inflammatory protein research offers treatment strategies for a rare, potentially fatal lung disease

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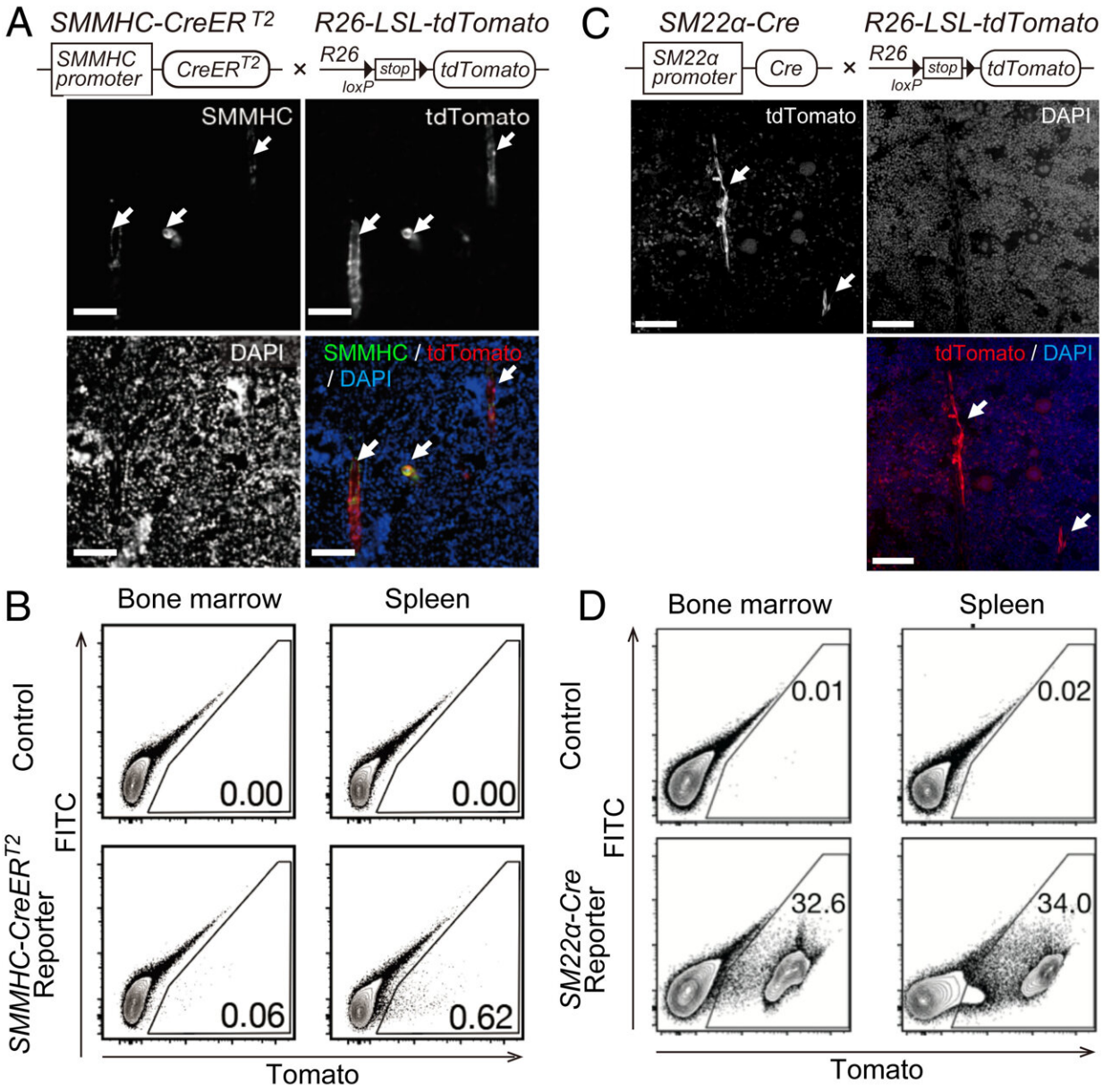

Unintended Cre recombination in all hematopoietic lineage cells in SM22α-Cre mice. Credit: *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2315123121

Most of the time, our immune systems do a great job defending against infection and keeping our bodies running smoothly. Sometimes, though, our immune system actually makes things worse. Case in point—researchers from Japan have now shown that a naturally occurring immune signaling protein may be a key player in the development of an incurable form of lung disease.

In a study published last month in *PNAS*, investigators from the National Cerebral and Cardiovascular Center (NCVC) Research Institute reported that an inflammatory protein called IL-6 activates specific immune cells in pulmonary hypertension, thereby worsening the associated symptoms.

Pulmonary hypertension is a rare and debilitating condition in which arteries in the lung become narrow or clogged. This causes symptoms such as difficulty breathing, exhaustion, fainting, and at advanced stages, even heart failure and death.

"There is currently no cure for pulmonary hypertension, so available treatments focus on reducing symptoms and improving quality of life," explains lead author Tomohiko Ishibashi.

"Recent studies have suggested that IL-6 plays a role in the progression of pulmonary hypertension and could therefore be a useful target for treatment; however, conflicting results were obtained using different mouse models, resulting in uncertainty about the effectiveness of this

approach."

To address this, the researchers used a mouse model in which a component of the IL-6 receptor is supposedly disrupted only in smooth muscle cells, but may also be inactivated in other cell types, to investigate which specific cells were affected by IL-6 signaling.

"Surprisingly, we discovered that expression of the IL-6 receptor component was disrupted in a wide range of blood cell progenitors," explains senior author Yoshikazu Nakaoka.

"Under normal conditions, the receptor is most strongly expressed by CD4-positive T cells, and deleting it in these cells significantly inhibited the development and progression of pulmonary hypertension in mice."

Next, the researchers deleted the gene that encodes IL-6 in rats. The team found that, regardless of whether rats' pulmonary hypertension was induced primarily by hypoxia, chemicals or combinations thereof, IL-6 deletion made the rats resistant to the pathological changes associated with pulmonary hypertension.

Treating the IL-6-deficient rats with drugs that are currently used to treat patients with pulmonary hypertension further improved symptoms and decreased damage to both the lungs and the heart.

"Our findings suggest that combining IL-6 inhibitors with current medications for pulmonary hypertension may decrease symptoms and improve patients' quality of life," says Ishibashi.

Given the current lack of effective treatments for pulmonary hypertension, the results from this study hold promise for developing new therapeutic strategies in the future. Although one recent clinical trial of an anti-IL-6 receptor antibody yielded disappointing results, targeting

IL-6 in specific cell types and targeting downstream effectors of IL-6 signaling remain potential approaches.

More information: Tomohiko Ishibashi et al, IL-6/gp130 signaling in CD4 + T cells drives the pathogenesis of pulmonary hypertension, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2315123121

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