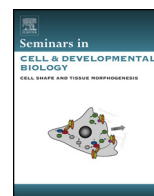




Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb



Review

Roles of immune microenvironment heterogeneity in therapy-associated biomarkers in lung cancer

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ARTICLE INFO

Article history:

Received 17 August 2016

Accepted 13 September 2016

Available online xxx

Keywords:

Lung cancer

Tumor microenvironment

Immune heterogeneity

Immune-targeted therapy

ABSTRACT

Lung cancer development is a complex and dynamic progression with cancer cell mutations itself and its' orchestrate with the tumor microenvironment. Targeted therapies have been stated to heterogeneous lung cancer mutations while have a modest consequence. The tumor immune microenvironment influences lung cancer outcome by balancing the suppressive versus cytotoxic responses. The immune microenvironment heterogeneity may play an important role in lung cancer heterogeneity. In this review, we summarized the immune cells, its related cytokines and partial immune genes diversity in tumor microenvironment and its targeted potential mono and combined therapies. It will help us to make better understand the lung cancer heterogeneity and mechanisms of the drug resistance to find a way out.

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Abbreviations: CAF, cancer associated fibroblast; GRP78, glucose-regulated protein 78; DC, dendritic cell; NK, natural killer cell; MDSC, myeloid-derived suppressor cell; TIL, tumor-infiltration lymphocyte; TAM, tumor-associated macrophage; NSCLC, non-small cell lung cancer; LUSC, squamous cell lung carcinoma; PD-1, programmed death-1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; MIF, macrophage migration inhibitory factor; PGE2, prostaglandin E2; OPN, osteopontin; FOXO3, forkhead box O3; PFS, progression-free survival.

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1. Introduction

Gene mutations orchestrated with the tumor microenvironment play critical roles in lung cancer development as a complex and dynamic progression. The lung cancer microenvironment is dependent upon intricate interactions among tumor cells and neighboring non-cancerous stromal cells such as endothelial cells, immune cells and fibroblasts [1]. The tumor microenvironment has been considered as a critical factor responsible for tumor progression and patients with high mortality [2]. Cancer associated fibroblast induced glucose-regulated protein 78 expression in lung cancer and promote lung cancer progression [3]. Immune cell

<http://dx.doi.org/10.1016/j.semcdb.2016.09.008>

1084-9521/© 2016 Published by Elsevier Ltd.

Please cite this article in press as: L. Wang, et al., Roles of immune microenvironment heterogeneity in therapy-associated biomarkers in lung cancer, Semin Cell Dev Biol (2016), <http://dx.doi.org/10.1016/j.semcdb.2016.09.008>

recruitment and localization in the tumor milieu vary and may indicate differential prognostic value. The density of CD8⁺ T cell and mature dendritic cell was heterogeneous among lung cancers and closely correlated with the survival rate [4], e.g. patients with larger CD8⁺ T cell density had better 5-year survival rate.

Tumor immune microenvironment heterogeneity is defined according to density, location and organization of immune cell types and cytokines in tumor microenvironment [5], where T cells coordinate the inflammatory functional networks and cells [6]. In the dynamic process of microenvironmental formation and function, innate and adaptive cells as an anti-tumor subtypes (e.g. effector T cells, mature dendritic cells or natural killer (NK) cells) can detect and destroy tumors, and genetic/epigenetic changes occur in those cells in response to the tumor [7–9]. The inflammatory cells become more immunosuppressive when cancer cells start to overgrow and migrate to the distant locations [10–13], although the heterogeneity between stages, durations, severities, and locations remains unclear.

The present review aims to highlight the role of immune microenvironment heterogeneity in lung cancer and the contribution of immune cells and inflammatory mediators in genes heterogeneity (Fig. 1). We further investigated molecular mechanism by which the heterogeneity can influence or dominate alterations of the lung cancer immune microenvironment in response to drug therapies and discuss potential strategies for targeted therapies on immune microenvironment to prevent the lung cancer from process and drug resistance (Fig. 2). We believe the understanding of heterogeneity of the immune microenvironment will benefit the discovery and development of systems therapies in lung cancer.

2. Immune microenvironment heterogeneity in lung cancer

2.1. Immune cell heterogeneity

Tumor-infiltration lymphocytes (TILs) can be differentiated among lung cancer types and stages, to be powerful prognostic factors with or without pathological criteria. The density of CD8⁺ T cells in the lung cancer tissue was suggested as a positive prognostic impact on patient survival [14], while that the number of CD8⁺ T cells were lower in metastatic lesions than in the corresponding primary tumors. The CD8/CD4 ratio as an activation indication of antitumor immunity reduced in metastatic lesions [15]. The frequency of circulating Tregs was considered as an independent prognostic factor in lung cancer [16], while the number of tumor infiltrating Tregs was associated with earlier recurrence and poorer prognosis as compared with those with low Tregs [6,17,18].

The infiltration of Th1/Th2 cells or tumor associated macrophages (TAMs) in tumor microenvironment was associated with the tumor progress and drug response in cancer [19–21]. High CD68⁺HLA-DR⁺ M1 macrophages were associated with a better outcome, while CD68⁺CD163⁺ M2 with worse overall survival in lung cancer [22–24]. Non-small cell lung cancer (NSCLC) subtypes had significantly higher infiltration of CD68⁺CD163⁺ M2 when compared to non-tumor tissues, while iNOS⁺ M1 decreased in patients with adenocarcinoma or LUSC, rather than those with large cell lung carcinoma [24]. It is indicated that other immune cell types were predominately involved in cancer microenvironment of large cell lung carcinoma than TAMs during the progression.

Monocytes originated from the same myeloid progenitor as macrophages also exhibit heterogeneity in lung cancer. Dendritic cells are heterogeneous group that play important roles in cancer for primary immune responses [25]. Dendritic cells infiltration in lung cancer was associated with an increase of TILs

and improved survival of NSCLC patients [26]. Myeloid-derived suppressor cells (MDSCs) compose of the monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (PMN-MDSCs) [27]. MDSCs play important roles in lung cancer progression and poor survival rate of patients with lung cancer [28], although the heterogeneity of MDSC infiltration in different lung cancer cell types and lung cancer stages remains unclear. MDSC biomarkers in human are defined with CD11b⁺CD33⁺HLA-DR^{low} and Lin^{1/low} [29]. A new subset of MDSC marked B7H3⁺CD14⁺HLA-DR^{low} was associated with reduced recurrence in patients with NSCLC and B7H3⁺ MDSCs were found only in the tumor microenvironment [30]. In addition, the infiltration density of CD20⁺ B cells [25], tumor-associated neutrophils (N1 and N2) [31] and NK cells [32,33] in lung cancer was associated with patient survival. Immune cells interaction with each other also found in the tumor microenvironment. For example, the number of CD8⁺ T cells was considered as an indication of the anti-tumor activity regulated by Tregs [34]. Thus, better understanding of immune cells infiltration and interactions in lung cancers will give us broader insights to treat lung cancer.

2.2. Heterogeneity of immune factors

Interactions and communications between cancer cells in cancer microenvironment are bidirectional, mainly through a complex network of immune factors such as cytokines, chemokines, and many growth factors [35]. The heterogeneity of predominant immune factors in the lung cancer microenvironment indicates diverse prognosis. The lung cancer microenvironment with increased concentrations of IL-10, TGF- β , IL-18, macrophage migration inhibitory factor (MIF), IL-8 and CXCL12 were associated with negative prognoses of patients with lung cancer, while pro-inflammatory cytokines such as IL-2, IL-12, IFN- γ , HLA-DR and IL-23 with longer overall survivals. IL-6 and TNF- α play a dual role in the progression of lung cancer [36].

TGF- β is a multifunctional cytokine to regulate cell proliferation, differentiation, and metastasis with immunosuppressive activity [37], and also has a potent interaction effect on other cytokines that systematically promote the progression of lung cancer [38]. TGF- β suppresses the production of pro-inflammatory cytokines, e.g. IL-12, IL-2 and IFN-substantially [39,40] and up-regulates the immunosuppressive cytokine IL-10 [40]. The expression of TGF- β 1 protein was up-regulated in the tumor microenvironment of NSCLC tissues, associated with the TNM classification of malignant tumors (TNM) stage of lung cancer. Survival analysis revealed that the five-year survival rate in patients with lower expression of TGF- β was higher than those with over-expression TGF- β [41]. TGF- β -up-regulated IL-10 also can positively feedback to enhance the expression of TGF- β and inhibit production of IL-12, IL-2, IFN- γ and IL-1. High expression of IL-10 was associated with negative prognosis in NSCLC [36]. IL-10 could over-expressed in lung cancer of patients with the IL-10 non-ATA haplotype with lower lymphocytes infiltration and a poor survival [42].

High concentrations of IL-18, IL-8, and MIF in the microenvironment were associated with advanced stages and a shorter overall survival of patients with lung cancer [36]. Oppositely, the IL-12-IFN- γ -HLA-DR axis was proposed to contribute to the improvement of patient survival rate. IL-12 increased IFN- γ expression in T cells and activated the process of local immune responses, followed by IFN- γ -stimulated HLA-DR expression to promote the innate immune response [43]. In such positive feedback loop, the immunosuppressive factors, such as TGF- β , prostaglandin E2 (PGE2), IL-4, were inhibited and Th1, CD8⁺ T cells, NK cells were recruited. The IL-12-IFN- γ -HLA-DR axis was down-regulated in the microenvironment of more advanced lung cancer at late stages [36]. IL-2 is responsible for T cell expansion and stimulates NK cells activation [44]. Reduced IL-2 in the microenvironment was asso-

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