Competing interests None.

Ethics approval This study was conducted with the approval of the East London and City Health Authority Ethic Committee.

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Inactivation of the N-terminal of ACE reduces bleomycin-induced lung fibrosis

This study examined bleomycin-induced lung injury in normotensive mice, termed N-KO and C-KO, which have point mutations inactivating the N- or C-terminal catalytic sites of angiotensin converting enzyme (ACE), respectively. N-KO, but not C-KO mice, exhibited a marked resistance to bleomycin-induced lung injury and fibrosis, as assessed by lung histology and hydroxyproline content (46% increase in hydroxyproline content in C-KO lungs compared with 6.9% in N-KO lungs, $p<0.001$). Furthermore, the N-KO mice showed enhanced survival when exposed to a dose of bleomycin lethal to wild-type mice. The importance of the tetrapeptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), an ACE N-terminal substrate, was demonstrated when N-KO mice were treated with S-17092, a prolyl-oligopeptidase inhibitor that reduces the concentration of AcSDKP. These mice developed lung fibrosis similar to wild-type mice in response to bleomycin injection. Conversely, the administration of AcSDKP to wild-type mice reduced bleomycin-induced lung fibrosis, as assessed by lung hydroxyproline content (7.7 μg/mg in mice given AcSDKP compared with 12.47 μg/mg in mice given saline, $p<10^{-4}$).

These results show that the inactivation of the N-terminal of ACE significantly reduces bleomycin-induced lung fibrosis and implicates AcSDKP as a mediator of this protection. A novel means to increase tolerance to bleomycin and to treat fibrosing lung diseases is thus proposed.

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