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Review

Myeloid-Derived Suppressor Cells: Possible Link Between Chronic Obstructive Pulmonary Disease and Lung Cancer☆

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are prevalent diseases and a leading cause of morbidity and mortality worldwide. There is strong evidence to show that COPD is an independent risk factor for LC. Chronic inflammation plays a significant pathogenic role in COPD comorbidities, particularly in LC. On the one hand, cellular and molecular inflammatory mediators promote carcinogenesis and, on the other, chronic inflammation impairs the capacity of the immune system to identify and destroy pre-malignant and malignant cells, a process known as tumor immune surveillance. This altered antitumor immunity is due in part to the expansion of myeloid-derived suppressor cells (MDSC), which are characterized by an ability to suppress the antitumor activity of T-cells by down-regulation of the T-cell receptor ζ chain (TCR ζ) through the catabolism of L-arginine. COPD and LC patients share a common pattern of expansion and activation of circulating MDSC associated with TCR ζ downregulation and impaired peripheral T-cell function. The objectives of this study were to review the evidence on the association between COPD and LC and to analyze how MDSC accumulation may alter tumor immune surveillance in COPD, and therefore, promote LC development.

Células mieloides supresoras: potencial vínculo entre la enfermedad pulmonar obstructiva crónica y el cáncer de pulmón

Palabras clave:
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RESUMEN

La enfermedad pulmonar obstructiva crónica (EPOC) y el cáncer de pulmón (CP) son enfermedades prevalentes y representan causas principales de morbimortalidad a nivel global. Existe firme evidencia que demuestra que la EPOC es un factor de riesgo independiente de CP. La inflamación crónica juega un rol patogénico significativo en el desarrollo de las comorbilidades en la EPOC, y en particular en el CP. Diferentes mediadores inflamatorios celulares y moleculares promueven la tumorigénesis e inhiben la capacidad del sistema inmunitario de reconocer y eliminar células premalignas y malignas, proceso conocido como inmunovigilancia tumoral. Esta alteración de la inmunidad antitumoral se debe en parte a la expansión de las células mieloides supresoras (*myeloid derived suppressor cells* [MDSC]), que se caracterizan por suprimir la función efectora antitumoral de linfocitos T mediante la reducción de la expresión del *T-cell receptor ζ* (TCR ζ) a través del catabolismo de la L-arginina. Los pacientes con EPOC y CP comparten un patrón similar de aumento y activación de las MDSC circulantes asociado a la reducción de la expresión del TCR ζ y a la alteración de la función de los linfocitos T periféricos. Los objetivos de este artículo son revisar la evidencia sobre la asociación entre EPOC y CP, y analizar cómo la acumulación de MDSC podría alterar la inmunovigilancia tumoral en la EPOC y favorecer el desarrollo de CP.

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Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are prevalent diseases and a leading cause of morbidity and mortality worldwide.[1] COPD affects approximately 10% of adults worldwide,[2] with a similar prevalence in Spain.[3] It is estimated that by 2020, COPD will become the third leading cause of death and disability.[4] LC is the major cause of cancer death in women and in men.[5,6] Five-year survival is poor, ranging from 6% to 14% in men and 7% to 18% in women.[7]

COPD is characterized by airflow obstruction associated with chronic inflammation of the airways and the lung parenchyma caused by the inhalation of gases and noxious particles, primarily tobacco smoke. Comorbidities and exacerbations add to the severity of the disease.[8,9] Clinical symptoms, progress and prognosis are crucially influenced by systemic manifestations and comorbidities, irrespective of the grade of airflow obstruction.[10,11]

In recent years, evidence has emerged of the pathogenic role of chronic inflammation in the development of comorbidities associated with COPD. One of the most significant, and a common cause of death in COPD patients, is LC.[12–14] Chronic inflammation plays an important role in tumorigenesis: mechanisms are many and varied. It enhances tumor formation, and also disarms the tumor immune surveillance capacity of the immune system, which would normally recognize and eliminate pre-malignant and malignant cells.[15–17] Phenomena associated with the mechanisms of cancer for evading antitumor immunity include the profound alteration of myelopoiesis and expansion of myeloid-derived suppressor cells (MDSC), which inhibit the main anti-tumor effectors, the T cells and natural killer (NK) cells. These phenomena are also associated with chronic non-malignant inflammatory processes, such as infectious diseases, inflammation and diseases caused by a dysregulated immune system.[16,18,19] Our group and others have observed expansion and activation of circulating MDSCs associated with T cell dysfunction in COPD patients.[20,21] The questions arising from these observations are the following: do COPD patients have altered tumor immune surveillance as a consequence of MDSC expansion? Would this explain, in part, the high incidence of LC in these patients? In this article, we aimed to review the studies that confirm the association between COPD and LC and to analyze how increased MDSC levels might alter tumor immune surveillance in COPD.

Chronic Obstructive Pulmonary Disease as a Risk Factor for Lung Cancer

Tobacco smoke is the main risk factor for LC and COPD, but not all smokers develop these diseases. However, patients who do develop COPD have a greater risk of developing LC, irrespective of the intensity of their exposure to tobacco smoke, their age or

Table 1
Characteristics of the Principal Studies of the Association Between Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer (LC).

Author	Year	Sample Size	Design	Follow-Up (years)	Outcome
Congleton and Muers[23]	1995	57 patients with LC	Cross-sectional	–	Prevalence of COPD: 49%
Loganathan et al.[24]	2006	294 patients with LC	Cross-sectional	–	Prevalence of COPD: Men: 72.8% Women: 52.5% OR: 0.41 (95% CI. 0.25–0.67; *P*=.0003)
Young et al.[25]	2009	301 patients with LC 301 paired controls	Cross-sectional	–	Prevalence of COPD in patients with LC: 50% Prevalence of COPD in paired controls without LC: 8% *P*≤.001
Skillrud et al.[32]	1986	226	Longitudinal	10	Accumulated 10-year incidence: 8.8% (cases) *vs* 2% (controls)
Van den Eeden and Friedman[28]	1992	171 311	Longitudinal	9	Incidence 1st quintile: FEV1 ≤66% predicted RR men: 1.86 (95% CI, 1.73–2.64) RR women: 1.95 (95% CI, 0.32–11.70)
Hole et al.[29]	1996	15 411	Longitudinal	15	Death 1st quintile: FEV1 ≤73% predicted RR men: 2.53 (95% CI, 1.68–3.82) RR women: 4.39 (95% CI, 1.86–10.38)
Mannino et al.[30]	2003	5402	Longitudinal	18	Incidence-death: RR: 2.8 (95% CI, 1.8–4.4)
Turner et al.[33]	2007	448 600 non-smokers	Longitudinal	20	Death: HR: 2.44 (95% CI, 1.22–4.90)
De Torres et al.[34]	2007	1166	Longitudinal	5	Incidence: RR patients with emphysema: 3.33 (95% CI,1.41–7.85) RR patients with emphysema and no airway obstruction: 4.33 (95% CI, 1.04–18.16)
Wilson et al.[35]	2008	3638	Longitudinal	3.7	Incidence: RR patients with emphysema: 3.56 (95% CI, 2.21–5.73) RR patients with emphysema and no airway obstruction: 3.14 (95% CI, 1.91–5.15)