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Cigarette smoke-initiated autoimmunity facilitates sensitisation to elastin-induced COPD-like pathologies in mice

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MMP12-generated elastin fragments serve as a self-antigen and drive cigarette smoke-induced autoimmune processes in mice. These findings provide experimental evidence for cigarette smoke-induced autoimmunity and represent a novel mouse model of COPD. https://bit.ly/2XK9dC6

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ABSTRACT It is currently not understood whether cigarette smoke exposure facilitates sensitisation to self-antigens and whether ensuing auto-reactive T cells drive chronic obstructive pulmonary disease (COPD)-associated pathologies.

To address this question, mice were exposed to cigarette smoke for 2 weeks. Following a 2-week period of rest, mice were challenged intratracheally with elastin for 3 days or 1 month. *Rag1*$^{-/-}$, *Mmp12*$^{-/-}$, and *Il17a*$^{-/-}$ mice and neutralising antibodies against active elastin fragments were used for mechanistic

investigations. Human GVAPGVGVAPGV/HLA-A*02:01 tetramer was synthesised to assess the presence of elastin-specific T cells in patients with COPD.

We observed that 2 weeks of cigarette smoke exposure induced an elastin-specific T cell response that led to neutrophilic airway inflammation and mucus hyperproduction following elastin recall challenge. Repeated elastin challenge for 1 month resulted in airway remodelling, lung function decline and airspace enlargement. Elastin-specific T cell recall responses were dose dependent and memory lasted for over 6 months. Adoptive T cell transfer and studies in T cells deficient *Rag1*$^{-/-}$mice conclusively implicated T cells in these processes. Mechanistically, cigarette smoke exposure-induced elastin-specific T cell responses were matrix metalloproteinase (MMP)12-dependent, while the ensuing immune inflammatory processes were interleukin 17A-driven. Anti-elastin antibodies and T cells specific for elastin peptides were increased in patients with COPD.

These data demonstrate that MMP12-generated elastin fragments serve as a self-antigen and drive the cigarette smoke-induced autoimmune processes in mice that result in a bronchitis-like phenotype and airspace enlargement. The study provides proof of concept of cigarette smoke-induced autoimmune processes and may serve as a novel mouse model of COPD.