This study throws us a few more questions in addition to some of the answers it provided. As stated above, it would be interesting to explore whether higher LBMI in adolescence is a predictor for slow decline in lung function, thereby reducing the risk of adulthood respiratory disorders. Could lifestyle modifications that reduced fat mass and the FMI trajectory alter decline in lung function in later life? Does the variable strength of association of FMI to lower lung function between boys and girls demonstrate the preprogrammed risk of COPD in adult men to be higher than in women? Are there specific factors that influence lung function through the adolescent growth phase?

An individual might be endowed with high or low lung function, but it appears to be within his or her own ability to avoid losing lung function by maintaining a healthy FMI. The public health implications are clear: maintain a healthy body composition with lower FMI to preserve adult lung function and reduce the risk of chronic respiratory disease. ■

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Sadasivam Suresh, M.B. B.S., M.R.C.P.C.H., F.R.A.C.P., G.C.Hlth.Sc.
Department of Respiratory and Sleep Medicine
Queensland Children's Hospital
Brisbane, Australia
and

Institute for Social Science Research
Faculty of Medicine
and

Centre for Children's Health Research
The University of Queensland
Brisbane, Australia

Peter Sly, A.O., M.B. B.S., M.D., D.Sc., F.R.A.C.P., F.A.H.M.S., F.E.R.S., F.Thor.Soc., F.A.P.S.R.*
Centre for Children's Health Research
The University of Queensland
Brisbane, Australia

ORCID ID: 0000-0001-5248-2310 (S.S.).

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Importance of Mcl-1 for Alveolar Macrophage Apoptosis–associated Bacterial Killing

Community-acquired pneumonia (CAP) is the most common type of pneumonia and remains a leading cause of morbidity and mortality worldwide (1–3). Although many different pathogens can contribute to pneumonia, *Streptococcus pneumoniae* is one of the common bacterial pathogens that underlie CAP (4). In healthy individuals, despite frequent colonization of the upper airways by pathogenic bacteria, multiple innate mechanisms help to protect the lower airways, and CAP is relatively uncommon.

Alveolar macrophages (AMs) are long-lived resident innate immune cells of the airways and key effectors of antibacterial host defense against microbes. Previous work has illustrated that effective bacterial elimination by AMs proceeds in two separate phases: an initial period of macrophage viability and intracellular bacterial killing followed by a later induction of apoptosis and clearance of bacteria (5). Although antimicrobicidal mechanisms contribute to early phagosomal killing of *S. pneumoniae*, AMs demonstrate a finite capacity for bacterial processing and must use a secondary mechanism to control infection.
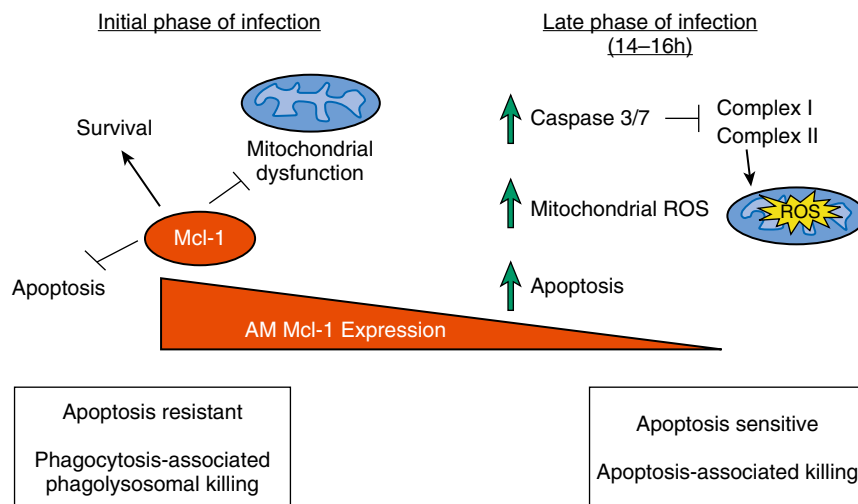
Figure 1. Effective bacterial elimination by alveolar macrophages (AMs) proceeds in two separate phases: an initial period of macrophage viability and intracellular bacterial killing followed by a later induction of apoptosis and clearance of bacteria. During the initial phase, Mcl-1 (myeloid cell leukemia sequence-1) maintains mitochondrial homeostasis and AMs remain resistant to apoptosis. AMs demonstrate a finite capacity for bacterial processing, and, in the later phase, decreased Mcl-1 expression contributes to increased caspase 3/7 activation and increased mitochondrial reactive oxygen species (ROS) production. The ability of AMs to make this transition from resistance to increased susceptibility to apoptosis is essential for effective host immune responses to *Streptococcus pneumoniae*.

Although initially resistant to apoptosis, in the later phase, AMs use the induction of apoptosis to enhance *S. pneumoniae* killing and minimize inflammation (5). The ability of AMs to make this transition from resistance to increased susceptibility to apoptosis is essential for effective host immune responses to *S. pneumoniae*.

Mcl-1 (myeloid cell leukemia sequence-1) is an essential regulator of macrophage lifespan and plays a key role in the switch from AM viability to apoptosis (5, 6). Mcl-1 is located in mitochondrial-enriched cell fractions and can heterodimerize with proapoptotic Bcl-2 (B-cell lymphoma 2) family members to maintain mitochondrial homeostasis (7). Recent work demonstrates that elevated Mcl-1 expression in AMs from patients at increased risk of CAP because of chronic obstructive pulmonary disease or HIV-1 infection is associated with reduced AM apoptosis and bacterial killing (8, 9). In this issue of the *Journal*, Preston and colleagues (pp. 84–97) propose that Mcl-1 upregulation prevents macrophage apoptosis–associated killing of *S. pneumoniae* (10). To examine the role of Mcl-1 in mediating bacterial clearance, Preston and colleagues design a transgenic mouse with macrophage-specific overexpression of human Mcl-1 (CD68.hMcl-1[+]) (10). In a series of meticulously designed experiments, they use controlled infections and interventions to explore the role, microbicidal mechanism, and therapeutic reengagement of macrophage apoptosis–associated bacterial killing. The authors illustrate that Mcl-1 overexpression in macrophages does not alter the early induction of phagocytosis-associated phagolysomal killing. In contrast, late-phase intracellular killing, which coincides with macrophage-associated apoptosis at 16 to 20 hours, is blunted in macrophages overexpressing Mcl-1. Specifically, overexpression of Mcl-1 decreases caspase-dependent mitochondrial reactive oxygen species (mROS) production during the late phase of bacterial exposure, resulting in decreased apoptosis-associated bacterial killing. In response to an intermediate dose of *S. pneumoniae*, which represents the "tipping point" at which AMs begin to fail at controlling the infection, CD68.hMcl-1[+] transgenic

mice exhibit a significant increase in bacterial burden accompanied by significant neutrophil recruitment. To investigate if reduced AM apoptosis-associated killing in CD68.hMcl-1[+] transgenic mice underlies impaired bacterial clearance, the authors use liposomes containing chlodronate to target AM or BH3 mimetics navitoclax (previously ABT-263) and sabutoclax to reengage macrophage apoptosis. Notably, reconstitution of AM apoptosis in CD68.hMcl-1[+] transgenic mice increases bacterial clearance from the lung, reduces bacterial levels in the blood, and decreases neutrophil recruitment.

The article by Preston and colleagues has several unique attributes (10). First, the development and usage of a macrophage-specific CD68.hMcl-1 transgenic mouse provides a unique insight into the role and mechanism of macrophage apoptosis–associated bacterial killing in the lung. Although the relevance of animal models to human disease does merit careful dissection, it is important to note that the design and use of a murine model allowed the authors to test the impact of Mcl-1 overexpression in the context of early-stage subclinical infection. Second, they convincingly demonstrate that Mcl-1 limits caspase-dependent mROS generation and, in turn, decreases apoptosis-associated killing of *S. pneumoniae*. Decreased late-phase bacterial killing results in increased neutrophil recruitment, a hallmark feature of pneumonia. Third, they establish that apoptosis-associated killing is required for bacterial clearance, and reengagement of AM apoptosis can enhance *S. pneumoniae* clearance in lung.

Although this study is elegant in its design and execution, these findings bring up a number of questions for future investigations.

Mcl-1: How might chronic adaptation to oxidative stress alter expression of upstream regulators of Mcl-1? When present on the outer mitochondrial membrane, Mcl-1 exerts its antiapoptotic activity, and when localized to the mitochondrial matrix, Mcl-1 is unable to inhibit apoptosis but instead facilitates mitochondrial homeostasis. Does overexpression alter Mcl-1 localization and thereby impact mitochondrial activity and integrity? Is it possible that Mcl-1 overexpression reduces mROS production by maintaining

mitochondrial homeostasis? What is the role of Mcl-1 overexpression in facilitating the generation of mitochondrial-derived substrates in response to *S. pneumoniae*? Are there changes in Mcl-1 turnover, specifically proteasomal degradation and stabilization, in AMs collected from chronically inflamed lung tissue?

Apoptosis-associated killing: If early phagocytosis is dysregulated, how might this impair late-phase macrophage apoptosis–associated killing mechanisms? What is the impact of impaired endosomal trafficking on apoptosis-associated killing? Is this a conserved mechanism of pathogen clearance used by other tissue-specific macrophage subtypes, such as Kupffer cells? Similar to *Staphylococcus aureus*, do other pathogenic stimuli use Mcl-1 upregulation to inhibit apoptosis-associated killing? What is the impact of pharmacological interventions for chronic diseases, such as chronic obstructive pulmonary disease, on late-phase AM apoptosis–associated clearance?

Pneumonia: How do chronic conditions, such as heart failure, cancer, or Parkinson disease, impact Mcl-1 expression and function in late-phase apoptosis-associated killing? The mortality rate of CAP is markedly higher for individuals 65 years of age or older. Is Mcl-1 expression and function in AMs altered in older persons?

Despite these unanswered questions, this study by Preston and colleagues contributes to our understanding of the role of Mcl-1 in mediating late-phase AM apoptosis–associated killing of *S. pneumoniae* (10). ∎

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Heather W. Stout-Delgado, Ph.D.
Department of Medicine
Weill Cornell Medicine
New York, New York

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