Another important limitation with this, and the vast majority of studies of air pollution on health outcomes, is that exposure assessments based on outdoor air pollution measures remain largely circumstantial. In general, people spend the majority of their time indoors, and air pollution components and concentrations can vary widely as the result of individual behaviors and microenvironmental exposures, regardless of ambient levels (11). Study designs such as those used here can shed light on whether ambient air pollution is associated generally with incident asthma, but cannot determine actual individual exposure levels and their influence on health outcomes (12). However, for the research question at hand, the study design remains strong in that it would be difficult to argue that their results are from exposures other than the Great Smog.

The authors' use of a single extraordinary exposure is rather clever in that it removes many potentially confounding variables, but also opens up a question of generalizability. Thankfully, most infants will never be exposed to the levels of pollution experienced in London in 1952. However, many in underresourced locations and urban environments will experience continual high levels of ambient pollution outdoors and indoors, and some will experience seasonal inversions with high particulate levels over the course of their childhood. With the increasing evidence from this study and others that ambient pollution in early childhood is a contributing factor in incident asthma, research into the complexities of varying pollution exposure levels, chemical components, duration, and their influence during key developmental windows in early childhood should be priority areas of study. ■

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Lost in Trans-IL-6 Signaling: Alveolar Type II Cell Death in Emphysema

In this issue of the *Journal*, Ruwanpura and colleagues (pp. 1494–1505) identify IL-6 trans-signaling (IL-6 TS; Figure 1) as a potential therapeutic target to inhibit alveolar epithelial cell death and preserve lung parenchymal structure and function (1). The substantial impact of these findings relies on the use of complementary transgenic and pharmacological approaches to inhibit IL-6 TS in animal models, combined with fingerprinting similar patterns of signaling molecules in human lungs with emphysema. The study does not exclude a contribution of classical IL-6 signaling to emphysema development; rather, it focuses on the proapoptotic effects of gp130 gain of function either by transgenic overexpression or in the context of acute and subchronic (3 mo) cigarette smoke exposure. Either soluble gp130 (sgp130) overexpression or administration of sgp130-Fc protein prevented airspace enlargement and improved static lung compliance in the two murine models studied. The interest in targeting IL-6 TS in emphysema is not surprising, given that this approach has been quite successful in reducing chronic inflammation in murine models of rheumatologic, central nervous system, allergic, and gastrointestinal disease (2).

The sgp130 augmentation approaches employed by Ruwanpura and colleagues to attenuate IL-6 TS activation in the lung had an impressive inhibitory effect on apoptosis; in particular, preventing alveolar type II (ATII) cell loss. This finding, from the group that first identified an association of IL-6 TS with airspace remodeling (3), supports the now well-accepted notion that alveolar cell fitness and survival are critically important to the maintenance of the integrity of alveolar structures (4). The demonstration that IL-6 TS was necessary and sufficient for inducing ATII cell apoptosis and an emphysema-like phenotype solidifies the notion that unrepaired loss of lung epithelial cells is associated with airspace destruction and increased lung compliance. These results add IL-6 TS to the list of several mechanisms, such as those mediated by innate antiviral immune responses (5) or

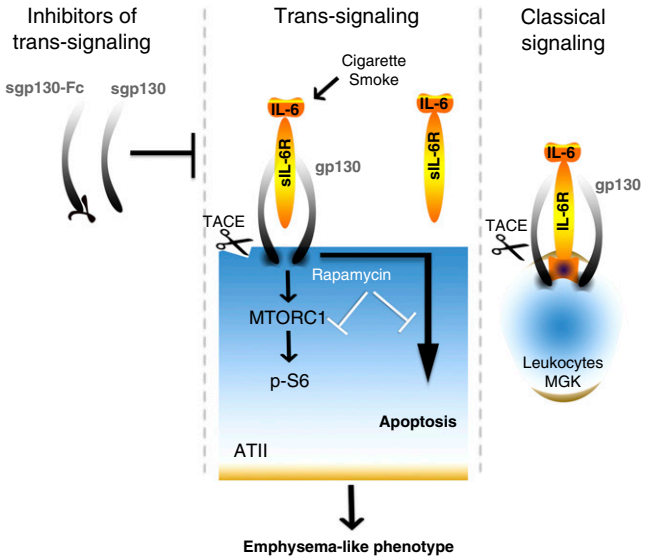

Figure 1. Schematic of IL-6 trans-signaling pathway involvement in lung cell apoptosis and emphysema-like disease. Ruwanpura and colleagues (1) have demonstrated that inhibitors of IL-6 trans-signaling ameliorate apoptosis and emphysema-like phenotype induced by either cigarette smoke or by transgenic overexpression of gp130. These effects were associated with increased mechanistic target of rapamycin complex 1 (MTORC1) signaling and were inhibited by rapamycin. ATII = alveolar type II cells; MGK = megakaryocytes; sIL-6R = soluble IL-6 receptor; sgp130 = soluble gp130; TACE = ADAM 17.

by augmentation of Fas–Fas ligand interaction (6), that trigger lung epithelial cell death associated with airspace enlargement. The role of IL-6 TS in initiating cell death of other structural lung parenchymal cells essential to alveolar maintenance, such as microvascular endothelial cells, remains to be explored. Although it would be alluring to infer that lung endothelial cells, which also express gp130, respond to IL-6 TS similar to ATII, reports point to potential cell-type specific responses. As an example, sgp130-Fc, rather than protecting from apoptosis, actually sensitized T cells to undergo cell death and improved outcomes in a murine model of experimental colitis (7). Although inhibition of inflammation was not noted as a main effect of IL-6 TS in the lung parenchyma in Ruwanpura and colleagues' work, the effect of IL-6 TS on inflammatory cell function in emphysema warrants further investigation. Furthermore, given the pleiotropic signaling induced by IL-6 TS (8–10), the activation of this pathway may extend beyond apoptosis and inflammatory cell modulation to other pathobiological mechanisms of importance to emphysema development such as senescence, mucus hypersecretion, and autoimmunity. Evidence of involvement of IL-6 TS in these processes in the lung will only magnify the interest to targeting this pathway to improve chronic obstructive pulmonary disease and emphysema outcomes.

In addition to the high potential for translation to bedside, the work by Ruwanpura and colleagues pointed to several interesting signaling responses to IL-6 TS activation. The finding that IL-6 TS activated ADAM-17 (TACE), a protease that cleaves gp130 to generate the ectodomain inhibitory molecule sgp130, indicated a potential autocrine negative feedback loop triggered by IL-6 TS. However, TACE, by cleaving IL-6 receptor (11), whose expression is restricted to only several cell types, including leukocytes, can also shed soluble IL-6 receptor, which serves to activate IL-6 TS, thus engaging a paracrine/endocrine positive feedback loop. Further, TACE has multiple other membrane receptor targets (12) (tumor necrosis factor α, epidermal growth factor receptor, selectins, or Fas ligand, among others) that may contribute to the effects reported here. The relative contribution, magnitude, and kinetics of these responses should be considered to better distinguish pathogenic from compensatory responses of lung cells facing chronic exposure to cigarette smoking.

Also intriguing was the fact that IL-6 TS activation triggered mechanistic target of rapamycin and its downstream ribosomal protein S6 kinase (S6) signaling, which was linked to apoptosis of ATII cells. The effect of this typically prosurvival signaling pathway on lung apoptosis and remodeling was mechanistically interrogated using rapamycin, a classical inhibitor of mechanistic target of rapamycin complex 1 (MTORC1). In mice exposed to cigarette smoking or to IL-6 TS hyperactivation, Rapamycin was protective, inhibiting apoptosis and airspace enlargement, simultaneously with the predictable inhibition on S6 phosphorylation. Although at first glance straightforward, the interpretation of these results in the context of other published reports reflects the intricate nature of the effects of rapamycin on normal and diseased lungs. Apart from indirect effects on MTORC2, the effects of rapamycin are highly dependent on the biological context of MTORC1 activation, the magnitude and duration of activation, and the downstream effectors engaged. In addition to protein synthesis and proliferation typically associated with survival, this pathway inhibits autophagy and regulates metabolic and mitochondrial functions, as well as aging (13). This complex involvement reconciles the findings that at certain doses, rapamycin had beneficial antiapoptotic effects during IL-6 TS hyperactivation in relatively older (6 mo of age) mice reported here, while being previously reported proapoptotic in otherwise healthy mice or antiinflammatory during acute cigarette smoke exposure of younger (3 mo of age) mice (14). In addition, in the absence of direct interrogation, the involvement of S6 activation in lung cell apoptosis remains speculative. Typically engaged by MTORC, along with 4E-binding protein 1, to stimulate protein synthesis, the activity of S6 in the lung may be contributed by surviving cells that withstand apoptotic stress or by those involved in repair. For example, compared with cells from nonsmokers, cultured primary microvascular endothelial cells from smokers exhibited significant up-regulation of signaling molecules associated with survival and had adapted to better withstand apoptotic stimuli (15). Further, given a recent report of involvement in lung carcinogenesis (16), it is conceivable that prolonged IL-6 TS-induced signaling may lead to both apoptosis and inappropriate cell proliferation, with potential relevance to the increased lung cancer risk in those suffering from emphysema.

Notwithstanding validation in other preclinical models, this is the first report to mechanistically link emphysema to IL-6 TS and offer a promising strategy to ameliorate apoptosis in emphysematous lungs by using IL-6 TS inhibitors. ■

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Intensive Care Unit Physician Discretion in Pediatric Critical Care
Polarized, Evaluated, and Reframed

Critical care physicians lead intensive care unit (ICU) care. Experience and previous literature suggest a dose–response effect of ICU physician involvement on patient-relevant outcomes. Greater doses of this highly trained, but finite, healthcare resource can improve outcomes (1, 2). This observation underpins recommendations of "high-intensity" ICU physician staffing (3), has been challenged in previous large adult studies (4–6), and has led to concerns about the ICU physician workforce, reduced trainee autonomy, and compromised training (7, 8).

In this issue of the *Journal*, Gupta and colleagues (pp. 1506–1513) report their comprehensive comparison of continuous (mandated) ICU physician presence with self-regulated (discretionary) ICU physician presence using prospective data from 455,607 patients younger than 18 years of age from 125 hospitals in the Virtual Pediatric ICU dataset (9). The 58.5% of patients cared for in the 60 ICUs with mandated continuous ICU physician presence had lower ICU mortality (odds ratio [OR], 0.52) and in-ICU cardiac arrest (OR, 0.73) and shorter durations of ICU stay (0.51 d) and mechanical ventilation (0.68 d) (9). These are important, credible, and provocative findings, with personal and professional implications for ICU physicians.

The study used an extremely large, multi-ICU dataset. The main results are from comprehensive logistic and linear regression models that accounted for reasonable patient- and ICU-level factors. The full models are accompanied by five sets of predominantly concordant sensitivity analyses and stratified subgroup analyses that demonstrate internal validity. Gupta and colleagues' work demonstrates the art and science of statistical comparison, includes an unfamiliar abundance of statistical power for many in pediatric critical care, and provides important insights beyond the main analyses (9).

First, raw ICU mortality over the 2009 to 2014 period was 2.4%. This is nearly 10-fold lower than reported in some adult ICUs, is lower than earlier decades in pediatric ICUs (PICUs) (10), and highlights the challenges of continued improvement. Large-scale work such as this is required to guide policy and practice. As ICU mortality approaches the zero asymptote, the link between survival and quality of care will require more nuanced understanding (11). Meanwhile, zero-seeking statistical models will continue to identify factors associated with lower ICU mortality. Gupta and colleagues' inclusion of not-for-resuscitation status at ICU discharge is an important initial acknowledgment of this emerging methodologic challenge (9). At some point, however, less may not be more.

Second, unadjusted mortality was 0.2% lower in favor of mandated ICU physician presence. This statistically significant absolute effect is smaller than an individual clinician may be able to discern; however, it is aligned with the direction of effects Gupta and colleagues observed in the incidence of cardiac arrest and durations of ICU therapies and constitutes an 8% relative risk reduction (9). Together, these findings lead us to seek