The role of myeloid-derived suppressor cells in the relationship between chronic obstructive pulmonary disease and lung cancer

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by chronic pulmonary and systemic inflammation. There is strong evidence showing that COPD is an independent risk factor for lung cancer (LC). Chronic inflammatory response can affect all stages of tumour development, from tumour initiation to metastasis. Inflammation also alters tumour immune surveillance. Myeloid-derived suppressor cells (MDSC) are a heterogeneous mixture of immature granulocytic and monocytic cells characterized by an ability to suppress the antitumour activity of T-cells by down-regulation of the T-cell receptor chain (TCR $\zeta$) through the catabolism of l-arginine. COPD and lung cancer share a common pattern of expansion of MDSC associated with TCR $\zeta$ downregulation and T-cell dysfunction. MDSC may impair tumour immunosurveillance in COPD and can potentially facilitate tumour initiation and growth, contributing to explain the increased incidence of lung cancer reported in these patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterized by airflow obstruction associated with destruction of lung parenchyma caused by chronic inhalation of gases and noxious particles, primarily tobacco smoke. Comorbidities and exacerbations contribute to the severity of the disease [1].

COPD is highly prevalent and affects approximately 10% of adults worldwide [2]. It is the third most common cause of death in the United States, and it is estimated that it will be the third leading cause of death and disability worldwide by 2020 [3].

Comorbidities associated with COPD crucially influence the clinical symptoms, progress and prognosis of the disease [1]. Lung cancer is one of the most significant and common causes of death in COPD patients. Although the underlying mechanisms are not fully understood, lung cancer and COPD are clearly associated, possibly due to chronic inflammation [4-6].

Rudolf Virchow first suggested the potential link between inflammation and cancer in the 19th century. During the last decades there has been clear evidence that chronic inflammation plays a key role at every stage of tumourigenesis, from tumour initiation to tumour progression and metastatic dissemination [7]. Inflammatory cells produce a variety of molecules that can cause DNA mutations, genomic instability, malignant cell proliferation, neovascularization, invasion and metastasis. Chronic inflammation may also favour cancer development by disarming the capacity of the immune system to detect and destroy premalignant and malignant cells, a property known as tumour immune surveillance [7-9].

Myeloid-derived suppressor cells (MDSC) are multi-potent progenitor cells defined by their myeloid origin and their remarkable ability to suppress T-cell responses. MDSC were initially reported to be expanded in cancer patients as a mechanism of immune escape used by the tumour cells [10]. However, the alteration of the myelopoiesis resulting in the expansion and activation of MDSC is also associated with infectious, autoimmune and inflammatory conditions [11].

Our research group and others have described circulating MDSC upregulation associated with T-cell dysfunction in COPD patients [12,13]. Moreover, our group has recently shown that the pattern of expansion and activation of circulating MDSC associated with T-cell hyporesponsiveness is similar in COPD and lung cancer patients [14]. These findings suggest that the tumour immune surveillance may be altered in COPD patients without lung cancer. In this review, we discuss the potential role of MDSC as a link between inflammation and cancer in COPD.

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Key words: chronic inflammation, immunosuppression, Arginase 1

Received: May 31, 2016; Accepted: June 20, 2016; Published: June 23, 2016
COPD and lung cancer are associated diseases

Lung cancer is the major cause of cancer-related death worldwide with a poor five-year survival rate of only 16% [15,16]. The number of lung cancer deaths is expected to rise to ten million per year by 2030 [17].

Evidence based on population studies during the middle decades of the 20th century converged to establish cigarette smoking as the leading cause of lung cancer [18]. But, it was later in the 1980s when some researchers focused on the association between COPD and lung cancer beyond a common etiology [19, 20]. Cross sectional and longitudinal studies confirmed that COPD is a risk factor for lung cancer development independent of smoking history [19-24]. A meta-analysis of prospective, population studies that included 204,990 participants found that 6,185 developed or died from lung cancer in a follow-up period of 9-18 years. Participants with poorer lung function had a greater risk of developing lung cancer, but patients with less compromised lung function (FEV1 80%-100% predicted) also had a high risk of presenting LC [25]. In a smaller, non-population study, the incidence of lung cancer was greater in patients with mild-to-moderate obstruction in baseline lung function tests [26]. The independent relationship between air obstruction and pulmonary emphysema (the two pathological components of COPD), and the risk of lung cancer was also explored. Results showed that even in the absence of airway obstruction, patients with emphysema had a substantially higher risk of lung cancer [27,28]. Taken together, this evidence suggests that there may be mechanistic links between the two diseases.

Myeloid-derived suppressor cells: Linking chronic inflammation and immunosuppression

Chronic inflammation and immunosuppression

Chronic inflammation is a common denominator in a variety of conditions that differ in aetiology, such as inflammatory, autoimmune diseases, infections and cancer [29,30]. While chronic inflammation proceeds, normal immune homeostasis becomes affected leading to an immunosuppressive environment [29]. Indeed, in recent years, a variety of studies confirmed a suppression of natural killer (NK) cells and T cells in several disorders characterized by chronic inflammation via induction of MDSC. Initially, this phenomenon was shown in hosts with tumours as one of the mechanisms to escape antitumour immunity orchestrated by tumours [10]. However, these findings were later shown in different chronic inflammatory non-malignant conditions [11,31].

Myeloid-derived suppressor cells

In a chronic inflammatory environment, several survival, maturation and blocking cytokines as well as growth factors, such as GM-CSF, G-CSF, M-CSF, SCF, INF-γ, IL-1β, VEGF and IL-3, are released by inflammatory cells and inflamed tissues affecting myelopoiesis by increasing the proliferation of myeloid precursors from immature myeloid cells (IMC) and partially blocking their differentiation. This perturbation of the myelopoiesis results in the generation of MDSC, a heterogeneous population of immature myeloid cells with a remarkable ability to inhibit both innate and adaptive immune response, including NK cells, dendritic cells, macrophages and T cells [31]. Signal transducer and activator of transcription 3 (STAT3) is regarded as the main transcription factor that regulates the expansion of MDSC [31]. MDSC can be subdivided into granulocytic/neutrophilic MDSC (G-MDSC) and monocytic MDSC (M-MDSC) and human MDSC have been described to commonly express the myeloid markers CD11b and CD33 as well as CD66b/CD15 for G-MDSC and CD14 for M-MDSC [31,32]. MDSC exert their immune suppressor function through a variety of mechanisms and molecules, including arginase 1 (ARG 1) [31,32]. ARG 1 converts L-arginine (L-Arg) into urea and L-ornithine. Human MDSC release ARG 1 and deprive L-Arg and, thereby, inhibit T-cell function [33-35]. The shortage of L-arginine inhibits T-cell proliferation by decreasing T-cell receptor ζ expression (TCR ζ) [36].

TCR ζ is a critical sub-unit of the antigen recognition complex receptor on the T cell membrane (TCR) that plays a key role in the process of intracellular signal transduction [37]. Reduced TCR ζ expression affects the normal functioning of the T cell by impairing signal transduction between the TCR and transcription and gene expression factors which cause lower lymphocyte proliferation and reduced production of effector molecules [30,37]. Similar to MDSC, various chronic inflammatory conditions, including cancer, chronic infections (e.g., HIV, active tuberculosis, leprosy), and autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), are characterized by a reduction in TCR ζ expression, associated with defective T cell function [30]. Both in vitro and in vivo studies have demonstrated that MDSC modulate T cell function by reducing the TCR ζ expression [38-41]. This observation has led to the interpretation that both are protective mechanisms orchestrated by the host for lessening potential tissue damage from a persistently stimulated immune system at the price of immunosuppression [30,31].

Myeloid-derived suppressor cells in COPD and lung cancer

COPD is characterized by an enhanced inflammatory response of the lungs to inhaled particles and gases, particularly cigarette smoke [1], associated with increased circulating levels of inflammatory biomarkers, cytokines, acute phase proteins, and inflammatory cells, indicating the presence of additional systemic inflammation [42-45]. Recent studies highlight an emerging and complex role for MDSC in chronic inflammatory pulmonary diseases of different aetiologies, including lung cancer, asthma, cystic fibrosis and tuberculosis [46-48]. Our group and others have shown that MDSC are involved in the immunopathogenesis of COPD [12,48]. Our study provides evidence that expansion of circulating MDSC in COPD patients is associated with increased serum levels of ARG 1 and TCR ζ downregulation [12]. Other researchers reported similar findings: MDSC expansion was associated with increased levels of functional suppressor regulatory T cells (T-reg) and exhausted T effector cells (programmed death 1 [PD-1]+) [13]. These observations suggest that MDSC may be a major cause of T cell dysfunction and immunosuppression in COPD, and might therefore contribute to impairing tumour immune surveillance by allowing the proliferation of nascent transformed cells [48-52].

In a second study we hypothesized whether this pattern of expansion and activation of circulating MDSC associated to TCR ζ chain expression reduction could contribute to the increased risk of developing lung cancer in COPD patients [14]. We found higher percentages of MDSC as well as higher serum concentration of ARG 1 to a similar extent in lung cancer patients, COPD patients and patients with both entities, lung cancer and COPD (Figure 1). In these groups of patients we also found a reduction in the surface expression of TCR ζ in circulating lymphocytes compared with smokers without COPD and control non-smokers. Moreover, TCR ζ down-regulation was associated with T cell hyporesponsiveness in COPD and LC patients.
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**Figure 1.** Circulating levels of MDSC (a), serum levels of arginase I (b), expression of TCR ζ chain (c) and CD3 ε (d) in circulating T lymphocytes in the five groups studied. Figure reproduced from Scrimini et al. [14] with the permission of Springer. COPD, chronic obstructive pulmonary disease; LC, lung cancer; MFI, mean fluorescence intensity.

**Figure 2.** Expression of TCR ζ chain (a) and T cell proliferation assay using CFSE dilution protocol (b) in three cases (two COPD patients and one LC patient) and three healthy controls. Histograms and flow cytometry dot plots of T cell proliferation representative of LC, COPD and non-smoker control subjects (c). Figure reproduced from Scrimini et al. [14] with the permission of Springer.
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Figure 3. The role of myeloid-derived suppressor cells in COPD and lung cancer. Human myeloid-derived suppressor cells (MDSC) release Arginase 1 (ARG 1) and deprive L-arginine (L-Arg). The shortage of L-arginine inhibits T-cell proliferation by decreasing T-cell receptor ζ expression (TCR ζ) and, thereby, impairs T-cell function and alters antitumor immunity.

(Figure 2). These observations indicate that the immunosuppressive environment generated in hosts with lung cancer is also present in COPD patients and supports our working hypothesis that tumour immune surveillance might be altered in COPD patients (Figure 3) [14].

Conclusion

MDSC expansion associated with TCR ζ downregulation and T cell dysfunction in COPD may alter tumour immune surveillance favouring the initial proliferation of tumour cells and contributing to the increased incidence of lung cancer in these patients.

Funding

Funding was received from the General Department of Research and Technological Development and Innovation of the Ministry of Innovation, Interior and Justice of the Autonomous Community of the Balearic Islands, and FEDER Funds. Competitive Groups (PRER-22528-2011).

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