World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i8.692

World J Cardiol 2014 August 26; 6(8): 692-705
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (1): Hypertension

Pulmonary hypertension and metabolic syndrome: Possible connection, PPARγ and Caveolin-1

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Received: January 3, 2014 Revised: April 29, 2014
Accepted: June 27, 2014
Published online: August 26, 2014

Abstract

A number of disparate diseases can lead to pulmonary hypertension (PH), a serious disorder with a high morbidity and mortality rate. Recent studies suggest that the associated metabolic dysregulation may be an important factor adversely impacting the prognosis of PH. Furthermore, metabolic syndrome is associated with vascular diseases including PH. Inflammation plays a significant role both in PH and metabolic syndrome. Adipose tissue modulates lipid and glucose metabolism, and also produces pro- and anti-inflammatory adipokines that modulate vascular function and angiogenesis, suggesting a close functional relationship between the adipose tissue and the vasculature. Both caveolin-1, a cell membrane scaffolding protein and peroxisome proliferator-activated receptor (PPAR) γ, a ligand-activated transcription factor are abundantly expressed in the endothelial cells and adipocytes. Both caveolin-1 and PPARγ modulate proliferative and anti-apoptotic pathways, cell migration, inflammation, vascular homeostasis, and participate in lipid transport, triacylglyceride synthesis and glucose metabolism. Caveolin-1 and PPARγ regulate the production of adipokines and in turn are modulated by them. This review article summarizes the roles and inter-relationships of caveolin-1, PPARγ and adipokines in PH and metabolic syndrome.

Key words: Adiponectin; Caveolin-1; Leptin; Metabolic Syndrome; Pulmonary hypertension; Peroxisome proliferator-activated receptor

Core tip: Pulmonary hypertension (PH) is a devastating disease with a high morbidity and mortality rate. Recent studies indicate that the metabolic alterations that occur during the course of PH have a negative effect. Importantly, PH has been observed in patients with metabolic syndrome. Caveolin-1, a membrane protein and peroxisome proliferator-activated receptor γ, a ligand activated transcription factor are abundantly expressed in vascular cells and adipocytes. They play a significant role in maintaining vascular health, and participate in glucose and lipid metabolism. Furthermore, the proximity of vasculature and adipose tissue facilitates reciprocal influence during health and disease.

Mathew R. Pulmonary hypertension and metabolic syndrome: Possible connection, PPARγ and Caveolin-1. *World J Cardiol* 2014; 6(8): 692-705 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i8/692.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i8.692

INTRODUCTION

Chronic inflammation plays a significant role in metabolic syndrome and vascular diseases including pulmonary hypertension (PH). Adipose tissue not only functions as an energy store, but also as an endocrine system producing bioactive substances that influence metabolic and vascular homeostasis. Adipocytes play an important role in regulating inflammatory response. Obesity is associated with chronic inflammation, activation of proinflammatory

cytokines, and with the infiltration of adipose tissue with macrophages and lymphocytes[1,2]. Interestingly, increased plasma and lung levels of pro-inflammatory cytokines[3,4] and perivascular infiltration of inflammatory cells and neo-lymphogenesis in peri-bronchial areas[5-7] have been reported in human and experimental forms of PH. Both caveolin-1, a plasma membrane protein and peroxisome proliferator-activated receptor (PPAR) γ, a ligand-activated transcription factor belonging to the nuclear hormone receptor family are expressed abundantly in adipose and vascular tissues. They modulate inflammation, vascular contractility, cell proliferation, cell cycle progression, and play a significant role in maintaining vascular health, and participate in glucose and lipid metabolism[8-11]. Furthermore, perivascular adipose tissue (PVAT) has been shown to modulate vascular function. Under normal circumstances, it produces relaxing factors including nitric oxide (NO), and participates in anti-contractile function[12].

PULMONARY HYPERTENSION

A mean pulmonary artery pressure ⩾ 25 mmHg constitutes PH. A number of disparate conditions are known to give rise to PH. PH is classified into 5 major clinical groups, that has recently been updated[13]. Group 1 labeled as pulmonary arterial hypertension (PAH) includes idiopathic, heritable PAH and PAH associated with bone morphogenic protein receptor Ⅱ mutation, congenital heart defect, connective tissue diseases, portal hypertension, infection and drug toxicity. Included in this group are pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis as subcategory 1', and recently, persistent pulmonary hypertension of the newborn was assigned the subcategory 1". The next 4 groups are labeled as PH; Group 2: PH associated with pulmonary venous hypertension secondary to left ventricular diseases, Group 3: chronic lung diseases and accompanying hypoxia leading to PH, Group 4: chronic thrombo-embolic PH and Group 5 includes miscellaneous diseases such as myeloproliferative diseases, thyroid, hematological and renal diseases. Irrespective of the underlying disease, the main features of PH are impaired vascular reactivity and remodeling, elevated pulmonary artery pressure and right ventricular hypertrophy, leading to right ventricular failure and premature death. Clinical and experimental studies suggest that the endothelial dysfunction/disruption may be an important underlying factor in the pathogenesis of PH. Importantly, endothelial dysfunction and molecular changes in pulmonary vasculature are reported to occur before the onset of PH[14,15].

Endothelial cells (EC) are heterogeneous; they play a specialized role in the context of a specific organ. EC modulate Ca^{2+} entry, produce vascular relaxants such as NO, prostacyclin and endothelium-derived hyperpolarizing factor and maintain vascular tone, and participate in barrier function. Inflammation plays an important role in the pathogenesis of PH. EC bear the major brunt of injuries such as increased pulmonary blood flow and shear stress, inflammation, chemical/drug toxicity, ventilation-induced injury and hypoxia resulting in endothelial dysfunction. In response to injury, EC become activated and secrete several cytokines and adhesion molecules that can affect coagulation, barrier function, and facilitate cellular adhesion and transmigration of leukocytes leading to EC dysfunction. Endothelial dysfunction leads to impaired vascular relaxation response, and the activation of proliferative and anti-apoptotic pathways, inflammatory response, and thrombogenic state leading to progressive vascular remodeling, elevated pressure and right ventricular hypertrophy[16].

Caveolin-1 and pulmonary hypertension

In the 1950s, Palade and Yamada independently described caveolae, 50-100 nm flask shaped invaginations rich in cholesterol and sphingolipids. Caveolae are a subset of lipid rafts found on the plasmalemmal membranes of a variety of cells including endothelial, smooth muscle, epithelial cells, fibroblasts and adipocytes. Caveolae serve as a platform and compartmentalize the signaling molecules that reside in or are recruited to caveolae. Caveolae are also involved in transcytosis, endocytosis, potocytosis, and in the regulation of cell proliferation, differentiation and apoptosis *via* a number of diverse signaling pathways. Three isoforms of caveolin gene family have been identified. Caveolin-3 is muscle specific, found primarily in skeletal and cardiac myocytes. Caveolin-2 co-localizes with caveolin-1 and requires caveolin-1 for its membrane localization. Caveolin-1 (22 kD) is the major constitutive protein of caveolae[17]. Polymerase 1 and transcript receptor factor (PTRF/cavin), a caveolar coat protein, however, is required for caveolar formation and sequestration of caveolin-1 into caveolae[18]. Caveolin-1 is expressed in terminally differentiated cells including adipocytes, EC, epithelial cells, fibroblasts and myocytes. Caveolin-1 interacts and negatively regulates proteins such as Src family of kinases, G-proteins and G-protein-coupled receptors, eNOS, integrins and several growth factor receptors; and these interactions occur through caveolin-1-scaffolding domain (CSD, residue 82-101 in caveolin-1). For optimal activation, eNOS is targeted to caveolae, and caveolin-1 inhibits eNOS through its interaction. Heat shock protein (HSP) 90 binds to eNOS in a Ca^{2+}-calmodulin-depedent manner, reducing the inhibitory influence of caveolin-1, and increasing eNOS activity. However, caveolin-1 is essential for proper eNOS activation. Caveolin-1 regulates Ca^{2+} entry into EC, which is important for eNOS activation as well as the activation of other vasodilators, prostacyclin and endothelium-derived hyperpolarizing factor[19]. In addition, caveolin-1 regulates not only eNOS-derived NO but also eNOS-derived superoxide. It is involved in the sequestration of uncoupled eNOS; it prevents eNOS oxidase activity, and inhibits superoxide formation[20]. Caveolin-1 keeps smooth muscle cells (SMC) in quiescence; and it modulates Ca^{2+} regulatory molecules, increases Ca^{2+} mobilization and facilitates contractile response to agonists. Disruption of caveolin-1 has been shown to reduce myogenic tone and impair contractile responses to several agonists[21,22]. The dynamic interrelationship

between caveolin-1 and eNOS is critical for vascular homeostasis.

In several experimental models, the loss of endothelial caveolin-1 and the reciprocal activation of proliferative and antiapoptotic pathways such as PY-STAT3, cyclin D1 and Bcl-xL have been shown to occur before the onset of PH. The rescue of caveolin-1 inhibits the proliferative pathways and attenuates PH[15,23,24]. Besides, the mutation of caveolin-1 gene in humans is reported to be associated with PH[25]. Studies with caveolin-1 knockout mice have further highlighted the importance of caveolin-1 in pulmonary vasculature. The re-expression of endothelial caveolin-1 has been shown to attenuate PH, vascular dysfunction and cardiomyopathy in these mice[26]. Increased expression of PDGF-R β, the activation of PY-STAT3 and its downstream signaling pathways, cyclin D1 and Bcl-xL have been reported in pulmonary arteries from patients with PH as well as in the MCT and hypoxia models of PH[24,27-29]. The activation of PY-STAT3 is essential for PDGF-induced cell proliferation; and the inhibition of the PDGF receptor suppresses cell proliferation *via* the inactivation of STAT3 signaling[30,31]. Importantly, caveolin-1 acts as a suppressor of cytokine signaling, and inhibits PY- STAT3 activation and modulates proinflammatory cytokines[32] and it inhibits other proliferative pathways including PDGF-R β, cyclin D1, Bcl-xL. It promotes cell cycle arrest *via* a $p53/p21^{waf1/cip1}$-dependent mechanism and regulates apoptosis by inhibiting survivin[33,34].

In the monocrotaline (MCT) model of PH, at 2 wk post-MCT, there is a significant loss of endothelial caveolin-1 associated with the activation of proliferative and anti-apoptotic pathways, PH and right ventricular hypertrophy. As the pulmonary vascular disease progresses, by 4 wk, extensive endothelial caveolin-1 loss and EC damage occur, followed by an enhanced expression of caveolin-1 in vascular SMC. This is associated with a significantly increased expression and the activity of matrix metalloproteinase (MMP) 2 that is known to participate in cell proliferation and cell migration. Normally, MMP2 is inhibited by caveolin-1; the activation of MMP2 in the presence of enhanced expression of caveolin-1 in SMC suggests that this caveolin-1 may have lost its inhibitory function[15]. Enhanced expression of caveolin-1 in SMC has been reported in patients with idiopathic PAH, PAH associated with congenital heart defect and drug-toxicity[35-37]. Pulmonary arterial SMC from idiopathic PAH revealed not only enhanced expression of caveolin-1, but also Ca^{2+} dysregulation and increased DNA synthesis which could be blocked by silencing caveolin-1[35]. This caveolin-1 in SMC becomes pro-proliferative, and facilitates cell proliferation and migration. The about face of caveolin-1 function in PH is not unlike what has been reported in cancer[17]. The effect of caveolin-1, thus, may depend on its location, conformation, state of the disease and cell context.

PPARγ and pulmonary hypertension

PPARs constitute a subfamily of nuclear receptors, the master transcriptional regulators of nutrient metabolism and energy homeostasis. Three isoforms of PPAR have been identified (α, β/δ and γ). PPARα is thought to regulate fatty acid oxidation and glucose homeostasis, and is predominantly found in liver, muscle and kidneys. Recent studies have shown that PPAR β/δ agonists relax pulmonary and mesenteric arteries independent of cGMP and cAMP mechanisms. PPARγ is expressed in several types of tissue, including adipocytes, EC and SMC. It is an important regulator of genes involved in cell differentiation, cell growth, inflammation and angiogenesis. It forms an obligatory heterodimer with another nuclear receptor, retinoid-X-receptor which binds to peroxisome proliferator response elements that is located in the regulatory domains of genes[38,39]. PPARγ inhibits the production of chemokines in EC and the activation of NFκB[40]. In addition, it inhibits inter cellular adhesion molecules (ICAM) and vascular cellular adhesion molecules (VCAM)[41]. Furthermore, PPARγ increases NO production from EC and regulates superoxide generation at the EC membrane[42,43]. PPARγ has also been shown to reduce vascular SMC proliferation and migration[44]. In an arterial injury model, PPARγ was shown to have attenuated neointimal hyperplasia by modulating protein kinase G[45]. Reduction in the expression of PPARγ has been reported in human PAH and several experimental forms of PH such as vascular endothelial growth factor (VEGF) receptor blocker + hypoxia[46] and a shunt model[47] Endogenous ligand 15-deoxy-Δ(12,14) prostaglandin J2 and thiozolidinedione (TZD) compounds used in the treatment of diabetes activate PPARγ. Interestingly, TZD compound has been reported to attenuate the hypoxia-induced PH in mice[48]. However, PPARγ has also been shown to increase plasminogen activator inhibitor type-1 expression in EC which can affect vascular disease adversely[49]. PPARγ within the atheromatous lesion has a propensity to facilitate angiogenesis[50]. Furthermore, PPARγ not only upregulates caveolin-1 expression but also promotes some forms of cancer[51,52]. PPARγ does play an important role in vasculature but its effects may depend on the state of disease and the cellular context; and the activation of PPARγ may not be effective in all forms of PH.

Pulmonary hypertension and associated metabolic alterations

Metabolic alterations that occur in PH negatively impact the disease. In PH, mitochondrial metabolic shift from oxidative phosphorylation to glycolytic pathway has been shown to occur in pulmonary vasculature as well as in the right ventricle. When this shift occurs in aerobic conditions, it is termed "Warburg effect" which leads to the down regulation of mitochondrial glucose oxidation. It is accompanied by fragmented, hyperpolarized mitochondrial reticulum, decreased superoxide dismutase2, metabolic shift, increased hypoxia inducible factor (HIF)-1α, and the activation of pyruvate dehydrogenase kinase[53]. Glycolytic pathway is associated with resistance to apoptosis; an important feature of PH. EC isolated from idiopathic PAH pulmonary arteries exhibit increased glyco-

lytic rate, decreased mitochondrial DNA levels and fewer mitochondrial numbers per cell. In addition, increased glycolytic rate has also been shown to occur in the lungs of patients with idiopathic PAH[54]. Hyperpolarization of the mitochondrial membrane is thought to be a feature of Warburg phenotype, and apoptosis is induced by the activation of voltage-gated K^+ channel (Kv) and depolarization of mitochondrial membrane[55]. Mitochondrial hyperpolarization is thought to be the underlying cause of the metabolic switch observed in PH. Importantly, the loss of caveolin-1 has been shown to lead to mitochondrial dysfunction, membrane hyperpolarization, and the mitochondrial production of oxidant species. Interestingly, the glycolysis inhibition abolishes the increase in oxidant species in caveolin-1 knock-down vascular EC[56], indicating that caveolin-1 may have a key role in the regulation of oxidative stress and metabolic switch. Recent studies have shown decreased expression of mitochondrial uncoupling protein2 and increased mitochondrial potential in pulmonary arterial SMC from patients with idiopathic PAH and from experimental models of PH. Interestingly, reactive oxygen species inhibitors decrease cell proliferation in pulmonary arterial SMC with absent mitochondrial uncoupling protein2 expression[57]. In addition, treatment with dichloroacetate that increases the mitochondrial oxidative phosphorylation has been shown not only to prevent but also to reverse MCT-induced PH[58]. Thus, controlling metabolic dysfunction in PH may be a valuable therapeutic measure to prevent the progression of the disease or possibly to reverse it.

ADIPOSE TISSUE AND VASCULATURE

Adipose tissue produces a number of bioactive substances including leptin, adeponetin, and inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and visfatin, and proteins such as apolipoprotein E (ApoE), plasminogen activator inhibitor 1 and apelin[59,60]. These substances influence adipose tissue and vasculature in health and disease.

PVAT surrounds blood vessels to provide support and to maintain vascular homeostasis. Close anatomical relationship between PVAT and blood vessels allows crosstalk which is essential for both vascular and metabolic homeostasis. Anti-contractile activity of PVAT is thought to be due to the release of adipose-derived relaxing factor[61]. In addition to the adipose-derived relaxing factor, PVAT releases other vaso-active factors including adiponectin, leptin, angiotensin (1-7) and NO. Under normal conditions these factors maintain vascular function and resistance[12]. PVAT shares common features with brown fat tissue, which is important for thermogenesis and plays a protective role[62].

Adiponectin was initially recognized as an insulin-sensitizing factor, now it has been found to have a role in vascular homeostasis and inflammation. Adiponectin is an anti-inflammatory adipokine; its levels are reduced in obesity. Adiponectin plays a central role in the development of metabolic syndrome and atherosclerosis; both have a low grade inflammation. Adiponectin knockout mice show an exaggerated inflammatory response and produce increased lipopolysaccharides-induced expression of VCAM-1 and ICAM-1. Treatment with adiponectin results in a dose-dependent inhibition of TNF-α-induced monocytes adhesion to EC and the expression of VCAM-1[63]. Interestingly, adiponectin is present in vascular EC at steady state, and it has been shown to have a significant role in vascular relaxation by activating eNOS[64], and PGI_2 synthase[65]. High molecular weight adiponectin stimulates eNOS phosphorylation accompanied by eNOS-HSP90-Akt complex formation and increases NO production in a dose-dependent manner; and it also inhibits caspase3 activity and promotes endothelial survival[66,67].

Adiponectin produced in perivascular tissue is highly regulated by PPARγ. Furthermore, PVAT regulates insulin-mediated vasorelaxation in adiponectin-dependent pathway. It increases eNOS activation as well as inhibits superoxide generation. Local expression of adiponectin gene and protein is increased in the presence of oxidative stress. Under oxidative stress and in the presence of low tetrahydrobiopterin, eNOS is uncoupled and generates superoxide. Under these circumstances adiponectin may increase superoxide generation by increasing eNOS activation[68,69].

Removal of PVAT has been shown to enhance neointima formation; and the local but not the systemic administration of adiponectin reduces neointima formation[70]. Obesity-induced inflammation causes increased production of pro-inflammatory adipokines and reduction in anti-inflammatory adiponectin, which contribute to pathological vascular remodeling in response to injury. Deletion of adeponectin in mice leads to PH, perivascular inflammatory infiltrates and the upregulation of E selectin[71]. Recent studies have shown increased plasma levels of adiponectin associated with endothelial dysfunction in diabetic nephropathy[72]. This suggests that the adiponectin levels increase in response to endothelial dysfunction and that the endothelial integrity may be necessary for normal adiponectin function.

Leptin, primarily expressed by adipocytes is involved in energy expenditure and plays a key role in inhibiting food intake and improving insulin sensitivity. In obese patients, the circulating leptin levels are high but they exhibit resistance to the effects of leptin. Congenital leptin deficiency is associated with marked obesity and hypogonadism[73]. Increased risk of cardiovascular diseases has been reported in obese patients with elevated levels of leptin. Leptin is considered a link between metabolic disorders and immune responses. Usually, leptin increases during the course of acute infection and inflammation. Leptin has been shown to have a direct effect on T lymphocyte type 1 helper response, and leptin alters T regulatory (Treg) response. Defective leptin receptor signaling in Treg cells reduces the development of atherosclerosis[74]. Leptin negatively affects the generation and the proliferation of the Treg cells[75], and it promotes chronic autoimmune disorders by regulating Treg cells and their

function[76].

Leptin receptors are expressed in EC, SMC and macrophages. Leptin induces vasoconstriction *via* the stimulation of sympathetic activity; and depending on intact and functional EC, it has a direct vasodilatory effect *via* NO release. In systemic hypertensive rats, a reduction in leptin levels is accompanied by a loss of perivascular anticontractile function secondary to the impaired activation of eNOS[77]. In contrast, obesity-induced increased expression of leptin enhances neointima formation. Even in the absence of obesity and increased circulating levels of leptin, overexpression of leptin in PVAT facilitates neointima formation[78]. In cell culture studies, leptin has been shown to induce vascular SMC proliferation and migration[79]. Furthermore, pulmonary arterial EC from patients with PAH, and PAH associated with scleroderma secrete leptin. In addition, Treg cells from these patients exhibit increased expression of leptin receptor (ObR) on the membrane[80], indicating that leptin may have a significant role in the pathogenesis and progression of PH.

ApoE is primarily produced in liver, but other cells such as adipocytes and macrophages also produce it, but not the preadipocytes[60]. Circulating ApoE plays an important role in the metabolism of lipoproteins. Adipocytes from ApoE knockout mice are smaller. Systemic deficiency of ApoE results in impaired clearance of triglycerides and resistance to obesity[81]. Diet-induced or leptin-deficient obesity produces a significant reduction in ApoE expression in adipocytes. Inflammatory cytokines such as TNF-α and reactive oxygen species suppress ApoE expression, whereas systemic administration of PPARγ increases ApoE expression. Interestingly, ApoE colocalizes with caveolin-1 in adipocytes, and the loss of ApoE results in the alterations in caveolar lipid composition and a significant reduction in caveolin-1 mRNA expression. Endogenous expression of ApoE preserves caveolar composition in adipocytes[82,83]. ApoE is not produced in EC, but macrophage-related ApoE is internalized by EC. ApoE increases the endothelial NO production by modulating caveolin-1/eNOS interaction and it suppresses endothelial activation, and inhibits VCAM-1 expression *via* eNOS stimulation and NO production. Interestingly, ApoE has been shown to co-precipitate with caveolin-1 but not with eNOS. Deficiency of ApoE is associated with hypercholesterolemia, and the loss of its effect on eNOS activation leads to endothelial dysfunction[84,85]. Ablation of caveolin-1 in ApoE knockout mice has shown to be protective against atherosclerosis[86]. However, PPARγ-induced increase in caveolin-1 expression in ApoE knockout mice confers protection against atherosclerosis[87]. The opposing effects of caveolin-1 may be dependent on its location and conformation. Interestingly, male ApoE knockout mice on high fat diet and associated insulin resistance have been shown to develop PH, which can be reversed by PPARγ activation[88].

Other bioactive substances produced by adipose tissue are visfatin and apelin. Visfatin has been shown to stimulate SMC growth and angiogenesis. Apelin causes NO-dependent vascular relaxation, but it is a potent vascoconstrictor in endothelium-denuded vessels[59]. The foregoing observations indicate that adipose tissue, especially PVAT possesses direct vascular protective effects which are reduced or lost in obesity, resulting in an increased incidence of vascular diseases. Even in the absence of obesity, but in the presence of alterations in the balance of bioactive substances produced by PVAT can significantly influence the state of the vasculature.

METABOLIC SYNDROME

Adipose tissue has a critical role in energy balance and insulin sensitivity. A complex network of transcripton factors is involved in adipogenesis. White adipose tissue is the predominant type in adults and it functions as a storage depot for energy; whereas the brown adipose tissue generates heat through mitochondrial uncoupling of lipid peroxidation. Adipose tissue consists of adipocytes, preadipocytes, leukocytes, macrophages and EC. Adipocytes are an active metabolic organ that secretes a number of adipokines including leptin, adiponectin and resistin, and are involved in glucose and lipid metabolism, energy homeostasis; and it modulates inflammation and vascular reactivity. In addition, adipose tissue secretes proinflammatory cytokines such as IL-6, IL-1, TNF-α and CC-chemokine ligand 2[89-92].

Inflammation plays a significant role in metabolic syndrome, and the adipocytes are considered the primary site of inflammation. Metabolic syndrome includes a number of alterations such as increased waist circumference, systemic hypertension, increased levels of glucose, and impaired cholesterol and triglyceride metabolism. The major categories included in the metabolic syndrome are obesity, disorders of adipose tissue and insulin resistance. There is a positive correlation between cardiovascular diseases and the components of metabolic syndrome such as abdominal obesity, atherogenic dyslipidemia, insulin resistance with or without glucose intolerance, and the presence of pro-inflammatory and pro-thrombogenic factors[93].

Recent studies show that EC play a key role in metabolic homeostasis. VEGF-B interacts with endothelial VEGF receptor1 also known as FLT1, and regulates endothelial transport of fatty acids into cardiac and skeletal muscle. Over expression of VEGF-B can lead to mitochondrial dysfunction, altered cardiac lipid metabolism and hypertrophy, and insulin resistance. Mice lacking VEGF-B have been shown to display decreased fatty acid uptake and lipid deposition in muscle cells. Furthermore, VEGF-B inhibition improves insulin sensitivity[94-96]. In addition to VEGF-B, PPARγ and apelin also have a role in fatty acid uptake by EC and coordinate it with the energy demand and to accommodate energy needs during fasting[97].

Caveolin-1 and metabolic syndrome

Caveolin-1 in adipocytes plays an important role in glucose and lipid metabolism. Insulin receptor (IR) colocalizes with caveolin-1, and caveolin-1 stabilizes IR-β sub-

unit at the cell membrane. It stimulates IR signaling and linking insulin action to glucose uptake. Insulin recruits glucose transporter (GLUT) 4 for glucose uptake and caveolin-1 is required for its internalization after insulin removal[98-101]. Thus, caveolin-1 plays an important role in the control of insulin signaling and facilitates GLUT4-mediated glucose uptake.

Leptin has been shown to increase the expression of caveolin-1 in adipocytes and EC, and in contrast, caveolin-1 impairs leptin signaling which in part may be responsible for inducing leptin resistance and endothelial dysfunction[102,103]. Interestingly, patients with obesity and obesity-associated type 2 diabetes, exhibit increased expression of caveolin-1 mRNA. This increase in caveolin-1 mRNA is associated with an increased expression of inflammatory markers such as leptin, C-reactive protein, MCP-1 and TNF-α[104]. In diabetic mice, increased expression of caveolin-1 mRNA and protein has been shown to be associated with impaired endothelium-dependent relaxation response despite normal eNOS expression[105]. It is likely that caveolin-1 forms a tight complex with eNOS inhibiting its activation, not unlike what is seen in the hypoxia-induced PH. In the hypoxia model of PH, the disruption of cholesterol results in the separation of caveolin-1 and eNOS resulting in increased NO production[106].

Caveolae are also the site of fatty acid entry. The enzymes involved in *de novo* synthesis of triacylglycerol from fatty acids, and glycerol-3 phosphatase are localized in the subclass of caveolae in the plasma membrane of primary adipocytes[107]. Caveolin-1 regulates triglycerides, lipoprotein metabolism and cholesterol homeostasis, and participates in lipid storage *via* transcytosis and also in its breakdown. In addition, it targets the lipid droplet accumulation in the cells. In atherosclerosis, caveolin-1 has been shown to promote cholesterol accumulation *via* transcytosis across EC, thus, negatively impacting the disease. Loss of caveolin-1 leads to decreased lipid accumulation resulting in progressive white adipose tissue atrophy[108-110]. Recent studies have shown caveolin-1 gene mutations to be associated with the atypical and severe forms of lipodystrophy and hypertriglyceridemia[111,112]. Furthermore, mutation of PTRF associated with a reduction in caveolin has been reported in patients with generalized lipodystrophy and muscular dystrophy[113]. Loss of caveolin-1 causes significant metabolic alterations, increased glucose production in the liver and metabolic inflexibility. Metabolic flexibility is the function of adjusting the changing nutrient availability. Adiponectin has been thought to provide the metabolic flexibility. Interestingly, caveolin-1 knockout mice exhibit low circulating adiponectin despite increased mRNA and intracellular adiponectin[114].

Studies with caveolin-1 knockout mice have revealed the importance of caveolin-1 in maintaining vascular and metabolic homeostasis. Caveolin-1 knockout mice exhibit PH and cellular hyperplasia in the lungs, cardiomyopathy, and metabolic deregulation. These mice are found to be resistant to diet-induced obesity, but have hypertriglyceridemia and develop insulin resistance on normal diet[98]. In addition, they exhibit increased macrophage infiltration, increased capacity for IL-6 production and an increased collagen deposition leading to increased fibrosis. Adipose tissue from these mice show increased lipolysis[115]. Re-expression of endothelial-specific caveolin-1 ameliorates cardiopulmonary changes, but has no effect on the lack of caveolin-1 in adipocytes that accounts for lipoatrophy. The endothelial-specific caveolin-1 expression, however, limits the macrophage extravasations into adipose tissue[116], indicating a significant role of endothelial caveolin-1 in modulating adipocytes-driven inflammatory response.

PPARγ and metabolic syndrome

Adipose tissue especially the white adipose tissue is the major site for PPARγ expression. PPARγ is required for adipocytes differentiation. Activation of PPARγ in fibroblastic cells leads to cell differentiation and lipid accumulation; and in addition, these cells acquire genes characteristic of fat cells[117]. PPARγ is expressed to a lesser degree in insulin target tissues such as liver and skeletal muscle. Muscle-specific PPARγ is critical for maintaining the whole body response to insulin. The loss of muscle-specific PPARγ leads to obesity and insulin resistance[118]. In addition, targeted EC deletion of PPARγ plays an important role in insulin resistance and hyperlipedemia-mediated hypertension[119].

Impaired PPARγ function is implicated in a number of metabolic disorders such as type2 diabetes, obesity and lipodystrophy. In humans, mutation of PPARγ leads to obesity and severe insulin resistance. Overexpression of this mutant gene in murine fibroblasts leads to accelerated differentiation into adipocytes and increased cellular accumulation of triglycerides[120]. PPARγ mutation is reported to be associated with insulin resistance, diabetes and hypertension[121], and also in cases of lipodystrophy associated with activated renin-angiotensin system and ensuing oxidative stress and hypertension[122]. Defect in PPARγ expression plays a significant role in PH as well as in the pathogenesis of fibrosis; importantly, scleroderma exhibits both these features[123]. The anti-fibrotic activity of PPARγ is thought to be mediated by hepatocyte growth factor and adiponectin. Adiponectin, an anti-inflammatory adipokine and a fat-specific target of PPARγ prevents hepatic fibrosis in mice[124] and hypoxia-induced PH[125]. The administration of leptin, a proinflammatory adipokine has been found to reduce the expression and activity of PPARγ in human lung fibroblasts and to augment TGF β-mediated fibro-proliferative response. Furthermore, the loss of leptin prevents bleomycin-induced lung fibrosis in mice[126].

PPARγ inhibits the production of adipokine/cytokines such as resistin, IL-6 and TNF-α, all known to promote insulin resistance. PPARγ agonist-induced adiponectin levels are reported to be low in type 2 diabetes[127]. Adiponectin increases fatty acid oxidation in liver and skeletal muscle, resulting in improved insulin sensitivity in skeletal muscle, and decreased glucose production in the liver, thus, leading to the reduction in circulating glucose,

free fatty acid and triglycerides[128]. These results suggest a protective role of PPARγ, and the crosstalk between PPARγ and adipokines determines the progression of a given metabolic/vascular disease process. PPARγ activators, TZD group of drugs have been used clinically to treat type 2 diabetes. TZDs increase the expression of proteins required for insulin signaling, and also reduce the circulating levels of low density lipoproteins and triglycerides. Furthermore, they attenuate the production of inflammatory mediators[129,130]. However, TZDs are also reported to have side effects such as increased fluid retention, increased risk of congestive heart failure, decrease in bone mineral density and fractures. Selective PPARγ modulator in experimental studies has been shown not only to increase insulin sensitivity but also to improve bone density[131,132]. Selective PPARγ modulation, thus, may significantly reduce the side effects of TZD.

Metabolic syndrome and pulmonary hypertension

Obesity is reported to be associated with PH, but the prevalence of PH in obesity is not known. The echocardiographic studies in 3790 normal subjects revealed higher pulmonary artery pressure to correlate with age, body mass index and gender; the incidence being higher in males[133]. Importantly, higher frequency of obesity, diabetes and hyperlipidemia was found in patients with precapillary PH[134]. Furthermore, obesity is a risk factor in patients with elevated pulmonary venous pressure and preserved left ventricular ejection fraction[135].

Diabetes is reported to be associated with PH independent of coronary artery disease and congestive heart failure[136], and insulin resistance is more prevalent in female patients[137]. Recent REVEAL registry analysis showed a high incidence of obesity (M:F, 31%:34%) among patients with PAH; and associated comorbidities such as diabetes and chronic obstructive pulmonary disease had a negative impact on prognosis[138,139]. In experimental studies, diabetes associated with moderate hypoxia is reported to exhibit significant endothelial dysfunction, elevated pulmonary artery pressure and RVH. It was diabetes and not the moderate hypoxia that was found to be responsible for endothelial dysfunction[140]. These observations suggest that obesity and insulin resistance negatively impact PH.

HYPOXIA, PULMONARY HYPERTENSION AND METABOLIC SYNDROME

HIF-1α, an O_2 sensor is a subunit of a family of HIF transcription factors. HIF-1α regulates numerous genes involved in adaptive responses to hypoxia and modulates metabolism, growth and angiogenesis; and promotes adaptation and cell survival under hypoxic condition. VEGF, critical for angiogenesis, is one of the target genes of HIF-1α[141]. Under normoxic conditions HIF-1α is degraded. Evidence is accumulating to suggest that reactive oxygen species (ROS) generated by mitochondrial complex Ⅲ is required for HIF-1α activation and stabilization; and in turn HIF-1α activation prevents increased production of ROS in hypoxic cells[142]. Under hypoxic conditions, cells depend on glycolysis for ATP production; and HIF-1α is necessary for metabolic switch during hypoxia[143]. Destabilization of HIF-1α has a negative impact on cell and tissue adaptation to hypoxia.

HIF-1α has been implicated in the pathogenesis of PH. HIF-1α plays a role in cell proliferation, angiogenesis, and participates in vascular remodeling. In plexiform lesions, the proliferating EC have been shown to express HIF-1α, its target gene VEGF and VEGF receptor 2[144]. Recent studies have shown that the deletion of HIF-1α in SMC attenuates hypoxia-induced PH and vascular remodeling[145]. In some types of cancer cells, HIF-1α under hypoxia conditions upregulates caveolin-1 and promotes ligand-independent activation of epidermal growth factor receptor, and increases cell proliferation and cell migration[146]. Interestingly, HIF-1α has also been shown to maintain pulmonary vascular tone during hypoxia and normoxia by decreasing myosin light chain phosphorylation; and the lack of HIF-1α increases pulmonary vascular tone[147]. In addition, the loss of HIF-1α in SMC from systemic vessels causes systemic hypertension and an exaggerated response to angiotensin Ⅱ. HIF-1α is reported to decrease the expression of angiotensin Ⅱ receptor type 1. Importantly, the HIF-1α-induced decrease in the expression of angiotensin II receptor type 1 is mediated by PPARγ[148]. In addition, HIF-1α has been shown to play a protective role in the adaptation of the heart and aorta to pressure overload by regulating TGF-β signaling in EC[149].

HIF-1α is an important regulator of glucose transport by altering GLUT1 expression in EC. Absence of HIF-1α is associated with significant defect in glucose uptake. Reduced glucose uptake in HIF-1α-deficient EC can be rescued by increased expression of GLUT1 DNA, underscoring the critical the role played by HIF-1α in glucose metabolism[150], and that the vascular dysfunction may contribute to abnormal glucose handling. Hyperglycemia has been shown to impair hypoxia-dependent stabilization of HIF-1α[151]. Both hyperglycemia and hypoxia are known to occur in diabetes. Hyperglycemia-induced destabilization of HIF-1α negatively affects the tissue adaptation to hypoxia, resulting in complications such as diabetic retinopathy, cardiovascular and renal diseases[152]. In addition, deficiency of HIF-1α has been shown to block stromal derived factor1 and impair mobilization of bone marrow-derived angiogenic cells, thus adversely affecting wound healing[153]. Interestingly, hypoxia has been shown to cause insulin resistance and the inhibition of HIF-1α in adipose tissue improves insulin resistance[154]. Thus, both in PH and metabolic syndrome, the role of HIF-1α may depend on the cells, disease state and the interaction of HIF-1α with other factors including caveolin-1 and PPARγ.

CONCLUSION

Caveolin-1 and PPARγ are abundantly expressed in EC and adipocytes. Under normal conditions, caveolin-1 and

PPARγ interact with adipokines (pro- and anti-inflammatory) and form a complex network to maintain metabolic and vascular homeostasis. Genetic mutations of caveolin-1 and PPARγ lead to vascular and metabolic diseases. PVAT has a direct role in maintaining vascular reactivity. Disruption of PVAT results in the loss of anti-inflammatory and anti-contractile factors leading to endothelial dysfunction. The initial loss of endothelial caveolin-1 results in the activation of proliferative pathways leading to vascular remodeling and PH. As the disease progresses, SMC develop enhanced expression of caveolin-1. This caveolin-1 becomes pro-proliferative and participates in cell proliferation and cell migration. In adipose tissue, the loss of caveolin-1 is associated with dysregulation of insulin and lipid metabolism. However, increased levels of caveolin-1 in diabetes and hypercholesterolemia result in eNOS dysfunction. Loss of PPARγ leads to vascular and metabolic diseases. Interestingly, PPARγ within the atheromatous lesion facilitates angiogenesis. Adiponectin, regulated by PPARγ increases insulin sensitivity, inhibits inflammation and facilitates NO production, thus, plays an important role in maintaining vascular and metabolic homeostasis. Leptin, a proinflammatory adipokine has an important role in food intake and energy conservation. Under normal conditions, leptin has a vasodilatory effect. However, obesity-induced increased levels of leptin cause endothelial dysfunction. It increases caveolin-1 expression which in turns inhibits leptin.

Vasculature and adipose tissue owing to their proximity share the complex network of transcription factors, and influence each other in health and disease. The network of these factors is rather complex and delicate, which can be deregulated by injury and/or inflammatory process leading to a stage where the cytoprotective factors become cytotoxic depending on the state of the cell/organ. Rudolf Virchow (1821-1902) a German physician is reported to have said "The body is a Cell State in which every cell is a citizen. Disease is merely the conflict of citizens of the State brought about by the action of an external force". It is not difficult to imagine that this conflict can easily spill into the neighboring organs/systems.

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P- Reviewer: Trimarchi H **S- Editor**: Wen LL
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