ÁREA DE ENFERMEDADES INFECCIOSAS, INFLAMATORIAS Y CRÓNICAS

GRUPO DE NEUMOLOGÍA

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INVESTIGACIÓN: Básica y Clínica

OBJETIVO GENERAL (Básica)

Identificación de **biomarcadores** de predicción y diagnóstico, perfiles clínicos y **dianas terapéuticas** en enfermedades respiratorias. Aplicación de proteómica, metabolómica y transcriptómica. Estudio de mecanismos de daño y reparación celular sobre modelos experimentales y de simulación

LÍNEAS DE INVESTIGACIÓN (Proyectos en marcha)

- **Enfermedad Pulmonar Obstructiva Crónica (EPOC):** **marcadores de hipoxia** en la **confluencia de EPOC/SAHS/CP**; **transcriptómica de la susceptibilidad** al desarrollo del daño pulmonar; nuevos mecanismos patogénicos en pacientes EPOC en fase estable y agudizada por medio del estudio de la **funcionalidad y muerte celular de neutrófilos**; **metabolómica** para la identificación de **marcadores de predicción y diagnóstico** en la historia natural de la EPOC; caracterización precoz del **enfisema subclínico** y factores de progresión

- **Cáncer de Pulmón (CP):** cohortes de **detección precoz** de CP; **epigenética** en muestras de punción por EBUS; **metabolómica** en suero de pacientes con alto riesgo de CP; **prevalencia de SAHS** en pacientes con CP; **radiómica aplicada a pacientes tratados con inmunoterapia**; estudio de los **niveles de PDL1** soluble en pacientes de los estudios de prevalencia de SAHS en CP

- **Apnea Obstructiva del Sueño (SAHS):** tratamiento del SAHS en la **insuficiencia cardíaca**; asociación entre los trastornos respiratorios del sueño y el pronóstico del **melanoma cutáneo maligno**; eficacia de la ventilación no invasiva ajustada automáticamente en el **síndrome de hipoventilación obesidad**; efecto de la CPAP en la **enfermedad renal crónica** y en la **nefropatía diabética**; valoración de la prevalencia de **hipertensión arterial en pacientes pediátricos** con trastornos respiratorios del sueño; impacto del tratamiento con **dispositivo de avance mandibular** en la calidad del sueño en pacientes con SAHS

PUBLICACIONES MÁS RELEVANTES

- Pérez-Rial S et al. Early detection of skeletal muscle bioenergetic déficit…in cigarette smoke-exposed mice. Plos One 2020
- Masa JF et al. Echocardiographic changes with positive airway pressure therapy in obesity hypoventilation síndrome... Am J Respir Crit Care Med 2020
- Seijo LM et al. New evidence on the chemoprevention of inhaled steroids and the risk of lung cancer in COPD. Eur Resp J 2019
- Ferrando C et al. Individualised perioperative open-lung approach vs standard protective ventilation in abdominal surgery... Lancet Resp Med 2018
- Suarez-Sipmann F et al. Physiological markers for ARDS: Let's get more efficient!. Am J Respir Crit Care Med 2018
- Martinez-Garcia MA et al. Sleep-disordered breathing Is independently associated with increased aggressiveness of cutaneous melanoma. Chest 2018
- Martínez C et al. Changes and clinical consequences of smoking cessation in COPD patients: a prospective analysis from the CHAIN cohort. Chest 2018
- Corral J et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax 2018
- Casanova C et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J 2017
- Navarrete A et al. A metabolomic approach shows SP1-P and…as mediators of the therapeutic effect of LGF in emphysema. J Pharm Biomed Anal 2017

PUBLICACIONES MÁS RELEVANTES (Básica)

> PLoS One. 2020 Jun 22;15(6):e0234606. doi: 10.1371/journal.pone.0234606. eCollection 2020.

Early detection of skeletal muscle bioenergetic deficit by magnetic resonance spectroscopy in cigarette smoke-exposed mice

Sandra Pérez-Rial [1 2], Esther Barreiro [2 3], María Jesús Fernández-Aceñero [4], María Encarnación Fernández-Valle [5], Nicolás González-Mangado [1 2], Germán Peces-Barba [1 2]

Abstract

Skeletal muscle dysfunction is a common complication and an important prognostic factor in patients with chronic obstructive pulmonary disease (COPD). It is associated with intrinsic muscular abnormalities of the lower extremities, but it is not known whether there is an easy way to predict its presence. Using a mouse model of chronic cigarette smoke exposure, we tested the hypothesis that magnetic resonance spectroscopy allows us to detect muscle bioenergetic deficit in early stages of lung disease. We employed this technique to evaluate the synthesis rate of adenosine triphosphate (ATP) and characterize concomitant mitochondrial dynamics patterns in the gastrocnemius muscle of emphysematous mice. The fibers type composition and citrate synthase (CtS) and cytochrome c oxidase subunit IV (COX4) enzymatic activities were evaluated. We found that the rate of ATP synthesis was reduced in the distal skeletal muscle of mice exposed to cigarette smoke. Emphysematous mice showed a significant reduction in body weight gain, in the cross-sectional area of the total fiber and in the COX4 to CtS activity ratio, due to a significant increase in CtS activity of the gastrocnemius muscle. Taken together, these data support the hypothesis that in the early stage of lung disease, we can detect a decrease in ATP synthesis in skeletal muscle, partly caused by high oxidative mitochondrial enzyme activity. These findings may be relevant to predict the presence of skeletal bioenergetic deficit in the early stage of lung disease besides placing the mitochondria as a potential therapeutic target for the treatment of COPD comorbidities.

PUBLICACIONES MÁS RELEVANTES (Básica)

> Respir Physiol Neurobiol. 2012 Jun 15;182(1):9-17. doi: 10.1016/j.resp.2012.02.001. Epub 2012 Feb 18.

Cigarette smoke-induced oxidative stress in skeletal muscles of mice

Esther Barreiro [1], Laura del Puerto-Nevado, Ester Puig-Vilanova, Sandra Pérez-Rial, Francisco Sánchez, Lourdes Martínez-Galán, Stephanie Rivera, Joaquim Gea, Nicolás González-Mangado, Germán Peces-Barba

Abstract

Cigarette smoke (CS)-induced oxidative stress may cause muscle alterations in chronic conditions such as chronic obstructive pulmonary disease (COPD). We sought to explore in AKR/J mice exposed to CS for 6 months and in control animals, levels of protein oxidation, oxidized proteins (immunoblotting, proteomics) and antioxidant mechanisms in both respiratory and limb muscles, body weight modifications, systemic inflammation, and lung structure. Compared to control mice, CS-exposed animals exhibited a reduction in body weight gain at 3 months and thereafter, showed lung emphysema, and exhibited increased oxidative stress levels in their diaphragms and gastrocnemius at 6 months. Proteins involved in glycolysis, ATP production and distribution, carbon dioxide hydration, and muscle contraction were carbonylated in respiratory and limb muscles. Blood tumor necrosis factor (TNF)-alpha levels were significantly greater in CS-exposed mice than in control animals. In AKR/J mice, chronic exposure to CS induces lung emphysema concomitantly with greater oxidative modifications on muscle proteins in both respiratory and limb muscles, and systemic inflammation.

PUBLICACIONES MÁS RELEVANTES (Básica)

> Am J Physiol Lung Cell Mol Physiol. 2014 Nov 1;307(9):L718-26.
doi: 10.1152/ajplung.00293.2013. Epub 2014 Aug 29.

Liver growth factor treatment reverses emphysema previously established in a cigarette smoke exposure mouse model

Sandra Pérez-Rial [1], Laura Del Puerto-Nevado [2], Alvaro Girón-Martínez [2], Raúl Terrón-Expósito [2], Juan J Díaz-Gil [2], Nicolás González-Mangado [2], Germán Peces-Barba [2]

Abstract

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease largely associated with cigarette smoke exposure (CSE) and characterized by pulmonary and extrapulmonary manifestations, including systemic inflammation. Liver growth factor (LGF) is an albumin-bilirubin complex with demonstrated antifibrotic, antioxidant, and antihypertensive actions even at extrahepatic sites. We aimed to determine whether short LGF treatment (1.7 μg/mouse ip; 2 times, 2 wk), once the lung damage was established through the chronic CSE, contributes to improvement of the regeneration of damaged lung tissue, reducing systemic inflammation. We studied AKR/J mice, divided into three groups: control (air-exposed), CSE (chronic CSE), and CSE + LGF (LGF-treated CSE mice). We assessed pulmonary function, morphometric data, and levels of various systemic inflammatory markers to test the LGF regenerative capacity in this system. Our results revealed that the lungs of the CSE animals showed pulmonary emphysema and inflammation, characterized by increased lung compliance, enlargement of alveolar airspaces, systemic inflammation (circulating leukocytes and serum TNF-α level), and in vivo lung matrix metalloproteinase activity. LGF treatment was able to reverse all these parameters, decreasing total cell count in bronchoalveolar lavage fluid and T-lymphocyte infiltration in peripheral blood observed in emphysematous mice and reversing the decrease in monocytes observed in chronic CSE mice, and tends to reduce the neutrophil population and serum TNF-α level. In conclusion, LGF treatment normalizes the physiological and morphological parameters and levels of various systemic inflammatory biomarkers in a chronic CSE AKR/J model, which may have important pathophysiological and therapeutic implications for subjects with stable COPD.

PUBLICACIONES MÁS RELEVANTES (Básica)

> PLoS One. 2014 Nov 17;9(11):e112995. doi: 10.1371/journal.pone.0112995. eCollection 2014.

Proliferative activity of liver growth factor is associated with an improvement of cigarette smoke-induced emphysema in mice

Álvaro Girón-Martínez [1], Sandra Pérez-Rial [1], Raúl Terrón-Expósito [1], Juan José Díaz-Gil [1], Nicolás González-Mangado [1], Germán Peces-Barba [1]

Abstract

Cigarette smoke (CS)-induced emphysema is a major component of chronic obstructive pulmonary disease (COPD). COPD treatment is based on the administration of bronchodilators and corticosteroids to control symptoms and exacerbations, however, to date, there are no effective therapies to reverse disease progression. Liver growth factor (LGF) is an albumin-bilirubin complex with mitogenic properties, whose therapeutic effects have previously been reported in a model of emphysema and several rodent models of human disease. To approach the therapeutic effect of LGF in a model of previously established emphysema, morphometric and lung function parameters, matrix metalloproteinase (MMP) activity and the expression of several markers, such as VEGF, PCNA, 3NT and Nrf2, were assessed in air-exposed and CS-exposed C57BL/6J male mice with and without intraperitoneal (i.p.) injection of LGF. CS-exposed mice presented a significant enlargement of alveolar spaces, higher alveolar internal area and loss of lung function that correlated with higher MMP activity, higher expression of 3NT and lower expression of VEGF. CS-exposed mice injected with LGF, showed an amelioration of emphysema and improved lung function, which correlated with lower MMP activity and 3NT expression and higher levels of VEGF, PCNA and Nrf2. Taken together, this study suggests that LGF administration ameliorates CS-induced emphysema, highlights the ability of LGF to promote alveolar cell proliferation and may be a promising strategy to revert COPD progression.

PUBLICACIONES MÁS RELEVANTES (Básica)

> PLoS One. 2013 Sep 13;8(9):e72975. doi: 10.1371/journal.pone.0072975. eCollection 2013.

Role of recently migrated monocytes in cigarette smoke–induced lung inflammation in different strain of mice

Sandra Pérez-Rial [1], Laura del Puerto-Nevado, Raúl Terrón-Expósito, Álvaro Girón-Martínez, Nicolás González-Mangado, Germán Peces-Barba

Abstract

This study investigates the role of proinflammatory monocytes recruited from blood circulation and recovered in bronchoalveolar lavage (BAL) fluid in mediating the lung damage in a model of acute cigarette smoke (CS)-induced lung inflammation in two strains of mice with different susceptibility to develop emphysema (susceptible -C57BL/6J and non susceptible -129S2/SvHsd). Exposure to whole-body CS for 3 consecutive research cigarettes in one single day induced acute inflammation in the lung of mice. Analysis of BAL fluid showed more influx of recently migrated monocytes at 72 h after CS-exposition in susceptible compared to non susceptible mice. It correlated with an increase in MMP-12 and TNF-α protein levels in the lung tissue, and with an increment of NF-κB translocation to the nucleus measured by electrophoretic mobility shift assay in C57BL/6J mice. To determine the functional role of these proinflammatory monocytes in mediating CS-induced airway inflammation, alveolar macrophages and blood monocytes were transiently removed by pretreatment with intratracheal and intravenous liposome-encapsulated CL2MDP, given 2 and 4 days prior to CS exposure and their repopulation was studied. Monocytes/macrophages were maximally depleted 48 h after last liposome application and subsequently recently migrated monocytes reappeared in BAL fluid of susceptible mice at 72 h after CS exposure. Recently migrated monocytes influx to the lung correlated with an increase in the MMP-12 protein level in the lung tissue, indicating that the increase in proinflammatory monocytes is associated with a major tissue damaging. Therefore our data confirm that the recruitment of proinflammatory recently migrated monocytes from the blood are responsible for the increase in MMP-12 and has an important role in the pathogenesis of lung disease induced by acute lung inflammation. These results could contribute to understanding the different susceptibility to CS of these strains of mice.

PUBLICACIONES MÁS RELEVANTES (Básica)

> J Pharm Biomed Anal. 2017 May 30;139:238-246. doi: 10.1016/j.jpba.2017.02.045.
Epub 2017 Feb 27.

A metabolomic approach shows sphingosine 1-phosphate and lysophospholipids as mediators of the therapeutic effect of liver growth factor in emphysema

A Navarrete [1], F J Rupérez [1], T O Mendes [1], S Pérez-Rial [2], A Girón-Martínez [2], R Terrón-Expósito [2], J J Díaz-Gil [2], G Peces-Barba [2], C Barbas [1], A García [3]

Abstract

Tobacco smoke exposure is the principal cause of lung tissue destruction, which in turn results in emphysema that leads into shortness of breath. Liver growth factor (LGF, a cell and tissue regenerating factor with therapeutic activity in several organs) has antifibrotic and antioxidant properties that could be useful to promote lung tissue regenerating capacity in damaged lungs. The current study has examined differences in metabolite profiles (fingerprints) of plasma from mice (strain C57BL/6J, susceptible to develop emphysema) exposed to tobacco smoke during six months. One group of mice received a treatment with Liver Growth Factor (LGF) after emphysema was established, whereas the other group did not receive the treatment. Age and sex-matched mice not exposed to smoke were also maintained with or without treatment as controls. Metabolic fingerprints (untargeted analysis) of plasma after protein precipitation were obtained by LC-QTOF-MS. The signals were processed and a large number of possible metabolites were found (23944). Multivariate data analysis provided models that highlighted the differences between control and smoke exposed mice in both conditions. Accurate masses of features (possible compounds) representing significant differences were searched using online public databases. Lipid mediators, related to intracellular signaling in inflammation, were found among the metabolites putatively identified as markers of the different conditions and among them, sphingosine, sphingosine 1-phosphate and lysophospholipids point at the relevance of such metabolites in the regulation of the processes related to tissue regeneration mediated by LGF. These results also suggest that metabolomic fingerprinting could potentially guide the characterization of relevant metabolites leading the regeneration of lungs in emphysema disease.

PUBLICACIONES MÁS RELEVANTES (Básica)

> Mol Imaging. 2011 Oct;10(5):398-405. doi: 10.2310/7290.2011.00010.

Early detection of susceptibility to acute lung inflammation by molecular imaging in mice exposed to cigarette smoke

Sandra Pérez-Rial [1], Laura Del Puerto-Nevado, Nicolás González-Mangado, Germán Peces-Barba

Abstract

Matrix metalloproteinases (MMPs) are extracellular proteolytic enzymes involved in acute lung inflammation in response to cigarette smoke exposure (CSE). We present the in vivo detection of MMP activity using a specific MMP-activatable, near-infrared, polymer-based proteolytic probe in strains of mice with different susceptibility to developing smoking-induced emphysema (susceptible mice, C57BL/6j, and resistant mice, 129S2/SvHsd) to characterize the distinctive profile of CSE-induced acute inflammation. In vivo imaging of pulmonary inflammation expressing MMPs revealed a significantly different median ratio twofold higher in smoker than in nonsmoker susceptible mice (C57BL/6j) and no significant differences between the smoker and the nonsmoker group in resistant mice (129S2/SvHsd). Ex vivo imaging of the lungs of each group of mice confirmed the same in vivo experiment results obtained for both strains of mice. In the biochemical study of lung tissue, the proteolytic signal colocalized with the endogenously expressed MMP protein levels, with MMP-9 levels that are 2.2 times higher than in the nonsmoke-exposed group in C57BL/6j mice and no significant differences in the 129S2/SvHsd mice. The MMP-activatable probe provides a useful reagent for the in vivo and ex vivo detection of MMP-selective proteolytic activity. We are able to distinguish between susceptible and resistant strains of mice in terms of the profile of MMP activity in the early stages of pulmonary disease.

PERSPECTIVAS FUTURAS

- Liderar nuevos proyectos de investigación en identificación de nuevas vías patogénicas y biomarcadores de diagnóstico y tratamiento
- Establecimiento de nuevas líneas de investigación en terapia celular y biomateriales
- Nuevas líneas de investigación sobre modelos experimentales y de simulación con creación de patentes
- Incremento de fuentes de financiación a través de becas de organismos públicos y privados
- Dinamización e incremento de recursos del laboratorio experimental
- Aumento de la colaboración y liderazgo en redes de investigación

PROPUESTAS DE COLABORACIÓN

- **OFERTA:** diseño de modelos animales (ratón) de enfisema, hipoxia y cáncer de pulmón; estudios de función pulmonar con el animal traqueotomizado; estudios de imagen molecular de fluorescencia y bioluminiscencia en ratones (IVIS Lumina)

- **DEMANDA:** técnicas de imagen para pequeños animales, (PET, CT, RMN,…); análisis de plataformas ómicas y técnicas de secuenciación masiva; estudiantes de doctorado

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