Is CC Chemokine Ligand 17 (TARC) Driving Disease Progression in Chronic Obstructive Pulmonary Disease?

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide (1). COPD is a progressive disease with deteriorating lung function over time (2). There is significant heterogeneity in COPD pathogenesis with varying rates of disease progression among affected individuals. New therapies are needed to halt disease progression, particularly in the early disease stages (3).

Machida and colleagues previously reported that thymus and activation-regulated chemokine (TARC/CCL17) is a predictive marker for rapid decline of lung function (forced expiratory volume in 1 second [FEV_1] or percentage of predicted FEV_1) in patients with COPD (4). Bradford and colleagues, previously showed no relationship between any of their COPD parameters and plasma/serum CCL17 levels (5). However, using a clever approach, Machida and colleagues stratified their cohort on the basis of disease progression and found that increased CCL17 was associated specifically with rapid decline in COPD (25th percentile in loss of FEV_1 per year). In other research conducted by Ying and colleagues, CCL17 expression was increased in epithelial cells as well as in BAL of individuals with COPD, particularly in current smokers (6). Therefore, there is a clear association between CCL17 levels, smoking status, and rapid lung function decline. In this issue of the *Journal*, Machida and colleagues (pp. 428–438) describe new studies attempting to identify the role of CCL17 in the pathogenesis of COPD in mouse models of pulmonary emphysema (7).

CCL17 is known to influence the pathogenesis of respiratory disease through T-helper cell type 2 pathways that drive allergic inflammation leading to increased eosinophil responses and IgE production, acting in concert with CCL22 through ligation with CCR4 (the receptor shared by both CCL17 and CCL22) (8, 9). However, given the growing body of evidence for the role of CCL17 in macrophage recruitment, along with the association between macrophage numbers and the severity of COPD (10), they set out to define the role of CCL17 in type 1 inflammation and macrophage recruitment in mouse models. First, by ELISA, they confirmed the presence of CCL17 production in the lung of cigarette smoke (CS)-exposed mice and, using immunohistochemistry and lung histology, determined that CCL17 production originates in the respiratory epithelium. To confirm the epithelial origin of CCL17 in response to CS, BEAS2B cells (an immortalized human respiratory cell line) were cultured with various concentrations of CS or H_2O_2, which revealed increased CCL17 gene expression and elevated levels of CCL17 production in the culture supernatant. This approach constitutes a "proof of principle," but these data could be strengthened by performing fully differentiated primary bronchial epithelial cell culture experiments using cells from donors with COPD and grown at an air–liquid interface, as done by others (11, 12). The cell line they employed exhibits characteristics more in line with mesenchymal stem cells than with epithelial cells (13).

Machida and colleagues then proceeded to elucidate the role of CCL17 in the pathogenesis of emphysema by administering recombinant CCL17 to the respiratory tract. Respiratory challenge with exogenous CCL17 alone resulted in increased macrophages in the airways. When administered in combination with CS, macrophage levels were increased over and above the levels seen in CS-exposed mice. In mice with elastase-induced emphysema, they found that CCL17 is again present in the epithelium, and co-challenge with elastase and recombinant CCL17 worsened lung deterioration (measured by mean linear intercept in lung histology). Using flow cytometry, they then investigated macrophage polarity to determine whether CS, exogenous CCL17, or the combination of CS and CCL17 influenced the M1/M2 polarity of the elevated macrophage populations. The gating strategy they used is outlined in detail in Figure 4 of their paper. Briefly, single cells (after debris/doublet exclusion by scatter area/height) were stained for M1 or M2 macrophage proportions (M1: $CD45^+$, $F4/80^+CD80^+$, $CD206^-$; M2: $CD45^+$, $F4/80^+CD80^-$, $CD206^+$) or dual M1/M2 macrophages ($CD45^+$, $F4/80^+CD80^+$, $CD206^+$). Dual-positive (M1 + M2) macrophages were increased in CS-exposed mice, and even though additional stimulation with exogenous CCL17 had no effect on polarization of macrophages, CCL17-deficient mice ($CCL17^{-/-}$) exhibited reduced macrophage numbers in response to CS. Polarity may not be affected by CCL17, but it would be interesting to investigate whether CCL17 affects the ability of macrophages to respond to viral or bacterial infection, in line with what we know about the role of defective macrophage responses during prolonged COPD exacerbations (14). To investigate the effect of CCL17 on macrophages, Machida and colleagues administered increasing concentrations of CCL17 to RAW264.7 cells (a macrophage cell line) and then quantified the inflammatory cytokine responses. Despite no effect of CCL17 on IL-1β, tumor necrosis factor-α, IL-6, or MMP9 gene expression, a dose-dependent effect was observed on CCL2 expression at 2 hours, which translated to increased protein levels in the culture supernatant at 8 hours after stimulation. This response was ablated by siRNA-mediated knockdown of CCR4 expression. Machida and colleagues also show that emphysema was reduced in CCL17-deficient mice studied using the elastase-induced emphysema model.

Machida and colleagues have thus identified a novel role for CCL17 in COPD progression, supporting the prevailing theory that noxious stimuli (such as CS) induce CCL17 expression in bronchial epithelial cells. CCL17 induces macrophage recruitment and subsequent CCL17 signaling through CCR4, which in turn induces the expression of CCL2 in infiltrating macrophages, perpetuating macrophage recruitment. This, along with other inflammatory cells

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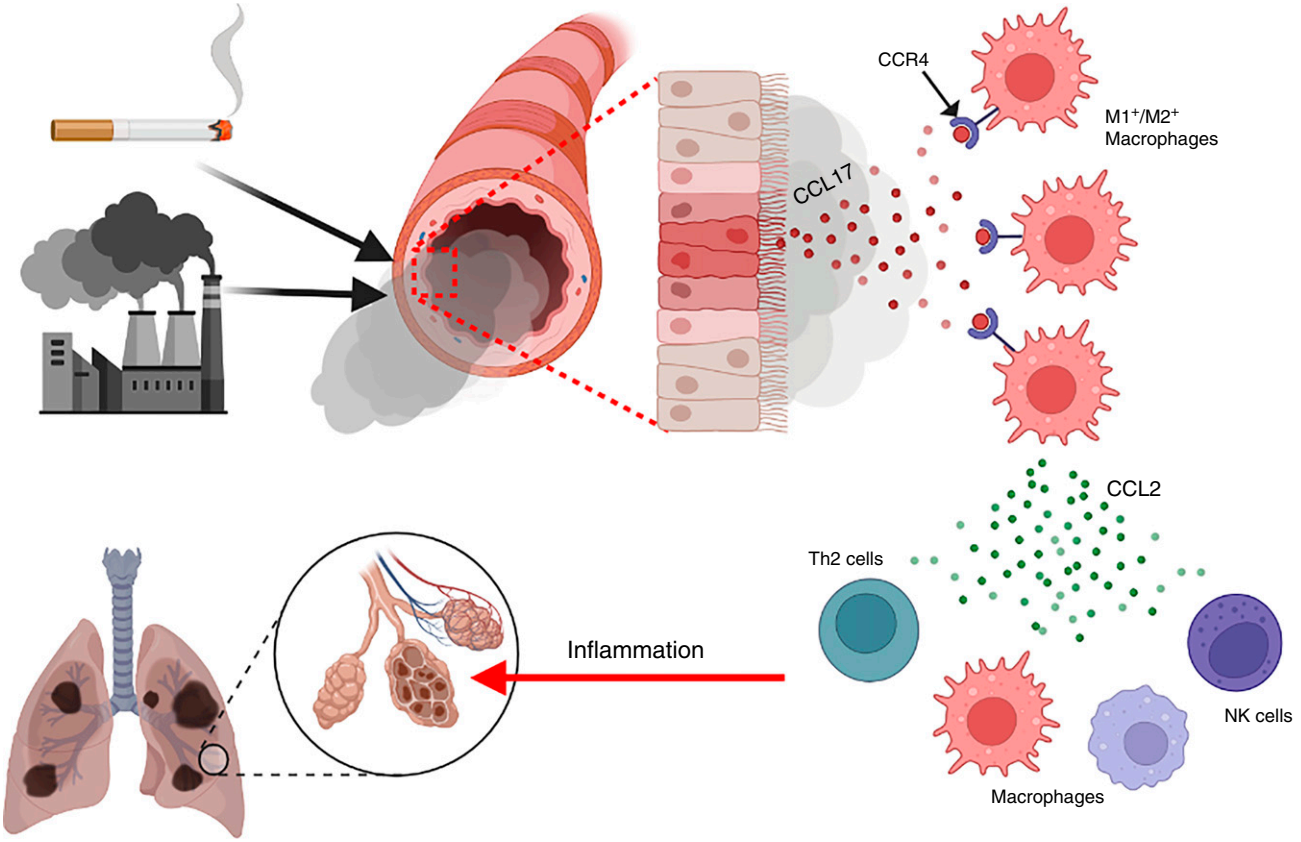

Figure 1. Proposed role of CCL17 in the pathogenesis of chronic obstructive pulmonary disease (COPD). Inhaled cigarette smoke or noxious stimuli cause the production of CCL17 by bronchial epithelial cells, resulting in the recruitment of macrophages (likely dual macrophages [M1/M2] phenotype) through ligation of CCL17 with the receptor CCR4 (expressed by macrophages). Macrophages then produce CCL2, perpetuating further macrophage recruitment and (potentially) the recruitment of lymphocytes such as natural killer (NK) cells and T-helper cell type 2 (Th2) cells (which may also respond to CCL17). The resulting inflammatory milieu then drives the tissue damage that leads to progressive decline in COPD. Created with BioRender.com.

(e.g., T-helper cell type 2 and natural killer cells that may respond to CCL17), leads to chronic inflammation and destruction of lung tissue (Figure 1). On the basis of the role of CCR4 in this process, Machida and colleagues suggest the therapeutic potential of blocking CCR4 with the use of mogamulizumab (15) or using CCR4 receptor antagonists (16). The authors also propose that future research should elucidate the roles of other inflammatory cells in CCL17-mediated pathogenesis. Finally, given that CCL17 was initially identified as a marker of rapid lung function decline, it would be interesting to confirm whether similar pathological changes and effects on lung function occur in these experimental models, using the methods published by Kim and colleagues (17). ■

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