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Previews

OLAH connects fatty acid metabolism to the severity of respiratory viral disease

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Respiratory virus infections may cause profound respiratory illness, yet the factors that underlie disease severity are not well understood. In this issue of *Cell*, Jia, Crawford, et al.[1] identify the role of oleoyl-ACP-hydrolase (OLAH) in mediating life-threatening inflammation associated with viral respiratory disease severity.

Respiratory virus infections are among the deadliest and most communicable infectious diseases worldwide.[2] The societal impact of these infections is best exemplified by the COVID-19 pandemic, which—to date—has resulted in millions of deaths and significant short- and long-term morbidity for patients with nonfatal illness.[3] Epidemiological data indicates that the elderly, young children, pregnant persons, indigenous populations, and patients with comorbid chronic medical conditions are most susceptible to severe outcomes from respiratory virus infections.[4] However, some patients with severe respiratory infections are previously healthy without these predisposing factors.[5,6] Thus, there is an urgent need to identify the biologic underpinnings of severe respiratory disease to better diagnose, stratify, and treat patients with pathogenic respiratory virus infections. In this issue of *Cell*, Jia, Crawford, et al. establish the role of oleoyl-ACP-hydrolase (OLAH), a key enzyme of fatty acid synthesis (Figure 1A), as a critical mediator of respiratory virus disease severity across distinct human patient cohorts and provide mechanistic insights into OLAH-mediated disease severity via a knockout mouse model.[1] Identification of this immune-metabolic pathway lays the foundation for the development of next-generation vaccines and therapeutics for severe respiratory virus infections.

This paper follows recent work coupling cellular metabolism to instruction of the immune system during normal physiology and disease.[7] Activation of immune cells by environmental cues results in dramatic reprogramming of native cellular metabolism. These dynamic changes in immune cell fate and function are also highly dependent on and regulated by nutrients, metabolic intermediates, and canonical regulators of cellular metabolism.[8] For example, during infection, regulation of host lipid factors and their metabolism can impact not only pathogen replication, inflammation, and spread but also intrinsic host defense mechanisms.[9] The importance of these immune-metabolic pathways in disease pathogenesis has prompted novel targeted therapies for infectious diseases, cancer, and autoimmunity.[9] Further study of the complex interplay between metabolic plasticity and the immune system in disease has the potential to reveal novel candidate genes for severe disease prophylaxis and treatment.

To probe for metabolic biomarkers of severe respiratory virus illness, Jia, Crawford, et al. conducted whole blood transcriptome analysis of a well-characterized cohort of patients hospitalized with avian influenza A(H7N9) viral infection at the Shanghai Public Health Clinical Center. High *olah* transcript levels were detected early in hospital admission and persisted in patients that succumbed to disease, while consistently low *olah* expression was observed in patients who had mild A(H7N9) influenza and recovered. A similar relationship between high *olah* expression and respiratory viral illness severity was present in adults with seasonal influenza infection or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and children with severe lower respiratory tract infection (LRTI) or post-infectious multisystem inflammatory syndrome (MIS). By contrast, analysis of peripheral blood microarray expression in human challenge models of mild respiratory illness, including A(H1N1) infection, A(H3N2) infection, human rhinovirus (HRV) infection, and respiratory syncytial virus (RSV) infection, demonstrated no differences in *olah* expression relative to sham infection controls. Interestingly, among adult patients diagnosed with SARS-CoV-2 infection, the downstream catalytic product of OLAH, oleic acid, was found to be increased in hospitalized versus ambulatory patients, consistent with transcriptomic analyses. Taken together, these data establish a previously undefined correlation between *olah* expression and the severity of respiratory disease across human patient cohorts with respiratory viral illness (Figure 1B).

To characterize the mechanisms by which OLAH is linked to severe respiratory disease, Jia, Crawford, et al. generated *olah*-deficient ($olah^{-/-}$) mice. Knockout

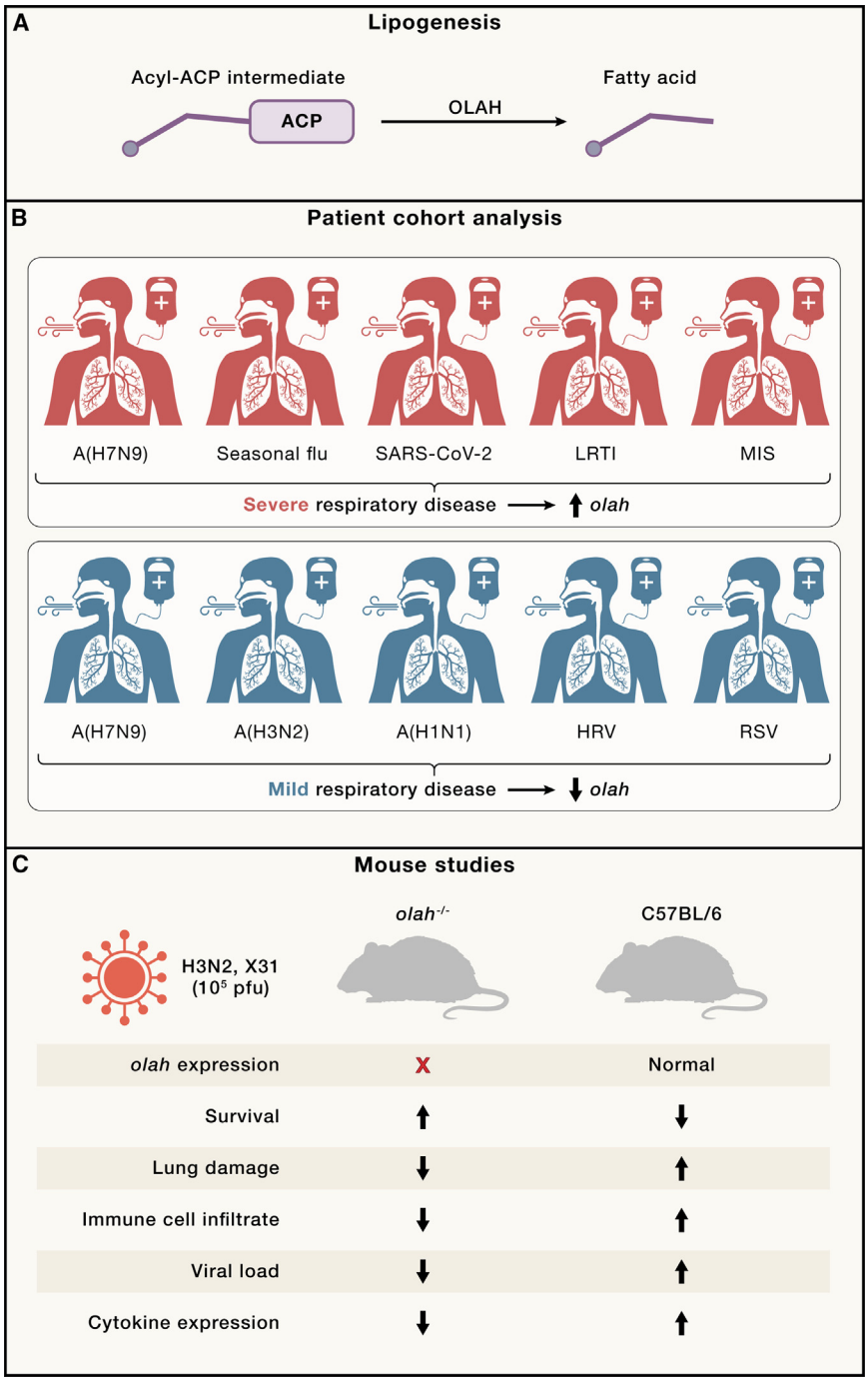

Figure 1. High expression of oleoyl-ACP-hydrolase (OLAH) underlies severe respiratory viral infection

(A) Schematic depiction of the metabolic action of OLAH.

(B) Overview of human studies linking the severity of patient respiratory disease (red, severe; blue, mild) to OLAH expression.

(C) Summarized outcomes after severe influenza (H3N2, X31) infection of *olah*$^{-/-}$ or C57BL/6 mice (X, knockout; ↑, increase; ↓, decrease).

ACP, acyl carrier protein; A(H7N9), influenza A virus subtype H7N9; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; LRTI, lower respiratory tract infection; MIS, multisystem inflammatory syndrome; A(H3N2), influenza A virus subtype H3N2; A(H1N1), influenza A virus subtype H1N1; HRV, human rhinovirus; RSV, respiratory syncytial virus.

of *olah* was confirmed by undetectable expression of *olah* transcripts, decreased levels of OLAH-derived fatty acids, and differential abundance of downstream serum lipids in *olah*$^{-/-}$ mice. The observed clinical association between OLAH expression and influenza disease outcomes was then investigated in *olah*$^{-/-}$ and C57BL/6 wild-type (WT) mice (Figure 1C). All *olah*$^{-/-}$ mice infected with a high dose of influenza virus survived, in comparison to ~50% lethality in infected WT mice. In line with these survival data, infected *olah*$^{-/-}$ mice had correspondingly milder pulmonary pathology and reduced viral titers, proinflammatory cytokines, immune cell infiltrates, and inflammatory lipid precursors in lung tissues. Remarkably, bone marrow chimera studies demonstrated that *olah* expression restricted to immune cells, but not other host cells, primarily mediated these effects. More specifically, severity of infection was associated with increased virus-induced lipid droplet accumulation, viral replication, and cytokine release in lung macrophages. Supplementation with oleic acid exacerbated influenza infection in WT mice and increased cytokine production in both *olah*$^{-/-}$ and WT macrophages. In sum, these data suggest that *olah* expression in macrophages plays a critical role in the severity of influenza infection.

This study by Jia, Crawford, et al. connects fatty acid metabolism to the severity of influenza infection, providing an explanation for the striking differences observed clinically among patients with respiratory viral illness. These findings raise important questions for future research. For example, although macrophages appear to play a pivotal role in driving OLAH-mediated disease severity, the roles of other lung-infiltrating immune cells (e.g., neutrophils and natural killer cells)—which were also found to be elevated in number in infected WT mice—remain to be characterized. Moreover, the exact mechanism by which the absence of *olah* leads to reduced viral infection of macrophages requires further investigation, potentially involving genome-wide knockout screens to elucidate subcellular pathways of viral evasion. While these data support an association between high *olah* expression and severe influenza infection, extension of this work to other respiratory virus mouse models (e.g., SARS-CoV-2 and RSV) may identify

properties of viruses that are most sensitive to *olah* expression. Through a clinical lens, the authors' conclusions motivate the stratification of patients hospitalized with respiratory infection by *olah* expression to study the effect of early therapeutic interventions (e.g., high-dose corticosteroids and antivirals) on patients most at risk for severe disease progression. Finally, *olah* may hold promise as a target for the development of precision therapeutic platforms, such as a small-interfering-RNA-based lipid nanoparticle therapy,[10] to mitigate severe outcomes of respiratory viral illness.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Memory B cell fitness and anergy has significant links to cancer lethality

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Two recent studies reveal that the extent of fitness or anergy in tumor-associated memory B cells is vital to anti-tumor immune response, cancer patient survival, and response to immune therapy. The impact of these seminal findings demonstrates the untapped potential for using B cells to combat the lethality of cancer.

B lymphocytes or B cells have the potential to limit cancer lethality but are still untapped in therapeutic strategy.[1] B cells can invoke powerful anti-tumor T cell responses and prompt tumor cell killing with local and systemic antibodies.[1–4] Yet, prior contradictions between the presence of B cells in tumors and patient clinical outcomes,[2] as well as opposing survival outcomes following depletion of B cells across mouse tumor models, have obscured the rationale for leveraging B cells in cancer treatment.[2] Demanding attention to therapeutic potential, recent work in *Science* from Ma, Wu, Ma, Yang, Zhang et al.[5] and new findings in *Cell* from Yang, Chen et al.[6] demonstrate the presence of memory B cell subsets that significantly predict patient outcomes across major solid tumor types.

B cell responses in tumors are frequently composed of varied proportions and lineages of activated B cells, class-switched and/or somatically hypermutated B cells, antibody-secreting cells (ASCs; plasmablasts and plasma cells), and memory B cells.[2] B regulatory cells emerge from any B cell subset[7] and oppose cytotoxic immune responses using multiple mechanisms.[8] Tumor B cells are also defined by their resemblance of extrafollicular (EF) and germinal center (GC) response pathways that occur in lymphoid organs. GCs function to diversify B cell receptors and select B cells for maturation based on affinity to antigens,