Cigarette smoke is the most common cause of pulmonary emphysema, which results in an irreversible loss of lung structure and function. Th1 and Th17 immune responses have been implicated in emphysema pathogenesis; however, the drivers of emphysema-associated immune dysfunction are not fully understood. In this issue of the JCI, Shan and colleagues found that peroxisome proliferator–activated receptor γ (PPARγ) is downregulated in APCs isolated from the lungs of emphysematous chronic smokers and mice exposed to cigarette smoke. Furthermore, treatment with a PPARγ agonist prevented emphysema development and appeared to reduce emphysema-associated lung volume expansion in mice exposed to cigarette smoke. Further work will need to be done to evaluate the potential of PPARγ agonists to restore lung capacity in emphysematous patients.
function mutations in mice and humans results in abnormal DYSF internalization (10, 16). Whether mislocalization of CAV3 and DYSF within the myofiber contributes to CNM disease progression remains to be determined. These data suggest that a common pathway links MTM1, DNM2, BIN1, DYSF, and CAV3 in the biogenesis and maintenance of muscle, specifically at the T-tubule. If DNM2 levels are found to be upregulated in these other forms of myopathy, then targeting DNM2 becomes a common therapeutic strategy for a wider range of muscle disease.

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PPARγ in emphysema: blunts the damage and triggers repair?

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Cigarette smoke is the most common cause of pulmonary emphysema, which results in an irreversible loss of lung structure and function. Th1 and Th17 immune responses have been implicated in emphysema pathogenesis; however, the drivers of emphysema-associated immune dysfunction are not fully understood. In this issue of the JCI, Shan and colleagues found that peroxisome proliferator-activated receptor γ (PPARγ) is downregulated in APCs isolated from the lungs of emphysematous chronic smokers and mice exposed to cigarette smoke. Furthermore, treatment with a PPARγ agonist prevented emphysema development and appeared to reduce emphysema-associated lung volume expansion in mice exposed to cigarette smoke. Further work will need to be done to evaluate the potential of PPARγ agonists to restore lung capacity in emphysematous patients.

Pulmonary emphysema is a major compo-nent of chronic obstructive pulmonary dis-

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The implication that neutrophil- and macrophage-derived elastases influence emphysema pathogenesis has justifiably led to an intense research focus on innate immunity; however, the observed increase in T lymphocytes in the lungs of emphysema patients suggests that the adaptive immune system facilitates the innate immune response (4). Our understanding of the crossstalk between innate and adaptive immunity in emphysema is far from clear, partly because murine research has thus far shown an inconsistent role for lymphocytes in disease progression. For example, mice with deficient T and B cell responses developed full-blown emphysema in response to cigarette smoke (5), yet CD8-deficient mice are completely resistant to the same insult (6). However, IFN-γ (through the action of the cytokine IP10) and IL-17A, the signature cytokines produced by Th1 helper subsets Th1 and Th17, respectively, have the potential to link the adaptive and innate responses by mediating the release of MMP12 from alveolar macrophages (7, 8). In addition to being elevated in smoke-exposed lungs, IFN-γ and IL-17A are strongly associated with autoimmunity and autoimmunity (9), and their preponderance supports the idea that auto-reactivity perpetuates the sustained decline of lung function observed in a subset of former smokers (10). In fact, some studies have shown that elastin fragments elicit a recall response in the peripheral T lymphocytes of emphysema patients (8), underscoring a potential link between autoimmunity and human emphysema.

**A link between smoking and autoimmunity**

But how does smoking lead to autoimmunity? In a series of reports, Shan and colleagues turned to APCs to address this question. In an initial human study (8), Shan et al. found that APCs isolated from emphysematous lungs induce naive CD4+ T cells to differentiate into Th1 and Th17 cells. In mouse models, which do not recapitulate the anti-elastin autoimmunity observed in human patients, Shan and colleagues showed that tobacco smoke exposure causes a phenotypic switch in lung APCs that is characterized by increased expression of the secreted phosphoprotein osteopontin (SPP1). These pathogenic APCs then directly differentiate Th1 and Th17 lymphocytes, mimicking the actions of APCs from human smokers (11). Furthermore, mice lacking IL-17A or SPP1 failed to develop airspace enlargement in response to long-term smoke exposure, highlighting the importance of APC-directed T cell differentiation in smoke-induced immune dysfunction.

Increasing evidence indicates that the nuclear hormone receptor PPARγ, best known as a regulator of tissue metabolism and adipogenesis, plays a role in lung development and inflammation. In this issue of the JCI, Shan and colleagues (12) provide further support that PPARγ regulates immune responses in the lung, with an initial observation that PPARγ is down-regulated in APCs isolated from human smokers with emphysema and from mice exposed to tobacco smoke. Additionally, deletion of Pparg in CD11c+ APCs, which include macrophages and myeloid dendritic cells (mDCs), caused spontaneous SPP1-dependent airspace enlargement in mice. Coupled with their previous work, the current study by Shan and colleagues suggests that by dampening PPARγ, tobacco smoke unleashes SPP1 to induce differentiation of Th1 and Th17 lymphocytes. When activated, Th1 and Th17 lymphocytes secrete IFN-γ and IL-17A, respectively, triggering the synthesis and release of destructive elastases from alveolar macrophages (Figure 1).

**PPARγ activation: a treatment for emphysema?**

Naturally, if functional antagonism of PPARγ by tobacco smoke worsens emphysema, then pharmacologic PPARγ activa-
tion with the thiazolidinediones (TZDs) should abrogate disease progression. As expected, Shan and colleagues (12) dem-

onstrated that the PPARγ agonist cigli-
tazone prevented murine emphysema due to cigarette smoke exposure. Less defin-

itively, mice exposed to cigarette smoke for 3 months followed by ciglitazone treat-

ment exhibited an apparent restoration of lung volume, suggesting that TZDs are able to reverse the course of emphy-

sema. Should these results be substanti-

ated, TZDs would join a growing list of agents with the potential to reverse rodent emphysema. In the first report of emphy-

sema reversal, Massaro and Massaro (13) demonstrated the initiation of new alveo-

lar growth by retinoic acid (RA) following elastase-induced emphysema in rats. Using a more pertinent smoke exposure model, albeit with a less rigorous physiological assessment, Seimetz and colleagues (14) reported that inhibition of inducible nitric oxide synthase (NOS2) reverses emphy-

sema in mice. In an interesting twist, NO has also been reported to increase the expres-

sion of SPP1 (15), suggesting that TZDs and NOS2 inhibitors may have an overlapping

therapeutic mechanism.

In light of the findings by Shan and col-

leagues, as well as the results of a recent study (16) that describes airway inflam-

mation and emphysema onset following expression of a dominant-negative PPARγ in alveolar epithelium, PPARγ appears to play a broad role in checking destructive inflammatory processes in the lung. Is it possible, then, that suppression of inflammation is enough to initiate murine lung regeneration? Per-

haps, but it may be that TZDs themselves trigger lung regeneration. In any discus-

sion of tissue regeneration, it is helpful to look to development for insight. Based on studies of children born to mothers who smoked during pregnancy, we know that smoking impairs alveogenesis (17), and the results of a recent case report (22) provides a glimmer of hope that alveogenesis may be possible in the fully developed human lung. As we move forward in the search for a medical cure for pulmonary emphysema, understand-

ing and exploiting the mechanisms behind this phenomenon offers our best chance of success.

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