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Editorial

The protective role of adiponectin in pulmonary vascular disease

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ADIPONECTIN (APN), a 30-kDa multimeric protein exclusively produced by fat cells, reverses insulin resistance (IR) and is independently associated with a reduced risk of type 2 diabetes in apparently healthy individuals (10). However, in IR states such as obesity and type 2 diabetes, its expression and circulating levels are decreased. Low APN and high proinflammatory C-reactive protein and IL-6 levels are associated with an increased risk for IR, "metabolic syndrome," diabetes, systemic and possibly pulmonary vascular disease (6). APN expression and secretion is downregulated by TNFα and IL-6 and upregulated by the transcription factor peroxisome proliferator-activated receptor γ (PPARγ). APN binds PDGF-BB, thereby reducing PDGF-BB bioavailability (12) and mitogenic postreceptor function in smooth muscle cells (1). Moreover, APN recently has been identified as endogenous antithrombotic factor (7), and APN overexpression significantly decreased pulmonary arterial wall thickening and right ventricular hypertrophy that develops in chronically hypoxic mice (9). Thus, APN may provide a link between insulin resistance, inflammation, thrombosis, and proliferative cardiovascular disease, e.g., pulmonary hypertension (PH) that is strongly associated with heightened PDGF-BB signaling (6).

Summer et al. (11) recently reported on male APN-deficient (APN−/−) mice that develop pulmonary hypertension at 1 yr of age compared with age-matched wild-type controls. The PH phenotype was characterized by moderate right ventricular systolic pressure (RVSP) elevation, right ventricular hypertrophy (in the absence of peripheral PA muscularization), increased perivascular infiltration of CD45-positive proinflammatory cells, and increased endothelial E-selectin expression as judged by histochemistry. The higher left ventricular end diastolic pressure and LV wall thickness found in the 1-yr-old APN−/− vs. control mice, indicating LV diastolic dysfunction and increased left atrial pressure, may have partly contributed to the RVSP elevation (i.e., non-category 1 PH). Nevertheless, the study by Summer et al. (11) is certainly important as it suggests APN may be a contributory molecule in the linkage between inflammation and PH. This is in accordance with another report by Medoff et al. (8) showing that induced chronic airway inflammation is exacerbated in 6- to 8-wk-old APN−/− mice and associated with severe PH and pulmonary vascular remodeling.

In accordance with the study of Summer et al. (11), we showed that male apoE-deficient mice (apoE−/−), when fed a high-fat diet, do not upregulate the insulin sensitizers APN and leptin (in contrast to control mice), but develop insulin resistance and severe pulmonary arterial hypertension (PAH) (5). The female mice on a high-fat diet had higher APN levels at baseline, did not develop insulin resistance, and had a less severe PAH phenotype compared with their male counterparts. Since testosterone inhibits the secretion of APN in adipocytes(13), we hypothesized that elevation of this vasoprotective adipocytokine may account for the less severe vascular phenotype in female apoE−/− mice. We therefore treated male apoE−/− mice with the PPARγ agonist rosiglitazone for 4 wk and documented an eightfold induction of plasma APN, improved insulin sensitivity, and complete regression of PAH, right ventricular hypertrophy and abnormal pulmonary arterial muscularization. This study (5) also underlined that additional target genes besides apoE, e.g., APN, must be implicated in the antiremodeling effects of PPARγ activation (4, 5).

To this end, both apoE and APN inhibited PDGF-BB-induced proliferation in apoE−/− and wild-type PASMC (4, 5). Others found that apoE internalizes the PDGFR-β (2) and APN sequesters the ligand PDGF-BB (12). Thus, in association with insulin resistance, reduced levels of apoE and APN (1) can be expected to enhance PDGF-BB-signaling. Moreover, Guignabert et al. (3) with our group recently reported that mice with targeted deletion of PPARγ in endothelial cells and macrophages (Tie2 Cre PPARγ$^{flox/flox}$) have threefold higher pulmonary PDGFR-β protein expression that is associated with mild PAH in both normoxia and recovery from hypoxia. It would be interesting to know whether PDGFR-β-mediated ERK phosphorylation is increased in the APN−/− mouse models, i.e., chronic hypoxia (9), allergic airway inflammation (8), and aging (11). Whether the 1-yr-old APN−/− mice (11) had insulin resistance or even overt diabetes, both of which could have been a contributing or even primary causal factor in the development of PH over time, is another important question to be answered.

Yudkin and colleagues (14) previously proposed that detrimental adipocytokines, such as TNFα and IL-6, are secreted from perivascular fat cells and inhibit the eNOS pathway of insulin signaling, leaving unopposed vasoconstriction mediated by endothelium-derived endothelin-1, a key player in PAH. A similar mechanism may explain the downregulation of APN in the proinflammatory milieu of insulin resistance. The source of circulating APN in the murine PH models (5, 9) and in human disease is likely visceral and subcutaneous as well as perivascular (14) adipocytes. High-molecular-weight APN binding to PDGF-BB in close proximity to endothelial PDGFR-β may or may not explain the strong APN staining at the luminal surface of the PA endothelium seen in the control animals that was absent in the APN−/− mice (11).

Zamanian et al. (15) recently demonstrated that IR and dyslipidemia are more common in female PAH patients than in the general population (45.7% vs. 21.5%; $P < 0.001$) and may represent a novel PAH risk factor or disease modifier. The presence of IR was associated with poorer combined 6-mo

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event-free survival from right heart failure, transplantation, or death (58% vs. 79%, $P < 0.05$; hazard ratio 2.57, 95% cardiac index 1.03–6.06, $P < 0.05$; adjusted for age and body mass index).

In summary and in accordance with Summer et al.(11), IR (15) and deficiency of PPARγ, APN, and/or apoE are potential risk factors or disease modifiers for PAH that might be reversible by PPARγ activation (4, 5).

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