help determine lung transplant candidacy or to predict pretransplant and post-transplant outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Is Pulmonary Hypertension a Metabolic Disease?

Pulmonary hypertension (PH) is a heterogeneous disorder likely to be composed of overlapping syndromes with varying origins and heterogeneous pathobiology and presenting with many phenotypes (1). Knowledge of the underlying pathobiology is necessary for understanding clinical disease manifestations and for devising specific and effective therapies. Enhanced pulmonary vascular cell proliferation, dysregulated cell apoptosis, increased angiogenesis, and vasoconstriction are hallmarks of the disease (Figure 1) (2) and lead to structural and morphological changes within the lung vasculature, including vascular remodeling and arterial wall narrowing. These dysfunctional processes lead to a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death (3). At the molecular level, genetic factors and derangements in signaling pathways, cytokines, chemokines, and growth factors have been linked to the pathobiology of PH (4).

More recently, metabolic dysregulation has emerged as a major area of research in the pathobiology of PH (Figure 1). Just like cancer, PH is characterized by cell proliferation, apoptotic resistance, and increased angiogenesis (5). Also much like patients with cancer, patients with PH exhibit excessive cellular glucose uptake and increased glycolytic metabolism compared with healthy individuals (6, 7). Patients with PH also exhibit alterations in levels of leptin, adiponectin, high-density lipoprotein cholesterol, and insulin resistance (8–11). Cancer cells exposed to these metabolic alterations reprogram their metabolism and protein homeostasis to adapt to nutrient stress conditions, as well as to establish tumor development, progression, and survival. Often, these cells undergo changes in glycosylation (i.e., O-linked *N*-acetylglucosamine modification of proteins and hyaluronan production) and lipid metabolism (12–14). These observed metabolic changes in cancer are increasingly becoming recognized in the pathogenesis of PH as well (15, 16).

One such example is dysregulation in sphingosine 1-phosphate (S1P) metabolism, which is increasingly recognized for its direct involvement in cell proliferation. Two lipid kinases, sphingosine kinase (SphK) 1 and 2, catalyze the conversion of the sphingolipid, sphingosine, to S1P. SphK1 has been linked to several signaling pathways involved in cancer cell proliferation and survival (17). Overexpression of SphK1 has been observed in many tumor tissues, which results in the accumulation of S1P, increased cell proliferation, apoptotic resistance, and disease development and progression (18). Conversely, a reduction in SphK1 activity and subsequent S1P levels is associated with increased cellular ceramide levels, which have been linked to apoptosis and cell cycle arrest (18). Indeed, the homeostatic balance between ceramide and S1P levels (the ceramide/

Supported by the Ruth L. Kirschstein F32 postdoctoral fellowship (F32HL120629 to J.B.) and the Programs of Excellence in Glycosciences (1P01HL10714 to R.A.D.), both from NHLBI.

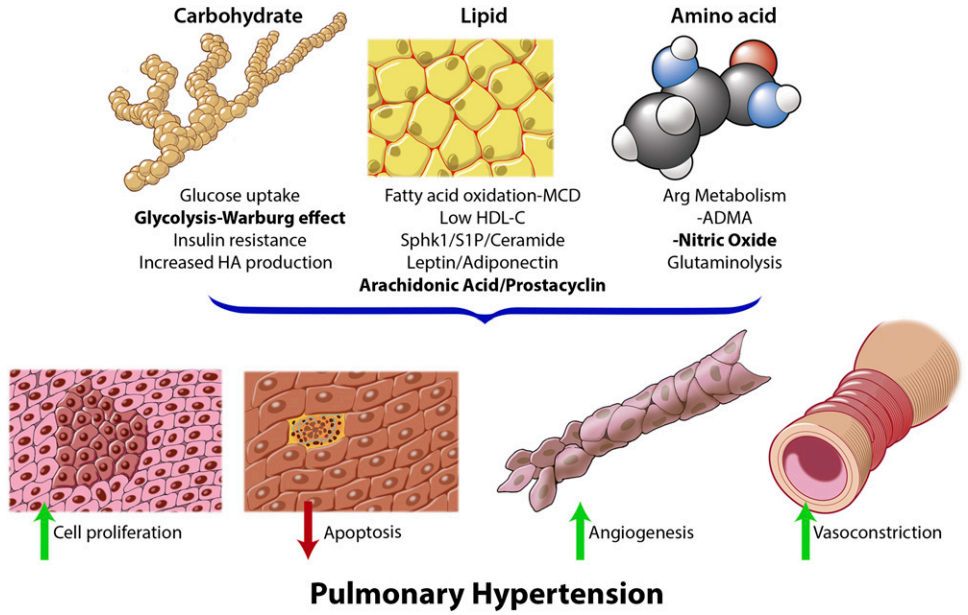

Figure 1. Select identified metabolic derangements in pulmonary hypertension (PH). Dysregulated carbohydrate, lipid, and amino acid metabolism impacts the central phenotypic features of PH. On alteration, these derangements govern the changes in cell proliferation, apoptosis, angiogenesis, and vasoconstriction. These same metabolic derangements have been documented in cancer. At this time, several metabolic pathways are targets for PH therapy (*bold*). ADMA = asymmetric dimethylarginine; Arg = arginine; HA = hyaluronan; HDL-C = high-density lipoprotein cholesterol; MCD = malonyl-CoA decarboxylase.

S1P rheostat) is a gauge for cell death or survival. A recent report made a possible link between SphKs and PH (19).

In this issue of the *Journal*, Chen and colleagues (pp. 1032–1043) examined the SphK1/S1P pathway in PH and show that it promotes pulmonary arterial smooth muscle cell (PASMC) proliferation (20). This finding was identified using a combination of rodent models of hypoxia-mediated PH, human explanted lungs, and isolated human PASMCs. By investigating the functional consequences of altering SphKs or S1P in PH, the authors show that overexpression of SphK1 or S1P stimulation promoted PASMC proliferation, whereas loss of SphK1 blocked the PASMC proliferation in PH. In human PH lungs and PASMCs, SphK1 (but not SphK2) was upregulated, which was consistent with their findings of increased S1P levels. In addition, the protective effect of SphK1 deficiency on hypoxia-induced PH was highlighted. These findings of the direct involvement of the SphK signaling pathway in PH vascular proliferation demonstrate the homeostatic balance that is required for sphingosine metabolism in PH. The molecular changes in the SphK1/S1P metabolic pathway, guided by the current knowledge of its role in cancer cell proliferation, may open new avenues to identify its role as a contributor to pulmonary vascular remodeling and a potential therapeutic target in PH.

In spite of the novel findings in this report, many questions remain unanswered. Are the metabolic features described here universal in PH? Or do they represent a novel phenotype? Because there were only a few samples from patients with PH analyzed in this study, it will be interesting to determine whether the same observations of increased SphK1 activity and S1P levels holds true in a larger population of patients with PH. What are the main contributors to the increased SphK1 and S1P levels (i.e., hypoxia, altered glucose, lipid, or protein metabolism)? Will targeting the SphK1 activity result in a reduction or reversal of the pulmonary vascular proliferation? Alternatively, could the direct delivery of exogenous ceramide or stimulation of ceramide synthesis slow or reverse the process? Addressing these questions will be necessary to determine the fate of this molecular pathway as a novel therapeutic target in PH. In the meantime, however, the findings by Chen and colleagues invite us to explore deeper the global effects of altered metabolism in the pathogenesis of PH, a journey that will hopefully open doors to new therapeutic targets in this deadly disease (3). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Eat and Suppress: The Two-Faced Role of Myeloid-derived Suppressor Cells in Tuberculosis

Despite advances in drug discovery (1), tuberculosis remains one of the leading causes of death worldwide with an estimated one-third of the world's population infected with this bacterium (2). While it is well known that *Mycobacterium tuberculosis* can invade and exploit host cells to escape from immune surveillance (3), the precise mechanism by which it evades adaptive immunity has not been fully understood (4). T cells, particularly $CD4^+$ Th1 and $CD8^+$ cells, are critical for protection against *M. tuberculosis* (5) and have been linked to disease susceptibility and progression (6). Patients with latent infection show protective T-cell responses in contrast to a lack of an efficient T-cell immunity in patients with active tuberculosis (7, 8), underscoring the importance of T-cell activities for controlling this disease. Although regulatory T cells (9) have been involved, the underlying innate immune mechanisms that regulate T-cell functions in tuberculosis remain poorly defined.

Using murine infection models, Knaul and coworkers (pp. 1053–1066) from the Max Planck Institute for Infection Biology in Berlin have dissected the complex interaction between *M. tuberculosis* and innate immune cells and discovered a multifaceted role of suppressive myeloid cells in this disease, reported in this issue of the *Journal* (10). They initially observed that an immature $Gr1^+$ myeloid cell population accumulated in lungs of susceptible mice. By using depleting antibodies, the authors went on to demonstrate that $Gr1^+$ cells are key determinants for tuberculosis susceptibility *in vivo*. Because $Gr1^+$ cells comprise a broad and heterogeneous group of myeloid cells, the scientists further sought to define this myeloid cell population more precisely using global gene expression profiles and immunostaining. These approaches revealed that the identified cell population resembled phenotypic characteristics of myeloid-derived suppressor cells (MDSCs), as they coexpressed arginase 1 (*Arg1*) and nitric oxide synthase 2 (*Nos2*) in line with other MDSC-signature transcripts (11).

MDSCs represent a distinct subset of innate cells, initially identified in cancer, which suppress T cells and help pathogens to undermine adaptive host defenses (12). Based on surface marker profiles, MDSCs can be classified into granulocytic/neutrophilic ($CD11b^+Gr1^+Ly6G^+$) and monocytic ($CD11b^+Gr1^+Ly6C^+$) subsets. In their tuberculosis model, Knaul and colleagues found that both MDSC subsets accumulated in the infected lungs. To functionally prove that the identified "MDSC-like" cell population indeed represented *bona fide* MDSCs, the authors analyzed their functional capacity to suppress T-cell responses. These studies demonstrated that lung-isolated MDSCs suppressed T cells, albeit heterogeneously depending on the time course of disease and the applied readout for T-cell activation (proliferation vs. IFN-γ secretion).