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Title: Coagulation factor IX deficiency does not afford protection from pulmonary fibrosis in the experimental murine bleomycin model

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Body: Introduction: Animal and human studies strongly suggest the importance of the coagulation cascade in acute and chronic lung injury. Indeed, beyond their role in hemostasis, coagulation factors can signal via their cellular receptors, the protease-activated receptors. We hypothesized that the absence of coagulation Factor(F)IX, which is essential for the activation of the coagulation cascade would reduce fibrosis development and progression. Methods: We used the murine model of bleomycin-induced pulmonary fibrosis in wild-type (WT; n=14) and FIX deficient mice (n=13). After 14 days, we assessed markers of tissue fibrosis, inflammatory cell influx in the bronchoalveolar lavage fluid (BALF), and cytokines levels in the BALF, blood and lung homogenate of the animals. Results: Mortality during the experiment was higher in the FIX deficient mice compared to wildtypes (23% versus 7%). The remaining FIX deficient mice (n=10) developed pulmonary fibrosis to a degree similar to WT (n=13). There was no significant difference in the Ashcroft score between WT and FIX deficient mice (4.011±0.4 versus 4.2±0.4), in the alpha-actin score (0.94±0.09 versus 0.70±0.07) and in the inflammatory cell number. In contrast, we observed in the plasma of the FIX deficient mice significant elevations in levels of cytokines IL-12, TNFα, IFNγ, MCP-1 and IL-6. Conclusion: Mice with a congenital deficiency of FIX are not protected against bleomycin-induced pulmonary fibrosis. These data strongly argue against an important role of the blood coagulation cascade in the progression of pulmonary fibrosis, and raise important concernsabout the use of anticoagulant therapy in patients.