



Metabonomics Followed of the Evolution of Bleomycin-Induced Pulmonary Fibrosis in the Rat

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Rec date: November 17, 2016, Acc date: February 10, 2017, Pub date: February 13, 2017

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Citation: Abidi A, Robbe A, Kourda N, Legrand A, Khamsa SB (2017) Metabonomics Followed of the Evolution of Bleomycin-Induced Pulmonary Fibrosis in the Rat. Immunol Disord Immunother 2: 111.

Keywords: Experimental pulmonary fibrosis; Evolution; Metabonomie; Bleomycin; Histone hypermethylation; DNA methylation

Introduction

The objective of this work is to look for biomarkers scalability of pulmonary fibrosis by metabonomics, genetics and immunohistochemical approaches in an animal model of pulmonary fibrosis induced by bleomycin in the Wistar rat.

Methods

Twenty Wistar rats, weighing 220 g to 240 g, were randomly divided into two groups: a control group (G1, n=10) and treated group (G2, n=10). The rats in group G2 were investigated at various times after instillation of Bleomycin (4 mg/kg) intra-tracheally (in days 3, 7, 14 and 21). The rats in the G1 group underwent the same treatment by replacing bleomycin with saline. During the experimental period, the rats were placed in metabolic cages for urine collection until the 21st day. Samples of urine, blood and bronchoalveolar liquid were analyzed by proton nuclear magnetic resonance (¹H NMR) and the spectra obtained by this technique have been further processed by two specific software: MestReNova and Simca-P+. The pulmonary tissues were used for histological and immunohistochemical analyzes.

Results

In the treated group (G2), a significant increase in inflammation and fibrosis score compared to the control group (G1) on days 3 and 7. For results obtained from NMR spectra, chemical shifts in the samples of urine showed an increase in the secretion of acetate, succinate dehydrogenase, α -ketoglutarate, creatine and taurine in days 3 and 7 corresponding to the inflammatory phase of fibrotic processes. For fibrosis phase (day 14 and 21), it is marked essentially by an increase in secretion of α -ketoglutarate and citrate. Bronchoalveolar lavage spectra, showed an increase in the rate of β -hydroxybutyrate, lactate and dimethylamine during the inflammatory phase, and a decrease of the choline secretion, trimethylamine, glycine and glucose during the

fibrosis phase. These results provide an indication of the inflammatory component (days 3 and 7) by increasing taurine and creatinine and the difficulties of oxygenation via the general increase in the Krebs cycle intermediates secreted by the liver. The fibrotic component (days 14 and 21) is marked by significant activity of mitochondrial oxidative phosphorylation and the development of fibrotic tissue.

These results concretize well with those obtained by Coward et al. [1] which revealed that histone H3K9 methyltransferase G9a and H3K27 methyltransferase EZH2 play a critical role in the suppression of cyclooxygenase-2 (COX-2) and involved in the initiation of processes of pulmonary fibrosis. These observations clearly indicate that establishment and maintenance of heterochromatin at specific loci triggers the occurrence of pulmonary fibrosis. In addition, as both G9a and EZH2 interact with DNA methyltransferases (DNMTs) [2,3], DNA methylation might also be involved in the progression of IPF. Actually, it has been revealed that apart from heterochromatic histone modifications, DNA methylation also exists at the promoter of COX-2 in patient-derived lung fibroblasts.

Conclusion

The pathological, metabonomic, patterns of H3K9/27me and DNA methylation results, in normal group compared to Bleomycin-induced pulmonary fibrosis could facilitate the understanding towards with mechanisms that involved in the initiation and development processes of pulmonary and other organ fibrosis and consequently could contribute to possible better target to find the appropriate treatment for pulmonary fibrosis.

References

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