Reversion Of Lung Fibrosis In C57BL6 Mice Using Statins

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Objective: In radiation enteropathy models, activation of Rho/ROCK signalling pathway trigger radio-induced fibrosis and constitutes a new therapeutic target as Rho inhibition using anti-fibrotic properties of statins. In this study we investigate whether the pathological activation of the Rho/ROCK pathway was specific to the gut or could represent a more general pathogenic path. Therefore, anti-fibrotic properties of Rho/ROCK pharmacological inhibitors were tested in murine models of lung fibrosis. Materials and methods: Pulmonary fibrosis was induced in pathogen-free 10-wk-old female C57BL/6 mice by 1) IP injection of Bleomycin at 40 mg/kg body weight on Days 0, 2, 4, 6 and 8 and 2) Thorax irradiation (16 Gy, 17 Gy; RX 250 KeV). Mice follow-up was performed twice a week for the overall experimental period and tissue collection was performed at Day 15 and 30 and at week 15 and 26 respectively for bleomycin and irradiation model. Safron stain was used for collagen quantification after slide scanning (Nikon Scan) and analysis by Pixcyt program. Fibrosis development was monitored by HES staining. CTGF and α SM actin expression were studied by Western Blot and Q-RT-PCR. Curative effect of Rho and ROCK inhibition were studied in vivo using respectively pravastatin (40 mg/Kg/d) and simvastatin (20 mg/Kg/d) delivered over 14 days via osmotic pump implantation. Results: histopathological examinations show inflammatory lesions mixed up with fibrotic areas at Day 15 whereas fibrosis is fully established D30. The fibrotic lesions are located in the subpleural zones and within the large peripheral vessels. Quantification of the collagen deposition show progressive increase of collagen after D15. Curative administration of pravastatin increased the body weight of the animals by 25% as compared to the vehicle-treated group and significantly improved survival (83% vs 56%). In the same groups, HES analysis showed an almost complete regression of fibrosis in all animals. These results were less impressive in simvastatin group with a survival gain equal to 10%. Experiments on irradiation-induced lung fibrosis are currently ongoing. Conclusion: This study confirms and extends the anti-fibrotic therapeutic action of statins and shows that bleomycin-induced lung fibrosis can be modulated by Rho/ROCK pathway inhibition. However, further investigation are required to investigate the distinct action elicited by pravastatin versus simvastatin. As the Rho family is composed of several members, one hypothesis is that pravastatin and simvastatin could target different member of the Rho family.

Article published by EDP Sciences and available at http://www.radioprotection.org
or http://dx.doi.org/10.1051/radiopro:2008590