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PROTECTIVE ROLE OF CORTISTATIN IN PULMONARY INFLAMMATION AND FIBROSIS

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February 19, 2021

Abstract

Background and Purpose: Acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary fibrosis remain major causes of morbidity, mortality and healthcare burden in the critically ill patient. There is an urgent medical need for identifying factors of susceptibility and prognosis and for designing new therapeutic tools for treating these disorders. Here, we evaluate the capacity of the immunomodulatory neuropeptide cortistatin to regulate pulmonary inflammation and fibrosis in vivo. Experimental Approach: ALI/ARDS and pulmonary fibrosis were induced experimentally in wild-type and cortistatin-deficient mice by pulmonary infusion of the bacterial endotoxin LPS or the chemotherapeutic drug bleomycin, and the histopathological signs, pulmonary leukocyte infiltration and cytokines and fibrotic markers were evaluated. Key Results: Partially-deficient mice in cortistatin showed exacerbated pulmonary damage, pulmonary inflammation, alveolar oedema and fibrosis, and subsequent increased respiratory failure and mortality when challenged to LPS or bleomycin, even at low doses. Treatment with cortistatin reversed these aggravated phenotypes and protected from progression to severe ARDS and fibrosis after high-exposition to both injury agents. Moreover, cortistatin-deficient pulmonary macrophages and fibroblasts showed exaggerated ex vivo inflammatory and fibrotic responses. The anti-fibrotic protective effect of cortistatin was also observed in experimental scleroderma, in which lack of cortistatin predisposes to develop more severe dermal lesions and associated pulmonary fibrosis. Conclusion and Implications: We identify to cortistatin as an endogenous break of pulmonary inflammation and fibrosis. Deficiency in cortistatin could be a marker of poor-prognosis in inflammatory/fibrotic pulmonary disorders. Cortistatin-based therapies emerge as attractive candidates to treat severe ALI/ARDS, including SARS-Cov-2-associated ARDS.

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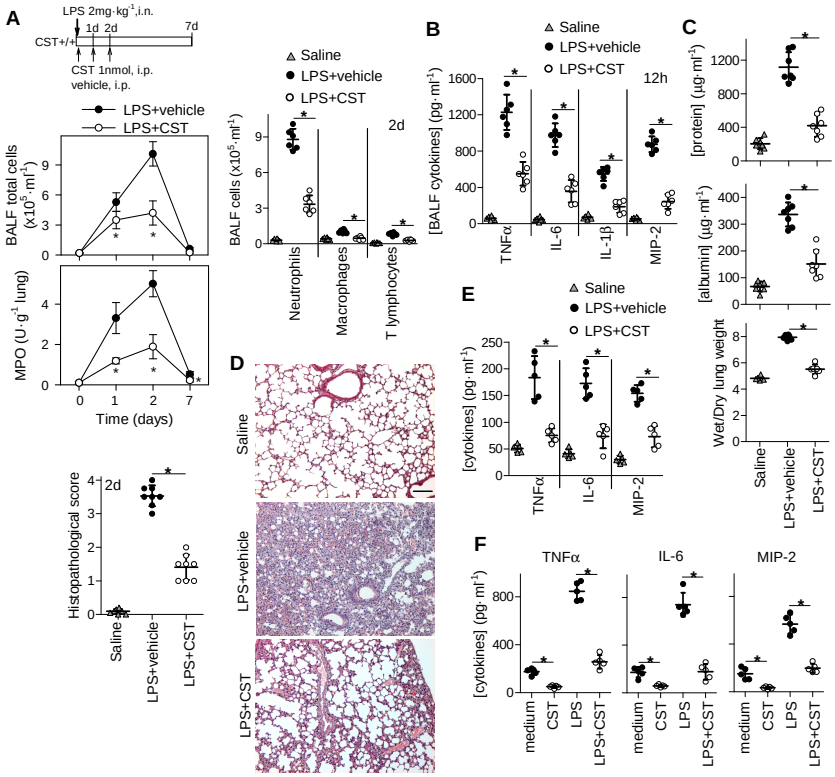

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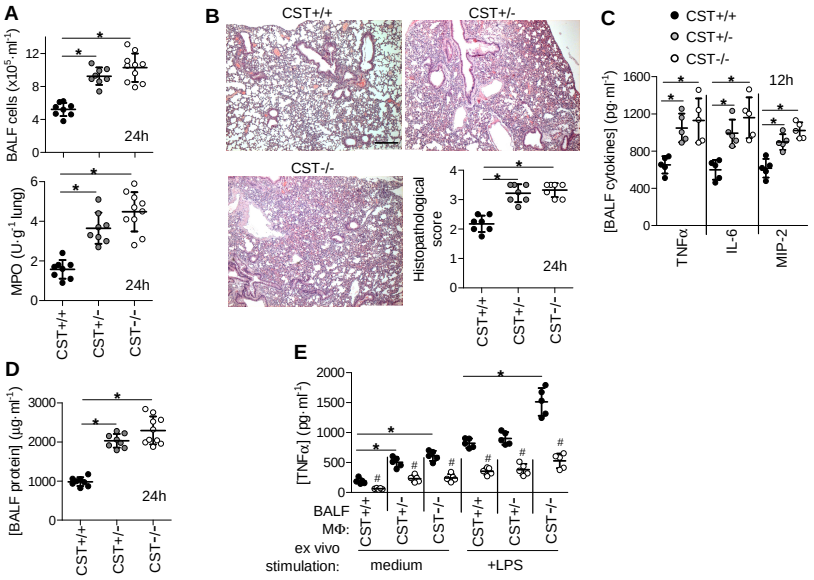

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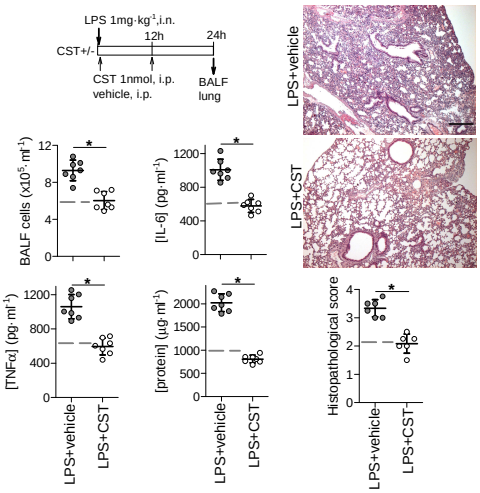

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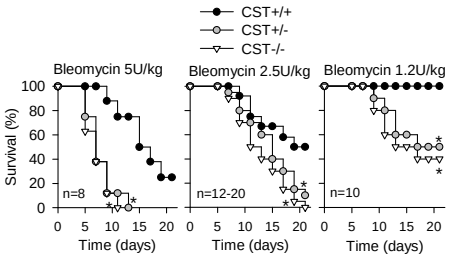

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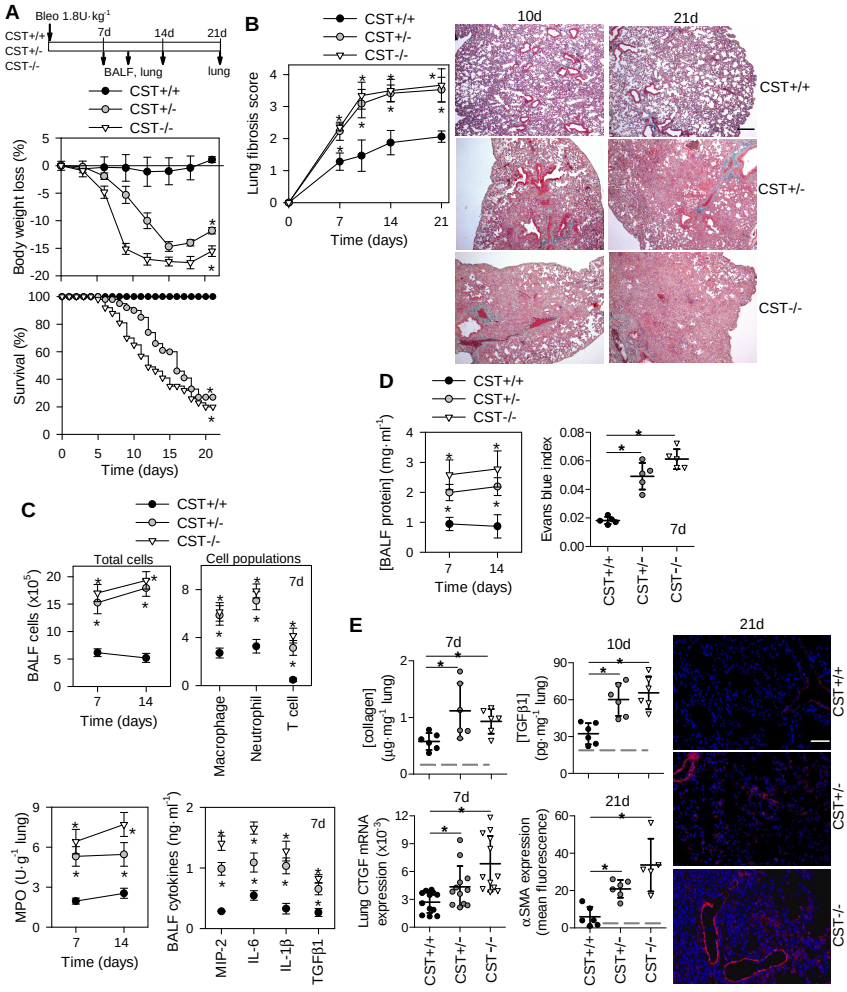

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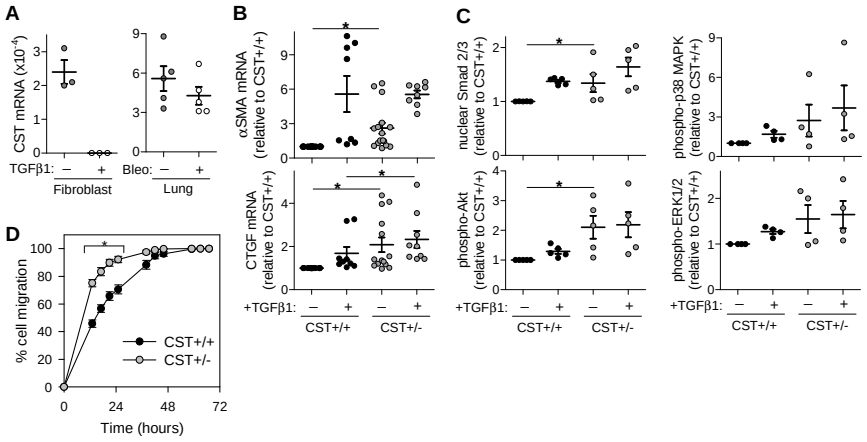

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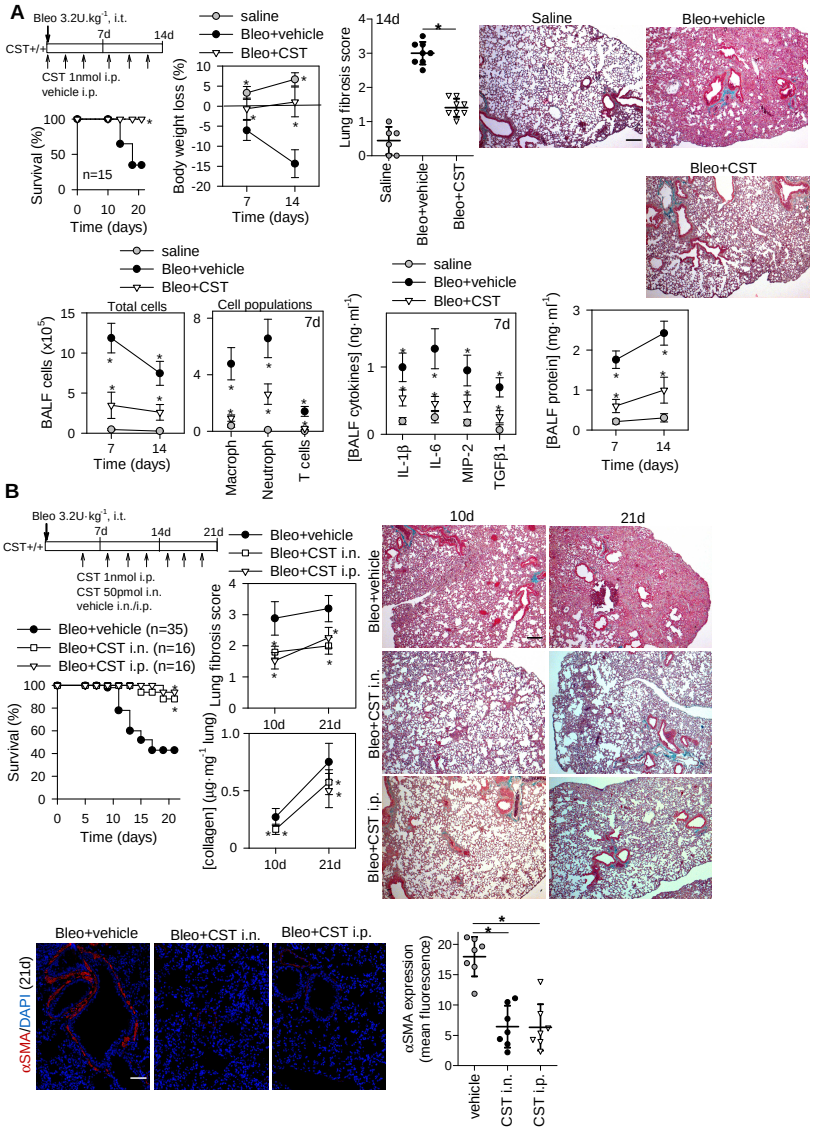

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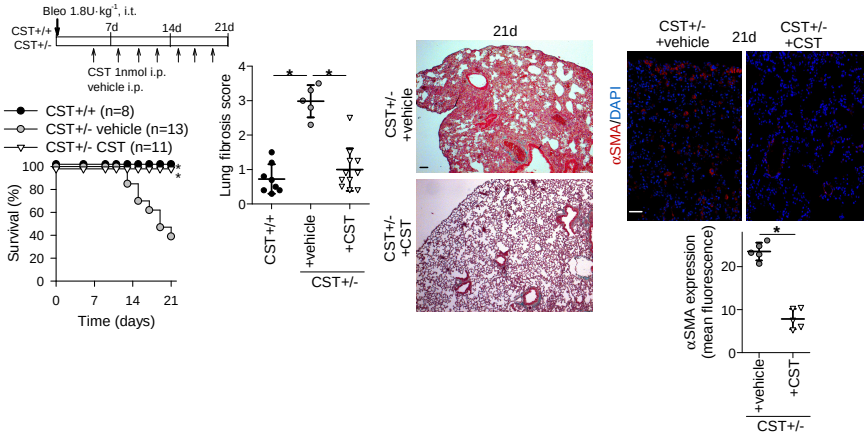

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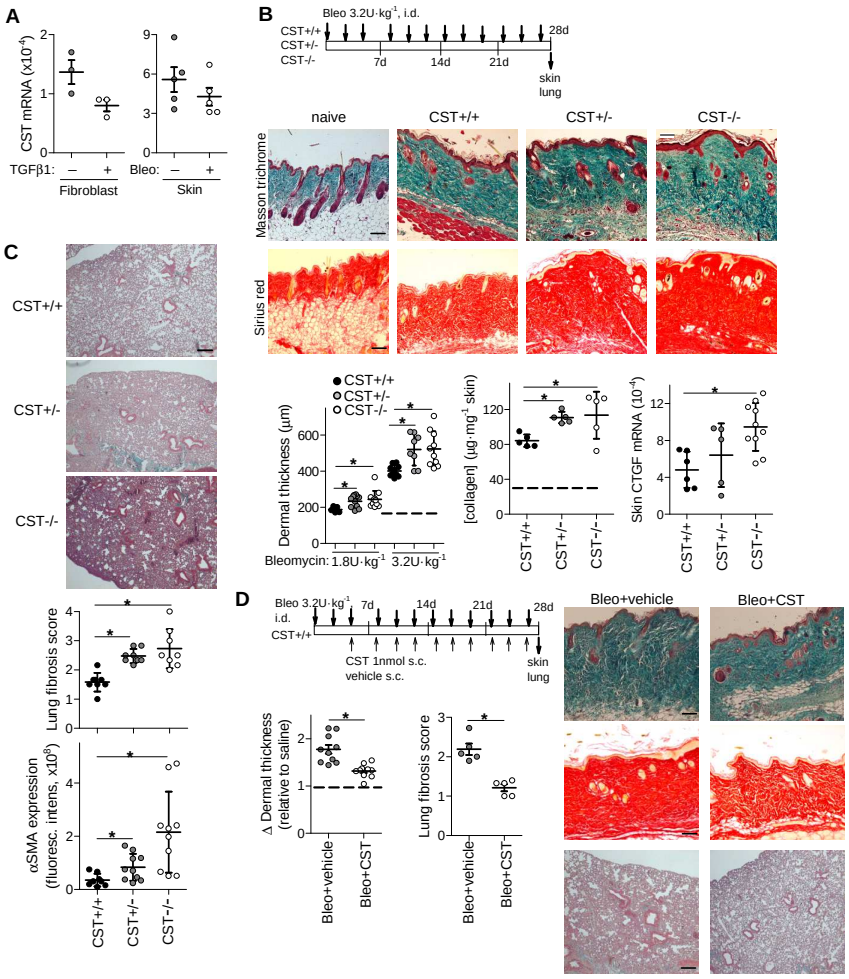

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