Review Article

Mechanisms of immune response regulation in lung cancer

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Abstract: Lung cancer is a leading cause of cancer deaths. As a solid tumor with low antigenicity and heterogenic phenotype lung cancer evades host immune defense. The cytotoxic anticancer effect is suppressed by a complex mechanism in tumor microenvironment. The population of regulatory T cells (Tregs) plays a crucial role in this inhibition of immune response. Tregs are defined by presence of forkhead box P3 (Foxp3) molecule. The high expression of Foxp3 was found in lung cancer cells and in tumor infiltrating lymphocytes (TIL). Cytotoxic T-lymphocyte antigen 4 (CTLA4) is constitutively expressed on Tregs and suppresses T cell activation. The elevated CTLA4 expression in lymphocytes in patients with lung cancer was found. Recently the antibodies blocking CTLA4 showed some clinical efficacy in patients with lung cancer. Cancer cells and immune cells release many cytokines capable to show suppressive immune effect in cancer microenvironment. The most active are transforming growth factorβ (TGFβ) and IL-10. The pleiotropic function of Th17 population is TGFβ related. The myeloid lineage of suppressor cells in lung cancer is represented by tumor associated macrophages (TAM) with phenotype of M2 macrophages and some regulatory properties with releasing amounts of IL-10 and TGFβ. The myeloid derived suppressor cells (MDSCs) control cytotoxic T cell activity in mechanisms which are highly dependent on the context of tumor environment. The mechanisms of anticancer immune response regulation need further investigation as an important target to new way of treatment.

Keywords: Lung cancer; regulatory T cells (Tregs); Th17 cells; cytotoxic T-lymphocyte antigen 4 (CTLA4); myeloid derived suppressor cells (MDSCs)

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Lung cancer is the main oncological problem worldwide. Lung cancer is the first cause of cancer death among patients with malignancy. There are more than 1,600,000 new cases yearly (1). The prognosis is very poor with less than 15% of the total survival (2). There was demonstrated a strong causal relationship of lung cancer with cigarette consumption (1) .

There are two main histological types of lung cancer: non-small cell lung cancer (NSCLC) occurring in more than 85% of lung cancer cases and small cell lung cancer (SCLC). Both these types are totally different in biological character, clinical course and response to treatment. The basic curative method of treatment in NSCLC is tumor resection, while in SCLC-chemotherapy. The NSCLC is classified as a squamous cell type, adenocarcinoma and a large cell type (3). At the present time it is crucial to perform an appropriate histological classification and to select patients individually for treatment strategy with deep analysis of molecular tumor characteristic and evaluation of predictive factors (4-6). In the advanced stages of NSCLC chemotherapy and targeted therapy are being used with some effectiveness. Unfortunately chemotherapy is capable to destroy not only malignant cells but also normal tissue and immune cells, so to determine patient immune status before treatment seems to be very important. On the other hand some new agents used in chemotherapy sensitize immune system to immunotherapy by reducing the number of suppressor cells (7). The main causative agent for lung

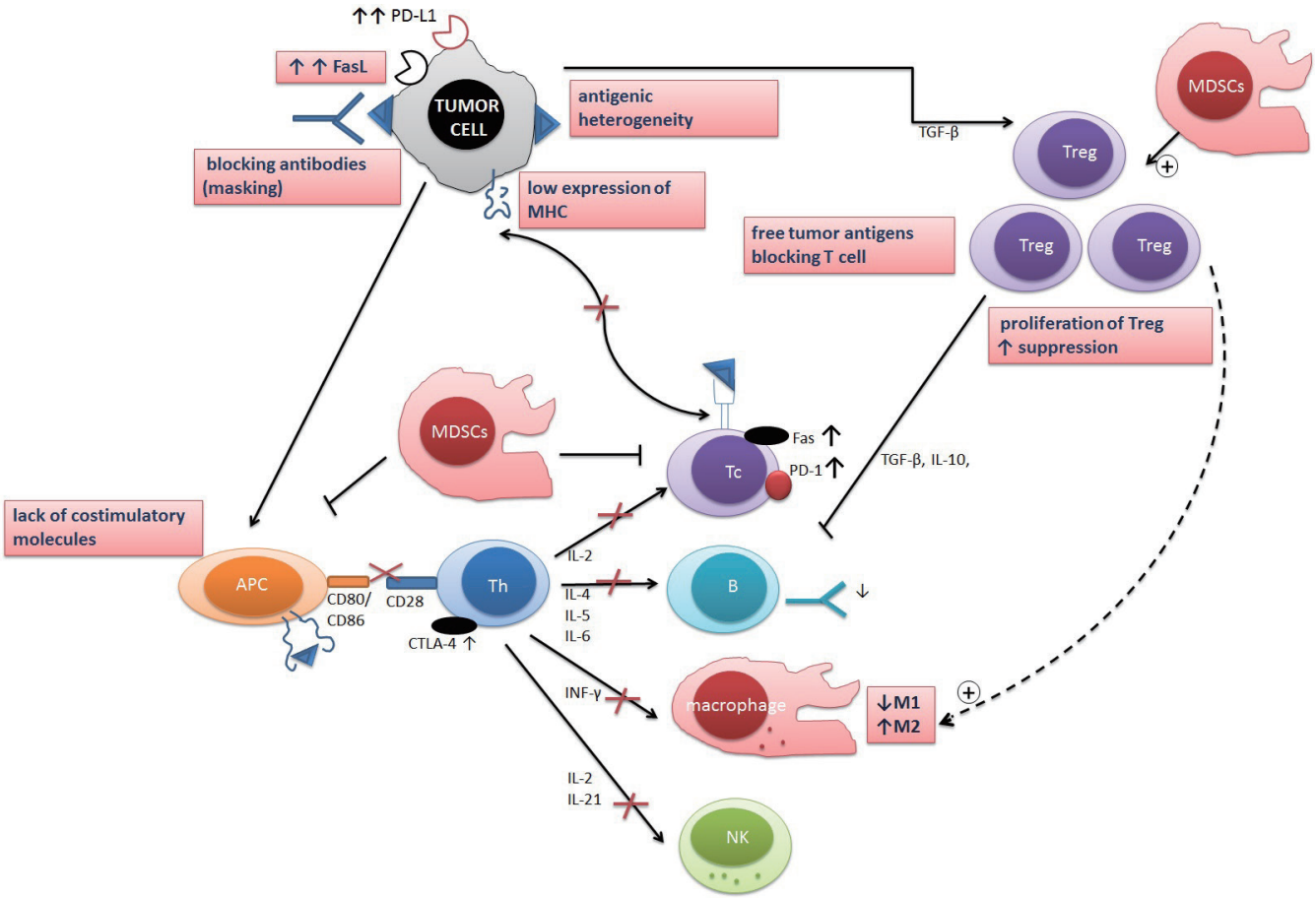

Figure 1 Mechanisms of lung cancer escape from immunosurveillance. Abbreviations: APC, antigen presenting cell; CTLA-4, Cytotoxic T lymphocyte antigen-4; Fas, apoptosis receptor; Fas-L, Fas ligand; PD-1, programmed cell death receptor; PD-L1, ligand to PD-1; MDSCs, myeloid derived suppressor cells; Th, T helper cell; Tc, cytotoxic lymphocyte; B, lymphocyte B; Treg, regulatory T cell; NK, natural killer; TGFβ, transforming growth factor β.

cancer development is tobacco smoke. However, in the last years the epidemiology of this malignancy changes with increasing incidence of lung cancer among non-smokers who never smoked (1). The last is considered to be a different disease: the adenocarcinoma type predominates, occurs most commonly in females and in patients at the older age (8). The total morbidity and mortality due to lung cancer are strongly correlated to the age. The senescence of immune system is a possible cause of this type of cancer. The following factors lead to lung cancer development in elderly: the impaired function of antigen presenting cells (APC), the increased concentration of IL-6, depletion of IL-2 with deficiency of effector T-cell population, Th2 polarization, the increased number of Th cells without costimulatory CD28 molecule (CD4/ $CD28^{null}$) (9,10). In all of the above the suppressor/ regulatory properties prevail over the activation of immune system in immunosurveillance of cancer. The mechanism of immunosurveillance in lung cancer is complex and declined in the course of the disease and the immunological tolerance i.e., the unresponsiveness of the immune system to specific antigens develops (11) (*Figure 1*).

The key immune cells active in tumor killing are cytotoxic T Lymphocytes (CTLs). CTLs with other effectors [among others—natural killer (NK) cells] are recruited thanks to tumor antigen presence mainly by dendritic cells (DCs) and macrophages. However, the antigen presenting function in malignancy is impaired. The anticancer defensive function is balanced and then outweighed by the regulation of immune response (12). As well as cytotoxic response is complex, the suppression of host anticancer answer is realized by a composite

network of cells and mediators modified by tumor microenvironment. This microenvironment is composed by tumor cells, fibroblasts, endothelial cells, macrophages, DCs, lymphocytes and the extracelluar matrix with many mediators: cytokines, chemokines, growth factors and enzymes (13). More other the tumor milieu is characterized by the altered conditions like hypoxia, which promotes angiogenesis and impact the epithelial-mesenchymal transition with increase metalloproteinase production (MMP-7, MMP-9). Tumor derived cytokines affect DCs thus the antigen presenting function is impaired. DCs in the course of cancer have immature phenotype and make T cells more tolerant to the autologous tumor cells (14,15).

The results of recent studies confirmed the important role of regulatory cells in the modification of immune response in malignancy. It was presented that regulatory T lymphocytes (Tregs) are capable to inhibit function of CD4+ and CD8+ lymphocytes, DCs and NK cells (16). Tregs play the important role in the immune surveillance and tolerance (16,17). Tregs are not numerous and not uniform lymphocyte subset [are present in peripheral blood (PB) in low proportion: 2-5% of lymphocytes] and are identified by the expression of the panel of the surface antigens. Tregs express: forkhead box P3 (Foxp3), CD25, glucocorticoid-induced TNF-receptor (GITR) (CD357), lymphocyte-activation gene 3 (LAG3), cytotoxic T lymphocyte antigen-4 (CTLA4) and downregulation of CD127 (IL-7R). However, Simonetta *et al.* observed high CD127 expression in the activated state (18). The specific inducing Tregs are triggered by the stimulation of tolerogenic DC, TGFβ and IL-10. The Tregs family is formed by: Tr1 (CD4+ cells induced by IL10), Th2, Th3 (acting by TGFβ), CD8+ cells, NKT (CD4–/CD8–) and "natural" T regulatory cells (Treg) (19). Natural Tregs are characterized by the expression of: CD4, CD25, Foxp3 and low CD127 and are derived from thymus, while induced Tregs (iTregs) are differentiated on periphery by cytokines and by contact with CD4+ cells (19). Foxp3 is a molecule which is necessary for proper Tregs function (20). Functionally the population of natural Tregs is derived from thymus having a strong suppressor function and expression of Foxp3, the second adaptive Tregs acquire Foxp3 expression after activation by antigenic exposure, known as a compression (20-22). The tumor milieu presents a good condition to conversion with specific antigenicity and high TGFβ concentration. DC plays a role in this process of conversion. The function of Tregs is widely explored. Recently Ju *et al.* described the population of CD13+/CD4/CD25^{high} Tregs in the PB of lung cancer patients with strong inhibitory properties (23). At this point it is worth noting that the CTLA4 molecule which is costimulator for Tregs is presented as an important factor in tumor progression. CTLA4 is constitutively expressed on Tregs and plays a role in regulating T cell tolerance (16,24,25).

The number and the function of Tregs are significantly depressed in the autoimmune diseases (17,26-28) while in malignancy both are augmented (21,29,30). The increased expression of Foxp3 was found in the cancer cells of different kinds of tumors and in tumor infiltrating lymphocytes (TIL) (31-33). The presence of Tregs as well as the expression of Foxp3 in lung cancer was found as a negative prognostic factor (34). Targeting of regulatory T-cells and negative regulatory molecules have been used in the attempt to circumvent immune tolerance (12,30,35). A significantly higher proportion of Tregs population in tumor and lymph nodes than in PB of lung cancer patients identified by flow cytometry was recently reported by Shigematsu *et al.* (36). In the other studies the Foxp3 expressing cells were detected by immunohistochemistry and their presence in tumor as well as in TIL was a negative prognostic factor (34,37-39). In the study of Tao *et al.* the Foxp3 expression was present in about one third of tumor cells. The prognostic importance was proposed when accompanied by Tregs infiltration: Foxp3 on tumor cells seemed to be a favorable factor for survival. The authors proposed Foxp3/Tregs index as a useful factor for prognosis using the same method for Foxp3 detection in cancer cells as well in lymphocytes (39). Of the other hand Liu *et al.* concluded that high Foxp3/CD8 ratio in biopsy specimens of patients with advance lung cancer is a predictor to response to chemotherapy (37). In the study of Fu *et al.* the Foxp3 was highly expressed in NSCLC cells and correlated with Toll like receptor 4 (TLR4) expression. TLR4 is present in lymphoid and tumour cells and promotes the immune tolerance in cancer by release of many active inflammatory mediators (40). Recently, Ju *et al.* defined highly suppressive cells with the phenotype: CD13+/CD4+/CD25^{high} Tregs which proportion in the PB correlated with the pathological stage of NSCLC. These cells expressed high levels of proteins known to have a strong immunosuppressive function: CTLA-4, mTGFβ1 and B7-H1 (PD-L1) (CD274) (23). The PD-L1 is the ligand to programmed death receptor-1 (PD-1), which is present on cytotoxic cells. The PD-1-PD-L1 interaction has a strong immunosuppressive effect and it was documented the blockade of PD-1/PD-L pathway using a fully humanized

anti-PD-1 antagonistic mAb increases the numbers and functions of tumor-specific T cells. Tregs are differentiated in the tumor environment by cytokines released by tumor cells and lymphoid cells: mainly by IL-10 and TGFβ. It was also found that Tregs are recruited from thymus by thymic stromal lymphopoietin (TSLP) by DC activation. The expression of TSLP was shown to be increased in lung cancer tissue and correlated with Tregs proportion (22). CD8+ Tregs are unknown in normal conditions however, in tumor environment the population of CD8/CD25+ and CD8/CD28– was described (7) with a higher proportion of the last population in the PB of lung cancer patients (41).

The other mechanism of the impaired anticancer defense and cancer cells hiding is the alterations of costimulatory molecules in cancer cells and in APC (11). T cells are the main cytotoxic population and recognize target cells by the action of APC (14). B7 molecule in the APC and their receptor CD28 in lymphocyte are necessary to activate their cytotoxic effect. B7 molecule is capable to present the suppressive signal by action with CTLA4, which inhibit the TCR signal on T cells (25). The augmentation of Tregs is accompanied by a higher expression of CTLA4. CTLA4 is 30% homological with CD28—costimulatory molecule with about 40× stronger affinity. By blocking CD28 CTLA4 leads to the depletion of a cell cycle, the decreased release of IL-2 and increased TGFβ production. CTLA4 is present only in TCR activated CD4 and in smaller number in CD8 cells. CTLA4 is needed for the regulation of activation: the CTLA4 knocked out mice develop sever lymphoproliferative disease with a massive polyclonal T-cell infiltration in organs (42). A gene encoding CTLA4 is a target for Foxp3 so CTLA4 is constitutively expressed on Tregs. This molecule appears on the surface of the cells after activation and is rapidly internalized into the cellular storage. It was found in NSCLC that the CTLA4 proportion was higher intracellular than on the surface of circulating CD4+ cells (43,44). However, the precise mechanism by which CTLA4 enhance immunosuppressive Tregs function is unknown. The antibody blocking CTLA4 is under investigation in lung cancer immunotherapy.

Cancer cells release many cytokines capable to show a suppressive immune effect in cancer microenvironment. The best recognized is TGFβ. The increased concentration of TGFβ in cancer tissue, bronchoalveolar lavage fluid from lung affected by cancer and the culture of cancer cells were reported (45-47). The following functions of TGFβ are strictly connected with the tumor progression: the inhibition of NK and CD8 cells function, the differentiation of Th to Th2 profile and the preservation of Tregs differentiation (48). On the other hand tumor cells are insensitive to inhibitory properties of TGFβ because of the loss of TGFβ receptors (49). Some interleukins present similar effect, among others IL-10 and IL-2, which induces CTLA4. IL-10 is present in high concentration when released by tumor cells as well as by immune cells. High concentration of IL-1, IL-6, IL21 and IL-23 in cancer milieu leads to the next part of the regulatory network in anticancer response i.e., Th17 cell differentiation (50). Th17 is a lineage of Th cells which is additional to the type Th1 and Th2. Th17 cells are defined by production of IL-17A. It was shown that the mouse Th17 has a common pathway with Treg Foxp3+. Both cell populations are produced after TGFβ stimulation but the differentiation to Th17 is mediated by IL-6. It is presumed that IL-6 inhibits Treg development with stimulation of Th17 TGFβ depended (51). In humans the interleukins: IL-1β and IL-23 are further required to the Th17 proliferation. The polarization Th17 is initiated by IL23 via IL23 R and Stat3 pathway to Th secreting IL17A. The second and stronger way is generated by TGFβ and IL6 via Smad family proteins (52). TGF at a low concentration contributes to the Th17 differentiation, while in high concentration to Foxp3 iTregs differentiation. These relations reflect a permanent balance between cytokines and Th populations and the Th17 plasticity. Th17 lymphocytes are active in antimicrobial defense, but their proliferative and cytotoxic effects are low. The role of Th17 cells in autoimmunity was documented (53). There are no direct data on the anticancer effect of Th17. Till now same results indicate that the effect of Th17 is complex as the IL-17 action in cancer milieu is pleiotropic: suppressive and stimulating (54). The stimulating effect is related to proangiogenic role of IL-17 (55). IL17A was present in high levels in a cancer tissue, PB and may stimulate angiogenesis by VEGF, recruit neutrophils and act as a tumor promoter (49,56). The immunosuppressive action of Th17 was also described (54). Recently, Zheng *et al.* described the IL-23R gene polymorphism connected with Tregs function and modification the susceptibility to lung cancer (57).

The main role of the cells originated from monocytes is antigen presentation. However recent data documented that this cell lineage plays a considerable regulatory function. In the solid tumors the population of tumor associated macrophages (TAM) was widely investigated. TAM are monocytes and local macrophages recruited to solid tumors playing several roles in tumor progression, rather promotion than suppression. Their infiltration,

which may be as great as 50% of tumor mass, results from the so-called "cancer education" (58-60). In general the function of TAM is impaired. Macrophages were previously considered as a uniform cell population, recently these cells are divided into different phenotypes: M1 and M2 and macrophages with regulatory properties (58,61). M1 and M2 are activated by different way and this polarization depends on the character of activation rather than the phenotype or the kind of released mediators. M1 are activated by LPS and INF while M2 by IL-4, IL-10, IL-13 and TGFβ (61). M1 macrophages are the effector cells, they play the immunostimulating role with secreting amounts of cytokines (IL-12 among others) and have phagocytic properties. The presence of M1 in TAM was found to be a favorable for survival in NSCLC (62). M2 macrophages with their suppressive function form about 70% of TAM population in NSCLC and promote angiogenesis, wound healing, release IL-10 (58,63). Recently Liu *et al.* described the relationship of M2 polarization in NSCLC environment with IL-17 and prostaglandin E2 (63). This different polarization of macrophages may be also detected by the immunocytochemistry with the following antibodies anti: CD206, CD163 (M2) and CD40 (M1). For regulatory macrophages (RMs) no defined surface antigenity is known, so the identification is based on the release of TGFβ and IL-10 (61). RMs present similar features to M2 producing high levels of IL-10 and being induced by IL4/IL13 network. These regulatory cells also express high levels of arginase. The Foxp3+ macrophage population inhibiting immune response was described in mice, however the strictly defined population of such macrophages in humans is unknown. The close functional relationship of Tregs with M2 macrophages was described in mice: CD4+/CD25+ cells are capable to enhance the expression of CD23, CD47, CD206, Toll Like Receptor 2 (TLR2) and TLR4 on macrophages and to potentiate the production of IL-10, TGFβ and arginase by macrophages (64). The investigation of TAM is possible in the samples from resected tumors while only about 30% cases of NSCLC are resectable; SCLC is nonresectable *per se*, so in the most of lung cancer cases the tumor microenvironment is not available for investigation. Nonetheless at the disposal of researchers there is BAL, the method of investigation of large part of the lung which provides the examination of cellular as well as humoral immune response (65,66). Alveolar macrophages present about 80% of BAL cells. Our previous investigation on the expression of ICAM-1 on BAL macrophages after stimulation by INFγ in lung cancer patients documented the usefulness of this method (67).

Myeloid derived suppressor cells (MDSCs) present a subpopulation of bone marrow derived hematopoietic cells, precursors of macrophages, granulocytes and DCs. The expansion of MDSCs in circulation was observed in sepsis, autoimmune disease as well as in malignancy (68,69). In NSCLC the lineage of MDSCs was defined by: CD11+CD14-CD15+CD33+ markers. The mediators secreting by cancer cells: GM-CSF, IL-6, IL1 support the survival of MDSCs in microenvironment. MDSCs inhibit activation of T cells, DC differentiation and promote Tregs. The mechanism of their action controlling T cell response involve the activity of arginase, nitric oxid (NO) synthase, the production of radical oxygen species (ROS) and the cysteine consumption (arginine, cysteine and NO are necessary for a proper T cell activation and memory type differentiation). MDSCs are capable to produce IL-10, MMP9 and TGFβ and favor angiogenesis, vasculogenesis and metastases (70). The COX2 overexpression in lung cancer and the process of epithelial-mesenchymal transition (EMT) seem to play an important role in the inhibition of antitumor response by MDSCs (7,71). EMT is necessary for tumor cells spread and it acts with MDSCs. The participation of transcription factors in this process was described. The recognition of MDSCs function leads to the development of therapy targeting these cells (12).

Conclusions

Lung cancer belongs to solid tumors of low antigenicity, heterogeneous and has a relatively low availability to research resulting from the low resection rate: about 70% of NSCLC cases are in the advanced stages at recognition and can't be qualified for curative treatment. The review of the literature shows that the studies on lung cancer immunity are being performed on resected tumors, samples of bronchial biopsies, PB, experimental studies or cancer cell lines. A very useful method but, so to say "wasteful", is the analysis of cells and mediators in the BAL. BAL may be performed in the advanced stages of lung cancer cases and in patients with SCLC. Our previous studies confirmed usefulness of this relatively low invasive method in the evaluation of immune status in the course of lung cancer (46,65,66,72,73). Taking into account the new promising results of immunotherapy and the tendency to personalized therapy to recognize the immune status before treatment is very important. It was mentioned that "the established tumors often also have the established regulatory cell

population" and it is particularly essential to assess the population of Tregs (CD4/CD25^{high}/FoxP3/CTLA4), M2, MDSCs and some cytokines: TGFβ, IL-10, IL-17A (30,74). The description of the immune status before treatment seems to be a new challenge for pathologists apart from the recognition of the histologic type of lung cancer and identification of molecular alterations (EFGR, ALK, KRAS).

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