RNAs (lncRNAs) also sustain macrophage polarization (Das et al., 2015). There are data that IL-12 introduced into the tumor in vivo leads to a phenotypic conversion of tumor-associated macrophages from anti-inflammatory M2 to proinflammatory M1 (Watkins et al., 2007). In vitro studies showed that IFN-γ-mediated activation of CD40 is necessary for the efficient reprogramming of tumor-induced M2 macrophages in activated M1 macrophages producing IL-12 (Heusinkveld and van der Burg, 2011). The macrophages

developed in response to prostaglandin E2 and IL-6 are capable of transformation into M1 phenotype when influenced by $CD4^+$ Th1 cells (Heusinkveld et al., 2011).

The above data demonstrate that T cells and macrophages possess high plasticity, thus determining diverse stromal IIRs. On one hand, their plasticity allows the tumor to change the T-cell and macrophage phenotypes to its own benefit; on the other, plasticity provides a basis for the design of drugs and treatments for a desirable reprogramming of IIRs.

Changes That Tumor Cells Induce in Stromal IIRs

The efficiency of stromal IIRs and the efficacy of immunotherapy are limited, because the tumor is capable of suppressing the specific immune response via several mechanisms. Overexpression of the HER2/ErbB2/Neu receptor induces phosphorylation of the signal transducer and activator of transcription (STAT1) in certain tumors, leading to inhibition of the Th1 immune response (Laoui et al., 2013). In addition, tumor cells can inhibit T-cell function directly, by expressing transmembrane inhibitory molecules (e.g., CD95L or PD-L1) or indirectly, by acting synergistically with Treg cells (Müschen et al., 2000; Wolf et al., 2003). PD-1 is expressed on $CD8^+$, $CD4^+$, and B cells. It acts as a receptor for PD-L1 and mediates inhibition of the specific immunoresponse. PD-L1 is expressed in tumor cells of many cancers, which are thereby capable of affecting activated T and B cells through their PD-1 receptors (Dong et al., 2002). To suppress this adverse reaction, drugs were designed on the basis of monoclonal antibodies that block the PD-1 ligand on tumor cells. Two such drugs, nivolumab and pembrolizumab, have been approved by the Food and Drug Administration (FDA) (Twomey et al., 2017). Their indications include unresectable melanoma and squamous and non-squamous cell lung carcinomas that progress after treatment with platinum-based chemotherapy. In addition, several other drugs are currently under testing in large-scale clinical studies.

It is clear that the above drugs are incapable of curing the patients in full. An objective response is observed in only 35% of patients (Gettinger et al., 2015), and metastasis-free and overall survival increases by only 2–4 months on average (Fenchel et al., 2016; Addeo, 2017). The efficacy depends to a great extent on the portion of tumor cells that express PD-L1. For instance, an objective response to nivolumab was reported for 28.4% of patients with PD-L1 expression in more than 5% of tumor cells, 23.8% of patients with PD-L1 expression in 1–5% of tumor cells, and 16.1% of patients with PD-L1 expression in less than 1% of tumor cells (Sharma et al., 2017).

An interesting question is what subpopulation of T cells act as targets of PD-L1. PD-L1 inhibitors are known to increase the Th1/Th17 immune response and to suppress Th2 in peripheral blood (Dulos et al., 2012). Special studies were not performed to understand how the drugs affect the composition of the tumor microenvironment in humans in vivo. In mice, PD-1 inhibition was shown to increase the amount of $CD8^+$ lymphocytes in lymphoid organs (Im et al., 2016). At the same time, there are data showing that the Th2 response is increased by PD-1 inhibitors (Zhou et al., 2016). A favorable effect is therefore possible to expect if PD-1 inhibition suppresses Th2 IIRs in the tumor and thus allows the development of a Th1 response. An opposite situation may stimulate tumor progression. An opposite effect of PD-L1 inhibitors is possibly responsible for their relatively low efficacy. Finally, tumor cells are capable of changing expression or masking tumor-associated antigens (TAAs), rendering them less accessible for effector cells (Milani et al., 2014).

A new mechanism was described for the elimination of $CD8^+$ T cells from intratumoral circulation. VEGF-A, IL-10, and PGE2 of tumor origin act together to induce CD95L expression on endothelial cells, while CD95L is not expressed in the normal endothelium. This causes the death of effector $CD8^+$ T cells, but not Treg cells, which express a FLICE-like inhibitory protein (Motz et al., 2014).

Dendritic cells may inhibit antitumor immunity in cancers (Ma et al., 2012). Several mechanisms mediate the effect. As the tumor progresses, immature dendritic cells find their way into tumor-draining lymph nodes, where Treg proliferation is stimulated selectively (Ghiringhelli et al., 2005). Tumor-associated dendritic cells were found to express costimulating molecules to low levels (Chaux et al., 1996). Several tumor-derived factors, such as gangliosides, neuropeptides, and nitric oxide, reduce the lifespan (Shurin and Lotze, 2009) and increase apoptosis (Esche et al., 1999) of dendritic cells. In addition, the tumor cell cytokine HMGB1 increases dendritic cell apoptosis and stimulates cell growth, invasion, and angiogenesis in carcinomas. The process is associated with lymphatic metastasis in colorectal cancer (Kusume et al., 2009).

Antitumor Efficiency of Spontaneous IIRs

Progress in evaluating the significance of spontaneous lymphoid infiltration in breast cancer has been made in large-scale randomized clinical studies in recent years. An international working group developed criteria to evaluate lymphoid infiltration in breast cancer (Salgado et al., 2015b). The molecular subtype of breast cancer is of importance for the prognostic significance of tumor-infiltrating lymphocytes (TILs). TILs are more often found in ER-PR-$HER2^-$ and $HER2^+$ breast cancers (Savas et al., 2016). A linear dependence was observed between an increase in the TIL amount and an increase in relapse-free survival in

patients with triple negative breast cancer. The average TIL percentages are 10% in ER^+HER2^- tumors, 15% in $HER2^+$ tumors, and 20% in ER^-HER2^- tumors. Tumors with 50–60% lymphocytic infiltration are classed as lymphocyte predominant breast cancer. However, a direct association with survival was demonstrated for any TIL amount (Denkert et al., 2010; Loi et al., 2013). TILs are thought to include mostly tumor-specific T cells in breast cancer (Savas et al., 2016).

Tertiary lymphoid structures (TLSs) found in the tumor are also of prognostic significance. Like lymph nodes, these structures provide room, immediately in the tumor, for antigen presentation and induction of a specific immune response with generation of polarized Th cells, $CD8^+$ or $CD4^+$ effector cells, and antigen-specific B cells (Dieu-Nosjean et al., 2014). Differentiated B cells, plasma cells varying in extent of maturation, and memory cells were observed to leave TLSs in the tumor stroma (Germain et al., 2015). Th17 cells play a certain role in TLS formation (Grogan and Ouyang, 2012). In contrast, Treg cells suppress TLS formation. The presence of TLSs in the tumor is presumably always associated with a better overall survival (Dieu-Nosjean et al., 2014). Antigen-dependent mechanisms possibly underlie the association. For example, B cells from TLSs are capable of binding with tumor antigens and triggering either antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity (Germain et al., 2015).

Based on immune cell contents in the tumor, colorectal cancer staging was developed to supplement the common TNM classification. In 2012, Jerome Galon was the first to propose such a classification, which is now known as TNM-immune (TNM-I). The Immunoscore (I, ranging from 0 to 4) is evaluated by counting the densities of two lymphocyte populations, cytotoxic and memory T cells (CD3/CD45RO, CD3/CD8, or CD8/CD45RO), in two tumor sites, the center and the invasive margin. Because the presence of cytotoxic T cells, memory T cells, and Th1 pathway cells is associated with a better survival, I = 4 suggests a good prognosis (Galon et al., 2014).

Sabatier et al. (2011) studied the expression of genes for 28 kinases in lymphocytic infiltrate cells from breast cancer patients by microarray technology. All breast tumors were divided into two subtypes, highly immune and weakly immune. Clinical and morphological factors and, in particular, the presence and character of lymphocyte infiltration, did not differ between the two groups, but the 5-year survival was 91% in the highly immune group and 49% in the low-immune group. To better understand the differences between the groups, the expression of 532 genes was profiled in addition to the study of the 28 kinase genes. The expression of immunity-related genes was found to differ between the two clinically and morphologically uniform groups. The activation of kinome genes suggested the presence of an activated lymphocytic infiltrate in highly immune patients. Lymphoid cells of the stromal infiltrate displayed upregulated expression of the genes responsible for lymphocyte survival (*IL2RG, IL23RB*, and *IL7R*), genes of Th1-associated receptors (*IL12RB1, IL15RA, IL18BP*, and *IL21R*), Th1 transcription factor genes (*STAT1*, *STAT4*, and *TBX21*), genes of certain interferon-inducible molecules (*GVIN1, ISG20, GBP2, IRF1, IRF4, IRF7*, and *IRF8*), and genes of cytotoxic granules and pore-forming molecules (*VAMP1*, *GZMA*, *GZMB*, *GZMH*, *GZMK*, *GNL*, *PRF1*, *CFLAR*, *CASP1*, and *CASP10*). In addition, upregulation was observed for a gene set characteristic of memory cells: *IL16*, *XCL1*, *CCL5*, *CXCL9*, *CXCR3*, *CCL19*, *CCR7*, and *CXCR6* (helper and cytotoxic T cells) and *CXCL13* and *CXCR5* (activated B cells). The cells were found to contain transcripts for proteins involved in lymphocyte migration or activation: ITGAL and ITGB2 heterodimers, ITGA4, ITGAX, ITGB7, SELL, SELP, SELPL, and CD69 (Sabatier et al., 2011). As can be seen, all groups of upregulated genes are related to the Th1 response.

However, Th2 IIRs are not always unfavorable. The M1/M2 macrophage ratio is not an optimal prognostic factor for predicting the course of the tumor disease in colorectal cancer. Edin et al. (2012) showed that infiltration with $NOS2^+$ M1 macrophages is associated with a favorable prognosis. Despite this, the M1/M2 ratio was not a significant prognostic factor because the presence of $CD163^+$ M2 macrophages was also associated with a better prognosis (Edin et al., 2012).

Another study showed that infiltration of a breast tumor by $CD68^+$, $CD4^+$, and $CD8^+$ cells has a prognostic value for the overall survival and that a high CD68/CD8α mRNA ratio in tumor tissue correlates with total morphological regression after a course of neoadjuvant chemotherapy in early breast cancer (DeNardo et al., 2011). An important association with survival in human breast carcinoma was observed for the intratumoral presence of $CD4^+$ Tfh cells, which occur in peritumoral TLSs. A comparison of breast tumors with extensive or minor lymphocytic peritumoral infiltration showed that the presence of Tfh cells secreting the CXCL13 B-cell chemoattractant correlates with extensive infiltration and the presence of TLSs. Moreover, higher contents of IFN-γ-producing Th1, $CD8^+$ T, and B cells in the tumor and a more favorable prognosis were associated with the presence of tumor-infiltrating Tfh cells (Gu-Trantien and Willard-Gallo, 2013).

In contrast to the above findings, the overall survival was lower when Th2 IIRs prevailed in the tumor microenvironment. For example, $CD4^+$ cells isolated from a breast tumor were shown to produce high levels of Th2 immune response cytokines, including IL-4 and IL-13, which play an important role in regulating TAM activity; their presence was associated with a poor prognosis (Treilleux et al., 2004).

Kohrt et al. (2005) showed that high $CD4^+/CD8^+$ and high Th2/Th1 ratios in tumor-infiltrating lymphocytes suggest poorer prognosis in breast cancer. Another research team observed that a higher CD68 content and a higher $CD68^+$ macrophage/$CD3^+CD20^+$ lymphocyte ratio in the invasive component are directly associated with a likely decrease in relapse-free survival in breast cancer (Eiró et al., 2012). Dendritic cells present in the infiltrate of a primary breast tumor correlate with unfavorable outcome, suggesting their contribution to disease progression in breast cancer (Treilleux et al., 2004).

Thus, a predominance of cells corresponding to Th1 IIRs in the stroma is mostly associated with favorable prognosis, while a predominance of Th2 IIRs is most likely associated with poor outcome.

IIRs and Tumor Progression

The mechanisms that underlie tumor progression include the epithelial–mesenchymal transition (EMT), invasive growth, and the formation of premetastatic niches at sites of future metastases. The roles that cells of an inflammatory infiltrate of the tumor play in the processes are considered below.

The Role of Various IIRs in EMT

EMT is a key event in both reparative regeneration and the acquisition of an invasive phenotype by tumor cells (Zeisberg and Neilson, 2009). EMT is initiated by four main stimuli (cytokines, growth factors, hypoxia, and extracellular matrix components) and proceeds via five signaling pathways (TGF-β, Wnt–β-catenin, BMP, Notch, and Hedgehog) (Gonzalez and Medici, 2014). Cells involved in regulating EMT usually belong to the above Th2 IIR type and include Th2 lymphocytes, M2 macrophages, and fibroblasts. The fact that TGF-β (a cytokine of the Th2 immune response) is a key molecule in EMT indicates that EMT is possible in the Th2 IIR. In addition, IL-4 and IL-17A (key cytokines of the Th2 and Th17 immune responses, respectively) are known to act synergistically with TGF-β to increase EMT (Ji et al., 2013).

As for the role of IL-22 in EMT, this cytokine was not shown to affect expression of epithelial and mesenchymal genes in the bronchial epithelium of asthma patients. However, IL-22 acting together with TGF-β1 facilitates expression of EMT transcription factors (Snail and Zeb) and significantly changes cadherin expression (Johnson et al., 2013).

The activation of the IL-8/IL-8R axis is possibly associated with EMT. It is noteworthy that IL-8 is secreted by tumor cells in the EMT state. Moreover, IL-8 promotes EMT in adjacent tumor cells (Fernando et al., 2011). Because IL-8 is induced in cells undergoing the TGF-β-induced EMT, IL-8 synthesis is probably secondary to EMT (Bates et al., 2004).

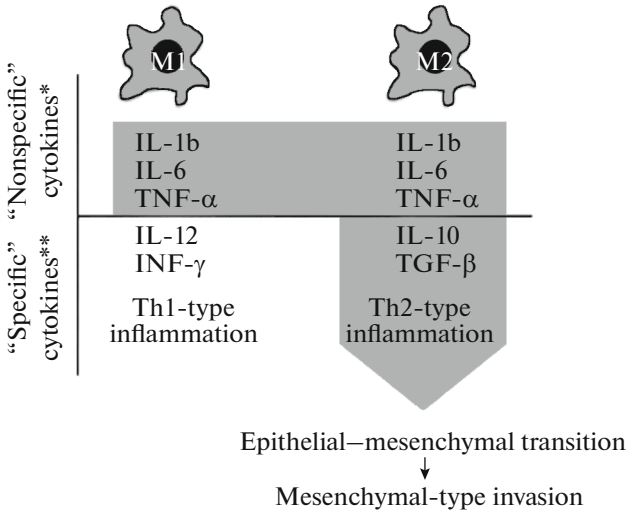

Fig. 2. Roles of macrophages in MET and invasive growth. * Nonspecific cytokines are those that are produced by both M1 and M2 macrophages. ** Specific cytokines are those that are produced by either M1 or M2 macrophages.

Ectopic expression of IL-6 was observed in the MCF-7 breast cancer cell line and was accompanied by downregulation of E cadherin and induced expression of vimentin, N cadherin, Snail, and Twist. The findings made it possible to conclude that IL-6 is capable of inducing EMT (Sullivan et al., 2009).

Cancer-associated fibroblasts (CAFs) are known to secrete several growth factors, including those of the fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and TGF superfamily, which play an important role in EMT (Thiery, 2002). Metalloproteinase secretion by CAFs also promotes EMT. EMT underlies mesenchymal-type invasion of carcinoma cells. CAFs were shown to facilitate tumor invasion by inducing EMT (Bhowmick et al., 2004; Mueller and Fusenig, 2004; Kalluri and Zeisberg, 2006).

There are data showing that M2 macrophages act through the TLR4/IL-10 signaling pathway to stimulate EMT in pancreatic cancer cells. Cocultured with M2 macrophages, these cells acquire a fibroblast-like morphology and elevated expression of the mesenchymal markers, vimentin and Snail, at both mRNA and protein levels (Liu et al., 2013). EMT most likely develops locally, in the invasive front of the tumor rather than in cells within multicellular structures (Brabletz et al., 2005; Spaderna et al., 2006; De Wever et al., 2008b). Type 2 inflammatory cytokines act as classical inducers of EMT and subsequent mesenchymal-type invasion. However, nonspecific proinflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α) are also capable of playing a role in EMT, since they are produced by any macrophage subpopulation (Fig. 2). Nonspecific proinflammatory cytokines possibly act together with anti-inflammatory cytokines in EMT.

For instance, IL-6 increases the EMT induced in tumor cells by TGF-β (Shintani et al., 2016).

Thus, EMT development is predominantly associated with Th2 IIRs, although proinflammatory cytokines may also induce EMT. It is still an open question as to whether EMT variants initiated by different triggers are equal, primarily, in terms of level, reversibility, and acquired cell motility.

Invasive Growth and IIRs

Invasive growth is currently explained with two cell migration models, namely, collective (group) and individual migration, whereby tumor cells spread to surrounding tissues. Collective invasion proceeds via a mesenchymal (fibroblast-like) mechanism, while single cell (individual) migration relies on both mesenchymal (fibroblast-like) and amoeboid mechanisms (Friedl and Alexander, 2011; Krakhmal et al., 2015).

How does the type of IIRs occurring in the tumor stroma affect the invasive properties of tumor cells? The data accumulated to date indicate that the Th2-IIR type of the microenvironment correlates with both collective and individual invasion. In particular, this was demonstrated for TGF-β, which may facilitate collective cell migration in breast cancer (Matise et al., 2012). Using proteolytic enzymes, fibroblasts, which form a Th2 IIR infiltrate in the tumor together with other cells, modify the extracellular matrix and create a path to allow collective migration of carcinoma cells (Gaggioli et al., 2007).

This type of invasion is additionally considered fibroblast-like, because the malignant cells that utilize the mesenchymal motility variant acquire an elongated, spindle-shaped morphology and resemble fibroblasts (Zijl van, et al., 2011). This transformation of a malignant epithelial cell is a manifestation of EMT. The role of inflammatory infiltrate cells in the EMT has been considered above (Fig. 2).

Certain cells of the microenvironment promote the acquisition of invasive properties by tumor cells (Elinav et al., 2013). For example, many infiltrating $CD4/CD25^+$ and CD4/CCR4 were observed in patients with metastatic cancer (Cózar et al., 2005). It is known additionally that myofibroblasts, which are activated fibroblasts, differ from fibroblasts in being capable of stimulating human colorectal carcinoma cell invasion in a 24- to 48-h experiment with type I collagen or matrigel. Myofibroblasts stimulate not only tumor cell invasion but also hematogenic and lymphogenic metastasis (De Wever et al., 2008a). The role that the inflammatory microenvironment plays in triggering amoeboid individual invasion is poorly understood.

Thus, any factor that induces EMT (see above) is capable of initiating mesenchymal invasive growth, including both collective and individual migration. This is most likely associated with Th2 IIRs.

The IIR Type in the Induction of Chemoattractant Synthesis and the Formation of Tumor and Metastatic Niches

Paget (1989) proposed a "seed and soil" hypothesis, which is now the most productive in studying the mechanisms of metastasis. Tumor cells that are capable of secreting proinflammatory cytokines or responding to them have a higher metastatic potential (Rollins, 2006). Lyden and colleagues (Kaplan et al., 2005) advanced a hypothesis that the formation of metastases is preceded by the formation of the so-called premetastatic niches with an optimal cell and molecular microenvironment ("soil") distant from the primary tumor. The process occurs because the tumor produces a number of chemoattractants (LOX, MIP2, VEGFA, TGF-α, and TNF-α).

The tumor niche forms in the primary tumor. Similar to the premetastatic niche, the tumor niche ensures the optimal conditions for the growth of transformed cells. As a key process in the formation of the tumor and premetastatic niches, precursor cells are recruited from bone marrow, and the optimal conditions are created for their differentiation and proliferation (Barcellos-Hoff et al., 2013). According to Lyden's concept, the tumor niche forms synchronously with the growth of the primary tumor. Tumor cells and cancer-associated fibroblasts secrete chemokines, such as TGF-β, IL-6, and CXCL12, which facilitate the formation of the niche. For example, hepatocellular carcinoma and stellate cells secrete the factors that cause migration of mesenchymal stem cells of a bone marrow origin into the tumor microenvironment both in vitro and in vivo (Garcia et al., 2011).

The formation of a premetastatic niche was assumed to be due to a chronic inflammation, which acts as a preniche and lacks clinical manifestation. Inflammation provides the conditions for recruiting precursors of premetastatic niche-forming cells from the blood and lymph (Perelmuter and Manskikh, 2012).

A question arises as to whether the stromal IIR type is capable of affecting the tumor potential to develop a metastatic phenotype (i.e., facilitating the generation of "seeds" and the formation of premetastatic niches, "soil").

The association of IIRs with premetastatic niche formation is possibly due to the initiated synthesis of proinflammatory cytokines, selectins, and chemokines (Keibel et al., 2009). The Th2 type of microenvironment favors metastasis. This is related to the cell composition of the microenvironment and its property to stimulate EMT. It was shown that $CD4^+$ Th2 cells induce breast cancer progression and metastasis by stimulating the production of proangiogenic and prometastatic factors in tumor-associated macrophages (TAMs) (DeNardo et al., 2009). The M2 macrophage count and a high M2/M1 ratio were found to predict liver metastasis in colorectal cancer (Cui et al., 2013).

Thus, Th2 IIRs in the tumor probably facilitate the production of several chemoattractants, which may create a necessary microenvironment in the tumor and may form premetastatic niches.

Stromal IIRs and Chemotherapy Effects

The intensity and type of IIRs play an important role in antitumor therapy. There is an association between the extent of lymphoid infiltration and the effect of chemotherapy. The presence of TILs is associated with a beneficial effect of anthracycline treatment in $HER2^+$ breast cancer (West et al., 2011). Another study demonstrated that the presence of $CD8^+$ T cells is associated with a beneficial effect of epirubicin, regardless of the histological type of breast cancer. Tumor cell death is thought to be of an immune nature (Mattarollo et al., 2011).

The IFN signaling molecule STAT1 was found to play a role in doxorubicin and lapatinib treatment of HER2/Neu-positive breast carcinoma (Hannesdóttir et al., 2013). Lapatinib acts as a ErbB2/HER2/Neu and ErbB1/EGFR double inhibitor and affects the immune reactivity. Doxorubicin and lapatinib increase the myeloid infiltrate (tumor-associated macrophages and monocytes) in the tumor, although $CD8^+$ T cells are partly involved in the process as well (Laoui et al., 2013). Hannesdóttir et al. (2013) observed that lymphocytes may appear in the tumor with paclitaxel treatment. In addition, the same researchers reported that *de novo* infiltration with IFN-γ-producing $CD4^+$ and $CD8^+$ T cells occurs in breast cancer after lapatinib and doxorubicin treatment. West et al. (2011) demonstrated that the presence of TILs expressing cytotoxic cell markers is directly associated with a favorable outcome of anthracycline therapy in patients with ER-negative breast cancer.

The efficacy of neoadjuvant chemotherapy with carboplatin combined with anthracyclines and taxanes was higher in patients with lymphocyte predominant breast cancer (LPBC) with a TIL content ≥60%. This was manifested as a higher rate of complete pathological response (pCR) in triple negative and HER2-positive breast cancers (Denkert et al., 2015). HER2-positive cancer with high TILs has favorable prognosis on neoadjuvant chemotherapy with lapatinib and trastuzumab regardless of whether pCR is achieved (Salgado et al., 2015a).

Tumor infiltration with T-bet^+ Th1 cells after neoadjuvant chemotherapy with trastuzumab–taxane is possibly an independent prognostic factor suggesting better outcome in HER2-positive breast cancer (Ladoire et al., 2011a). A high $FoxP3^+/CD8^+$ cell ratio in the tumor infiltrate is an independent factor associated with a poor outcome of platinum-based chemotherapy. Observations make it possible to assume that the presence of $CD8^+$ and $FoxP3^+$ Treg cells in the peritumoral infiltrate represents a prognostic factor that predicts the response to neoadjuvant chemotherapy with platinum drugs in patients with small cell lung cancer (Liu et al., 2012). Ruffell et al. (2012) showed that the CD8/CD4 T-cell ratio in tumors of breast cancer patients receiving neoadjuvant chemotherapy is higher than in tumors resected from patients without this therapy. Ladoire et al. (2011b) demonstrated that the CD8/FoxP3 ratio provides an independent prognostic factor predicting a better survival in breast cancer patients after neoadjuvant chemotherapy.

Thus, the presence of cells with a Th1 IIR phenotype in the tumor microenvironment is associated with favorable outcome of neoadjuvant chemotherapy according to the literature data.

DISCUSSION

Although the concept of Th1 and Th2 immune response variants and corresponding IIRs does not exhaust the total diversity of cell and molecular events that occur in the tumor microenvironment, we think that this concept is still the most productive. The functional antagonism of the effects exerted by cytokines of the Th1 and Th2 spectra suggests that only one of the IIR variants can occur in a tumor locus at each moment of time. Two conditions are to be met for cytokines to affect their target cells: there are proper receptors on the target cells, and they are in close proximity to cytokine source cells. The latter condition is of importance, because cytokines can travel only a limited distance in the intercellular matrix. T-cell and macrophage plasticity play an important role in determining the character of the inflammatory microenvironment, promoting the development of different stromal IIRs and their intermediate variants.

Thus, theoretically, the following factors create the prerequisites for IIR heterogeneity: (1) conditions in the tumor favor the initiation of differentiation for different Th cells, (2) antagonistic effects are exerted by cytokines of the Th1 and Th2 spectra, (3) phenotypic plasticity is characteristic of lymphocytes and macrophages, (4) proper receptors are essential for cytokines to exert their effects on target cells, and (5) the paracrine effect of cytokines on their target cells is limited by the distance that the cytokines are capable of traveling in the intercellular matrix. At present, scarce, experimental findings have accumulated to support IIR heterogeneity in the tumor.

In view of the antagonistic relationship between the major types of IIRs, it is possible to expect that cell and molecular events resulting in a Th1 IIR in a particular tumor locus will prevent a Th2 IIR in the adjacent tumor regions within the effective distance of Th1-spectrum cytokines. If a Th2 IIR initially develops far away from the first tumor locus as a result of the proper antigen specifics, proper dendritic cell polarization, and conditions allowing Th0 polarization to

Table 1. Effects of Th1 immune inflammatory responses

Cells	Effector molecules	Expected effects		
		inflammation	wound healing	tumor progression
ILC1	IFN-γ, TNF-β (Bernink et al., 2013)	Stimulation (Bernink et al., 2013)	Stimulation of phase 1	Inhibition
Th1	IFN-γ, IL-2 and TNF-β (Zhu and Paul, 2010)	Stimulation (Zhang et al., 2014)	Stimulation of phase 1	Inhibition (Wieder et al., 2008)
CD8	Perforins and granzymes (Zhu and Paul, 2010)	Stimulation	Stimulation of phase 1	Inhibition (Fridman et al., 2012)
M1 macrophages	IL-6, IL-12, IL-23, TNF-α, iNOS and ROS, (Sica and Mantovani, 2012)	Phagocytosis, attraction of CD8 and Th1 cells, activation of NK and Th1 cells (Sica and Mantovani, 2012)	Stimulation and prolongation of phase 1 (Barrientos et al., 2008; Sindrilaru et al., 2011)	Inhibition
N1 neutrophils	TNF-α, IL-12, ICAM-1, FAS, CCL3, CXCL9 and CXCL10 (Fridlender et al., 2009)	Stimulation (Scapini et al., 2000; Fridlender et al., 2009)	Stimulation and prolongation of phase 1, prevention of fibrosis (Barrientos et al., 2008; Crome et al., 2010; Sindrilaru et al., 2011)	Inhibition (Scapini et al., 2000). Facilitation of antitumor activity of $CD8^+$ cells (Shen et al., 2014)
Th17	IL-22, IL-17A, IL-17F (Paris et al., 2012)	Stimulation (Paris et al., 2012)	Stimulation and prolongation of phase 1, prevention of fibrosis (Crome et al., 2010; Paris et al., 2012)	Associated with favorable prognosis (Lu et al., 2011)
Tfh	Can produce Th1, Th2, and Th17 cytokines, such as IFN-γ and IL-21 (Gu-Trantien and Willard-Gallo, 2013)	Increase amounts of IFN-γ-producing Th1 cells and $CD8^+$ T cells (Gu-Trantien and Willard-Gallo, 2013)	No data	Associated with favorable prognosis
$CD27^+$ B lymphocytes				Provide favorable prognostic factor together with $CD8^+$ T cells (Nielsen et al., 2012)

Th2, then Th1 IIRs will be impossible within the effective distance of Th2-spectrum cytokines. Thus, tumor cell structures are exposed to the effects of Th1 IIRs in the first locus and Th2 IIRs in the second. Therefore, Nx loci with different types and intensities of IIRs may be expected to occur within the tumor; therefore, they have different effect on tumor progression. Evaluation of the effects of Th1- and Th2-like IIRs shows that the former underlie the first inflammatory phase of reparative regeneration and are more likely to prevent fibrosis and EMT and to inhibit tumor progression, including the acquisition of invasive properties and a metastatic potential (Table 1). Th2-like IIRs underlie the second phase of reparative regeneration. This phase is characterized by the generation of granulation tissue and mature connective tissue, allows EMT, and promotes the development of invasive and metastatic properties in tumor cells (Table 2).

Since the morphology of a lymph node at a particular moment of time is an integral reflection of numerous synchronous immune responses that arise to a variety of antigens and employ different immune mechanisms, the inflammatory infiltration of a tumor is an integral reflection of numerous IIR scenarios with different initiation mechanisms. Contributions may vary among possible scenarios, and the predomi-

Table 2. Effects of Th2 immune inflammatory responses

Cells	Effector molecules	Expected effects		
		inflammation	wound healing	tumor progression
ILC2	IL-4, IL-5, IL-9 and IL-13 (Neill et al., 2010)	Production of anti-inflammatory cytokines (Neill et al., 2010)	Stimulation of phase 2 (Rak et al., 2016)	Are associated with tumor progression
Th2	IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 (Shen et al., 2014)	Suppression of Th1 inflammation, production of anti-inflammatory cytokines (Shen et al., 2014)	Maintenance of phase 2 (Wynn, 2008)	Stimulation (Fridman et al., 2012)
M2	IL-10, IL-4 and IL-13, TGFb, PGE2, EGF, IL-6, CXCL8, VEGF, TGFα and MMPs (Sica and Mantovani, 2012)	Production of anti-inflammatory cytokines (Sica and Mantovani, 2012)	Stimulation of phase 2 (Ferrante and Leibovich, 2012)	Stimulation of tumor growth (Allavena et al., 2008)
N2	CXCR4, VEGF, gelatinase, IL-8 and MMP9 (Fridlender et al., 2009)	Inhibition of $CD8^+$	Stimulation of phase 2 (Gregory and Houghton, 2011)	Stimulation of tumor growth (Gregory and Houghton, 2011)
Myofibroblasts	FGFs, HGF, TGF-β and SDF-1 (Hinz, 2016)	Production of anti-inflammatory cytokines (Hinz, 2016)	Stimulation of phase 2 (Hinz, 2016)	Promote tumor growth by stimulating Th2 immunogenesis (Erez et al., 2010)
Treg	IL-10 and TGF-β1 (Bilate and Lafaille, 2012)	Suppression of CD4, Cd8, NK, NKT, DC, macrophage, and B-cell activities (Bilate and Lafaille, 2012)	Stimulation of phase 2 (Murphy et al., 2005)	Stimulation of tumor growth. Inhibition of CD8 (Huang et al., 2012)
MDSCs	IL-10, IL-6 and TGF-β (Shipp et al., 2016)	Suppression of NK activity and induction of Treg (Shipp et al., 2016)	Stimulation of phase 2 (Motz and Coukos, 2011)	Stimulation of tumor growth. Inhibition of CD8 (Bronte et al., 2003)
Th22	IL-17A, IL-17F, IL-22, FGF1, FGF5, CCL7, CCL15 and CCL23 (Akdis et al., 2012)	Production of anti-inflammatory cytokines (Akdis et al., 2012)	Stimulation of phase 2 (McGee et al., 2013)	Stimulation of tumor growth (Numasaki et al., 2003)
Th17	IL-17A, IL-17F, IL-21, IL-22, bFGF, HGF and VEGF (Akdis et al., 2012)	Production of anti-inflammatory cytokines (Akdis et al., 2012)	Stimulation of phase 2 (Numasaki et al., 2003)	Stimulation of tumor growth (Numasaki et al., 2003)
B lymphocytes	TGF-β and IL-10 (Gorosito Serrán et al., 2015)	Production of anti-inflammatory cytokines (Gorosito Serrán et al., 2015)	Maintenance of phase 2	Stimulation of tumor growth (Gorosito Serrán et al., 2015)

nance of one scenario may create an illusion of homogenous inflammation in the tumor.

A comparison of the manifestations currently known for Th1- and Th2-like IIRs occurring in the stroma of epithelial cancers indicates that aggressive properties of cancer cells are associated with Th2-like inflammation, which underlies the second phase of reparative regeneration with connective tissue generation and epithelization of skin and mucosa lesions (Eming et al., 2007; Arnold et al., 2015). The cellular and molecular events occurring in Th2-like inflammation that are characteristic of the second regeneration phase favor EMT and the mesenchymal mechanism of collective and individual invasion. There are grounds to believe that Th2 IIRs in the tumor microenvironment facilitate the synthesis of chemokines, which are necessary for the formation of premetastatic niches at sites of future distant metastases.

The published data demonstrate that the presence of cells with proinflammatory phenotypes (Th1 and M1) in the tumor microenvironment after neoadjuvant chemotherapy is associated with a favorable outcome and a lower metastasis rate. The association indicates again that suppression of the Th2 phenotype of the microenvironment (the antagonistic effect of a predominant Th1 response) deprives tumor cells of stromal support, which is essential for the acquisition of locomotor and metastatic properties, thus decreasing their potential to produce metastases after neoadjuvant chemotherapy.

To control stromal IIRs, the following important regularities of IIRs and their significance for tumor progression should be taken into account.

Tumor cell damage of any nature causes the changes that are characteristic of productive inflammation, which underlies wound healing.

If persistent, the first inflammation phase (wound healing), which is characterized by Th1 response, prevents the second regeneration phase and tumor progression, the stimulation of which is associated predominantly with the second phase.

Tumor progression is promoted to the greatest extent by processes characteristic of the second phase (wound healing), which is based on Th2 IIRs.

Specific immune responses to tumor antigens, the stimulation of innate inflammation, and the activation of iLT, Th22, Th17, Tfh, B cells, macrophages, and fibroblasts are factors that affect tumor progression, because they may facilitate or suppress IIRs of the anti-inflammatory Th2 type.

IIRs are heterogeneous in the tumor, because different Th and macrophage subpopulations most likely differentiate in the tumor, phenotypic plasticity is intrinsic in macrophages and T cells, and Th1 and Th2 responses are antagonistic.

Since both stromal IIRs and tumor cells are heterogeneous, different tumor–microenvironment relationships develop at different sites of the tumor, differing additionally in the likelihood of stimulation or inhibition of invasive and metastatic properties of the tumor.

CONCLUSIONS

In view of the above, the effect of stromal IIRs on tumor cells seems to depend on the efficiency of specific immune responses to a lesser extent than on the IIR type, which determines the cellular and cytokine spectra in the tumor microenvironment.

The following strategies seem promising for antitumor therapy based on the effect on the immune system and inflammatory reactions in the tumor.

(1) Induction of Th1 specific immune responses and inhibition of Th2 responses. The method has its limitations, because the corresponding antigens must be present in the tumor, tumor antigens are weakly immunogenic, and Th1 IIRs are difficult (if possible at all) to maintain for a long time without their transformation. Moreover, because tumor cells are capable of affecting their microenvironment, T cells and macrophages recruited into tumor tissue are affected by various tumor factors, which may change the potentially inhibitory phenotype of the cells.

(2) The design of anti-inflammatory treatment to suppress any inflammatory reaction in the tumor stroma. An especially appealing strategy is the use of effective anti-inflammatory drugs in combination with surgical resection of the tumor, chemotherapy, and radiotherapy. With means to efficiently affect the key components of inflammatory reactions available, the strategy will make it possible to distort the conditions that favor acquisition of invasive and metastatic properties by tumor cells and to prevent the formation of the tumor and premetastatic niches.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

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