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TGF-β: The missing link in obesity-associated airway diseases?

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ABSTRACT

Obesity is emerging as a global public health epidemic. The co-morbidities associated with obesity significantly contribute to reduced quality of life, mortality, and global healthcare burden. Compared to other asthma comorbidities, obesity prominently engenders susceptibility to inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), contributes to greater disease severity and evokes insensitivity to current therapies. Unlike in other metabolic diseases associated with obesity, the mechanistic link between obesity and airway diseases is only poorly defined. Transforming growth factor-β (TGF-β) is a pleiotropic inflammatory cytokine belonging to a family of growth factors with pivotal roles in asthma. In this review, we summarize the role of TGF-β in major obesity-associated co-morbidities to shed light on mechanisms of the diseases. Literature evidence shows that TGF-β mechanistically links many co-morbidities with obesity through its profibrotic, remodeling, and proinflammatory functions. We posit that TGF-β plays a similar mechanistic role in obesity-associated inflammatory airway diseases such as asthma and COPD. Concerning the role of TGF-β on metabolic effects of obesity, we posit that TGF-β has a similar mechanistic role in obesity-associated inflammatory airway diseases in interplay with different comorbidities such as hypertension, metabolic diseases like type 2 diabetes, and cardiomyopathies. Future studies in TGF-β-dependent mechanisms in obesity-associated inflammatory airway diseases will advance our understanding of obesity-induced asthma and help find novel therapeutic targets for prevention and treatment.

1. Introduction

Excess food intake and positive energy balance increase the risk of obesity, promote fat storage in the form of white adipose tissue (WAT), and elicit metabolic disturbances. Obesity is among the leading risk factors for co-morbidities such as type 2 diabetes, hypertension, atherosclerosis, and asthma (Lambert et al., 2017) (Natsis et al., 2020) (Schütten et al., 2017) (Peters et al., 2018) (Kahn et al., 2006). Obesity has thus been characterized as not a single disease, but a multitude of different disease states that may manifest as a variety of clinical symptoms. The systemic changes associated with obesity are collectively called metabolic syndrome. Obesity associated with metabolic syndrome versus obesity without have shown different risks, with an increased risk of cardiovascular disease noticed in metabolic syndrome-free obesity (Lind et al., 2011). Increased WAT in obesity functions as an energy depot and an endocrine organ (Rosen and Spiegelman, 2006). Obesity which induces a wide range of comorbidities such as hypertension, type 2 diabetes, cardiomyopathies, renal disease, and chronic airway diseases, manifests with low-grade systemic inflammation driven by phenotypic changes in adipose tissue-related macrophages (ATMs) (Martinez-Santibañez and Lumeng, 2014). The ATMs in obesity show a pro-inflammatory M1 phenotype, compared to pro-resolving M2 macrophages in lean subjects. The low-grade chronic systemic inflammation in obesity is mechanistically linked to the pathogenesis of various co-morbidities (Stępień et al., 2014). Among the pulmonary diseases, asthma and chronic obstructive pulmonary disease (COPD) are the two most prominent co-morbidities coupled with obesity. However, pulmonary fibrosis, though not thoroughly explored, is associated with prominent markers of obesity such as leptin (Gui et al., 2018). Obesity increases patient mortality in idiopathic pulmonary fibrosis (IPF) (Gries et al., 2015) (Shah et al., 2014).

In studies elucidating a link between airway hyperreactivity in obesity, we showed that the airway smooth muscle (ASM) cells obtained from morbidly obese lung donors retained a hyper-reactive phenotype *in vitro* (Orfanos et al., 2018). With increased body fat mass in obesity, the

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Abbreviations

AHR	airway hyperresponsiveness
Akt	Protein kinase B
AMPK	AMP-dependent kinase
Ang II	angiotensin II
Ang III	angiotensin III
ASM	airway smooth muscle
ATM	adipose tissue-related macrophage
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BAT	brown adipose tissue
BMI	body mass index
BMP	bone morphogenic protein
CaMKII	Ca^{2+}/Calmodulin-dependent protein kinase II
CBP	cyclic AMP response element-binding protein
Cdc42	cell division cycle 42
C/EBP	CCAAT-enhancer binding protein
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
Co-Smads	common Smads
COX	cyclooxygenase
CRC	chromatin remodeling complex
CTGF	connective tissue growth factor
DPP4i	dipeptidyl peptidase 4 inhibitor
EC coupling	excitation-contraction coupling
ECM	extracellular matrix
ecNOS	endothelial cell nitric oxide synthase
EMT	epithelial-mesenchymal transition
ERK	extracellular receptor kinase
FGF-2	fibroblast growth factor-2
FMT	fibroblast-myofibroblast transformation
FOX	forkhead box protein
GPCR	G protein-coupled receptor
GSIS	glucose-stimulated insulin secretion
HASM	human airway smooth muscle
HDAC	histone deacetylase
HFD	high fat diet
IL	interleukin
iNOS	inhibitory nitric oxide synthase
IPF	idiopathic pulmonary fibrosis
I-Smads	inhibitory Smads
JNK	c-Jun N-terminal kinases
MAPK	mitogen-activated protein kinases
miRNA	microRNA
MLC20	myosin light chain 20
MLCK	myosin light chain kinase
MLCP	myosin light chain phosphatase
mTOR	mammalian target of rapamycin
mTORC	mammalian target of rapamycin complex
NF-κB	nuclear factor kappa B
NO	nitric oxide
NOX	NADPH oxidase
p110	catalytic subunits of PI3K
PAH	pulmonary arterial hypertension
PAI-1	plasminogen activator inhibitor-1
PAWP	pulmonary arterial wedge pressure
PGE	prostaglandin
PI3K	phosphoinositide 3-kinase
pMLC20	phosphorylated MLC20
PPM1A	protein phosphatase magnesium-dependent 1A
RAAS	renin-angiotensin-aldosterone system
Rac	Ras-related C3 botulinum toxin substrate
Redox	reduction-oxidation
RhoA	Rho-small GTPase RhoA
ROCK	Rho-associated coiled-coil kinase/Rho-activated kinase
ROS	reactive oxygen species
R-Smads	receptor-activated Smads
RTK	receptor tyrosine kinase
Smurf	Smad ubiquitination regulatory factor
TβR	TGF-β receptor
TF	transcription factor
TGF-β	transforming growth factor-β
Treg	T regulatory cell
UCP-1	uncoupling protein-1
VSM	vascular smooth muscle
WAT	white adipose tissue

profibrotic cytokine transforming growth factor beta β1 (TGF-β1) levels increase in the adipose tissue, suggesting a role for this cytokine in obesity-associated diseases (Alessi et al., 2000). In animal models of high fat diet (HFD)-induced obesity, increased TGF-β1 signaling in the bronchial epithelium induced lung dysfunction by increasing fibrosis and releasing inflammatory mediators (Park et al., 2019). Collectively, these observations support a hypothesis that TGF-β1 has an amplifying role in obesity-associated asthma and COPD. This review summarizes the role of TGF-β1 in various obesity-related disorders to propose a mechanistic model in obesity-associated inflammatory lung diseases, such as asthma and COPD.

1.1. TGF-β1 signaling

The TGF-β1 family comprises 33 structurally and functionally related growth factors. A multifunctional growth factor, TGF-β1 regulates cell differentiation, proliferation, matrix remodeling, and wound healing (Blobe et al., 2000) (Wrighton et al., 2009). Acting through a heteromeric receptor complex made of TGF-β type I and type II receptors, TGF-β1 signals downstream through Smad-dependent and Smad-independent pathways (Fig. 1). Receptor-activated Smads (R-Smads), key signaling entities, mediate TGF-β1's cellular effects. TGF-β1 receptors belong to a family of dual-specificity serine/threonine kinases; TGF-β1 receptor subtypes, type I and type II, provide selectivity and context-dependent signaling by TGF-β1 family members (Blobe et al., 2000) (Feng and Derynck, 2005). Phosphorylated type I receptor phosphorylates Smad proteins targets, with R-Smads (Smad 2/3) forming a complex with Smad4, translocating into the nucleus to regulate gene expression (Fig. 2). The protein phosphatase magnesium-dependent 1A (PPM1A) negatively modulates TGF-β1 signaling by dephosphorylating the SXS motif on the C-terminal of R-Smads (Annes et al., 2003), thereby downregulating activation of Smads. In addition to Smads, TGF-β1 also signals through other downstream signaling pathways, such as mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and Rac/Cdc42 (Fig. 1) (Lee et al., 2007) (Wang et al., 2008) (Wang et al., 2006) (Hamidi et al., 2017) (Wilkes et al., 2003).

Smads are the main transcriptional regulators mediating TGF-β1 signaling through nuclear translocation (Derynck and Zhang, 2003). Three types of Smads, namely, R-Smads, common Smads (co-Smads), and inhibitory Smads (I-Smads) are involved in TGF-β1 signaling. The TGF-β1 type I receptors phosphorylate the R-Smads at their C-terminus, forming a complex with Smad 2/3 and Smad4, the only known co-Smad in humans known to facilitate transcription of TGF-β responsive genes when fused with the C-terminal domain (Fig. 2) (Shi et al., 1997). This complex translocates into the nucleus and interacts with transcription factors at

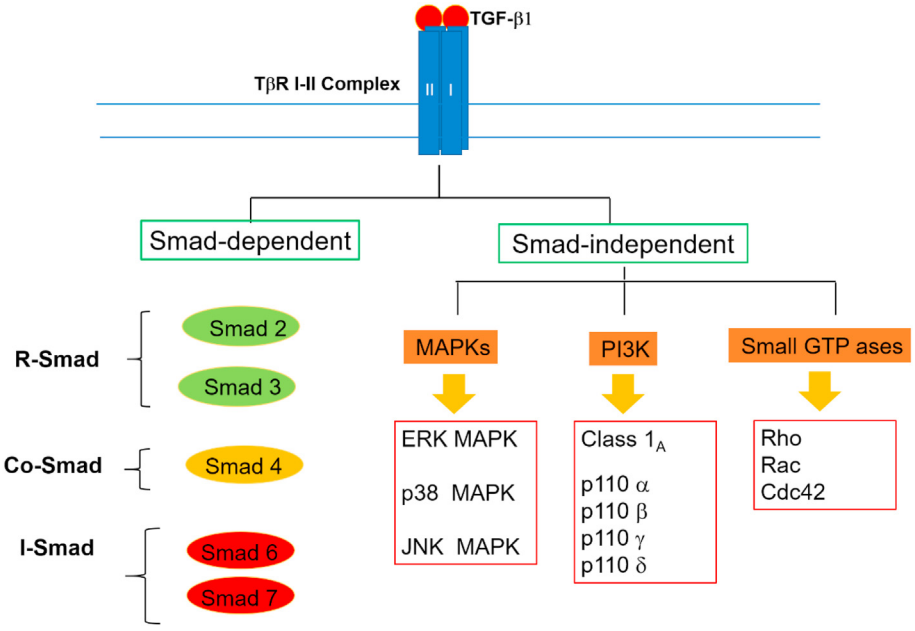

Fig. 1. Smad-dependent and independent TGF-β1 Signaling. Downstream signaling by TGF-β1 is mediated both through Smad-dependent and Smad-independent signaling cascades. Major parts of TGF-β1-induced genomic regulation are mediated through Smad-dependent signaling. Smad 2 and 3 are the major receptor-activated Smads (R-Smads) in humans. The common-Smad (co-Smad) Smad 4 is necessary for Smad2/3 complex formation and nuclear translocation. Inhibitory Smads (I-Smads) Smads 6 and 7, negatively modulate TGF-β1 activity by blocking Smad2/3 phosphorylation and activation. The predominant Smad-independent pathways involve mitogen-activated protein kinases (MAPKs), class 1_A phosphoinositide 3-kinases (PI3Ks) and small GTPases. Smad-independent pathways can modulate genomic functions of TGF-β1 via other transcription factors, i.e: nuclear factor-kappa B (NF-κB). (Cdc42 – cell division cycle 42; ERK – extracellular receptor kinase; JNK – c-Jun N-terminal kinases; MAPK – mitogen-activated protein kinase; p110 – catalytic subunits of PI3K; PI3K – phosphoinositide 3-kinase; Rac – Ras-related C3 botulinum toxin substrate).

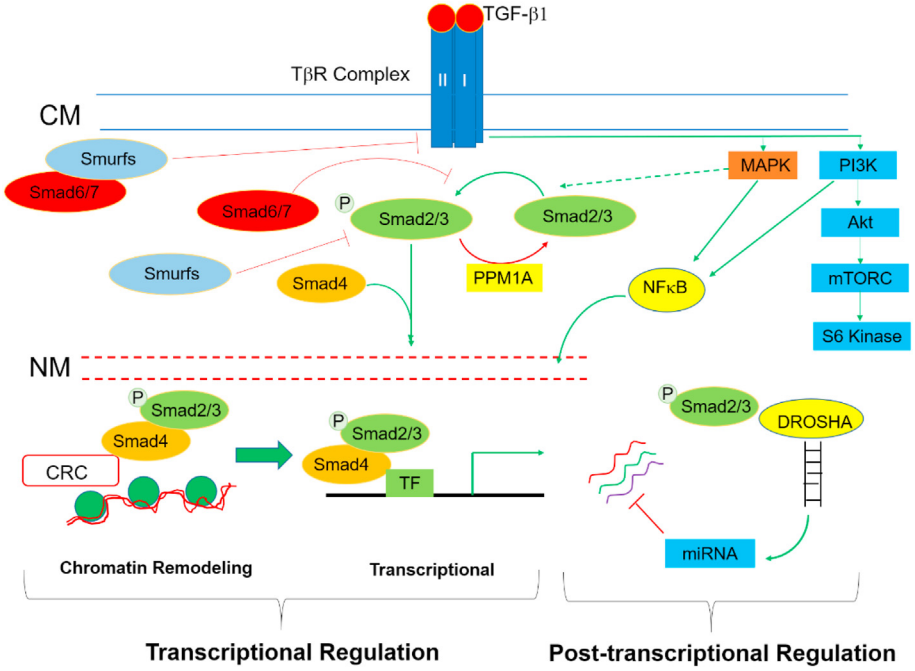

Fig. 2. Mechanisms of TGF-β1-Regulated Gene Expression. Predominantly, Smads mediate TGF-β1-regulated gene transcription via chromatin remodeling and transcriptional activation/repression/derepression. Post-transcriptional regulation is mediated through an array of miRNA originating from Smad 2/3 interaction with the microRNA (miRNA) processing complex DROSHA. Smad-independent signaling cascades also mediate gene expression through other transcription factors. At the TGF-β receptor level and downstream, I-Smads (Smads 6 and 7), negatively regulate signaling alone or in cooperation with Smad ubiquitination regulatory factors (Smurfs). (Akt – protein kinase B; CM – cell membrane; CRC – chromatin remodeling complex; MAPK – mitogen-activated protein kinase; miRNA – microRNA; mTORC – mammalian target of rapamycin complex; NF-κB – nuclear factor kappa B; NM – nuclear membrane; PI3K – phosphoinositide 3 kinase; PPM1A – protein phosphatase, Mg2+/Mn2+-dependent 1A; TβR – TGF-β receptor; TF – transcription factor; Smurf – Smad ubiquitination regulatory factors).

the response elements in gene promoters. Because of weak binding to DNA, this complex can also mediate transcriptional regulation near a Smad-binding sequence that is associated with a cognate sequence for other transcription factors (Morikawa et al., 2013). The Smad2/3/4 complex is therefore considered a coactivator, interacting with cyclic AMP response element-binding protein (CBP) and p300 to enhance gene expression through transcriptional activity. In a parallel mechanism, the Smad complex interacts with chromatin remodeling complexes in the nucleus to regulate active chromatin status, therefore promoting gene transcription (Ross et al., 2006) (Xi et al., 2011). Complementary to Smads' roles in transcriptional regulation, post-transcriptional regulation of gene expression by Smads is mediated by interaction of R-Smads with the microRNA (miRNA) processing Drosha complex (Davis-Dusenbery and Hata, 2011) (Davis et al., 2008) that drives the RNA decay associated with miRNAs (Fig. 2). Inhibitory Smads 6 and 7 inhibit both Smad2 and Smad3 phosphorylation to attenuate complexing with Smad4 for translocation and transcriptional activity in the nucleus (Jeon and Jen, 2010) (Roberts, 1999). The negative regulation is mediated by competing with R-Smads by stable association with the type I receptors, preventing phosphorylation of Smad2/3 (Imamura et al., 1997) (Nakao et al., 1997). The I-Smads can also induce receptor degradation through interacting with Smad ubiquitination regulatory factors (Smurfs) responsible for reducing signaling (Murakami et al., 2003) (Asano et al., 2004). Taken together, the Smad-dependent signaling drives genomic responses to TGF-β1 through multiple mechanisms.

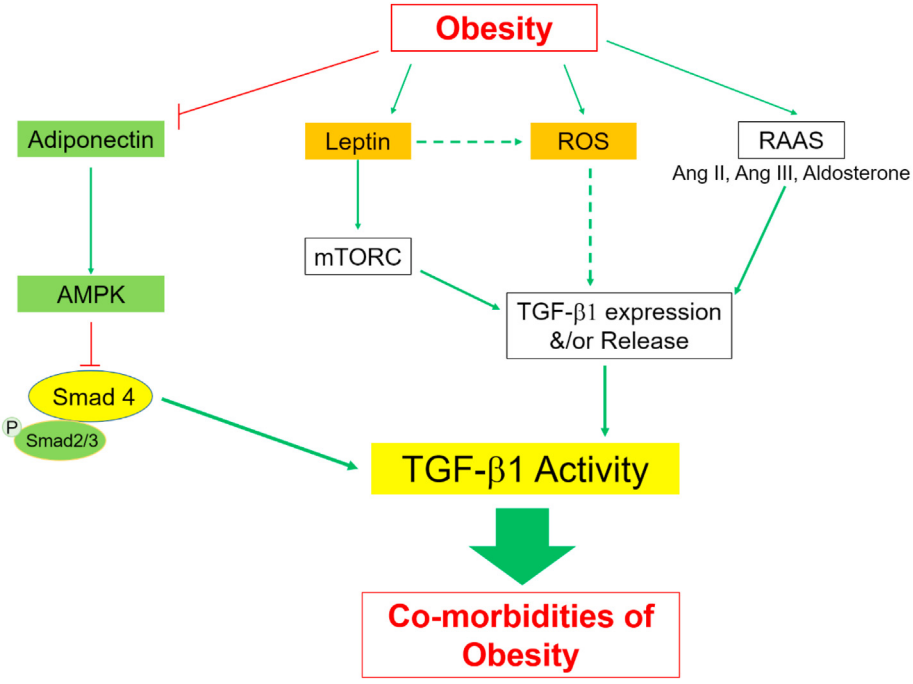

Fig. 3. Regulation of TGF-β1 Activity in Obesity. Three major pathways have been identified as upstream regulators of TGF-β1 activity in obesity. Serum adiponectin levels are reduced in obesity. Reduced activation of AMP kinase (AMPK) promotes TGF-β1 activity in various systems through increased Smad4 translocation into nucleus. Another adipokine leptin, is elevated in obesity and induces TGF-β1 expression and release, via mammalian target of rapamycin complex (mTORC). Similarly, Renin-angiotensin-aldosterone system (RAAS), increases TGF-β1 expression and release. These mechanisms, collectively, increase TGF-β1 activity in various systems to mediate the disease mechanisms related to the co-morbidities. (AMPK – AMP kinase; Ang II – angiotensin II; Ang III-angiotensin III; mTORC – mammalian target of rapamycin complex; RAAS – renin-angiotensin-aldosterone system; ROS – reactive oxygen species).

2. TGF-β1 in metabolic regulation

Substantial evidence supports a pivotal role for TGF-β1 in regulation of metabolism in a variety of tissues. TGF-β1/Smad3 signaling has regulatory roles in key aspects of metabolism, such as energy homeostasis, insulin resistance and phenotypic switching in brown adipose tissue (BAT) and WAT (Yadav and Rane, 2012) (Yadav et al., 2011) (Tan et al., 2012) (Lee, 2018). Evidence shows that obesity increases hepatic TGF-β1 activity along with other markers of inflammation (Yadav and Rane, 2012) (Samad et al., 1999) (Samad et al., 1997) (Alessi et al., 2000) (Fain et al., 2005) (Lin et al., 2009a) (Seong et al., 2018). Smad2 and 3 activities have been shown to promote adipogenesis, while Smad6 and Smad7 inhibit adipogenesis and inhibit TGF-β-mediated differentiation in adipose tissue (Choy et al., 2000). In animal models of high fat diet-induced obesity, TGF-β and plasminogen activator inhibitor-1 (PAI-1) mRNA levels were elevated in the adipose tissue (Sousa-Pinto et al., 2016). Findings from an *in vitro* study show that Smad3 physically interacts with CCAAT-enhancer binding proteins (C/EBPs) to inhibit its transcriptional function, thereby affecting adipocyte differentiation (Choy and Derynck, 2003). In animal models, silencing of Smad3 improved pancreatic β-cell function by elevating insulin secretion, lowering glucose intolerance, and through the uncoupling of mitochondrial ATP generation from the electron transfer chain (Lin et al., 2009b). Smad3-deficient mice were protected from obesity and diabetes, suggesting that Smad3-induced genomic regulation has a key role in metabolic disorders potentially by decreasing adipokines such as leptin and resistin (Yadav et al., 2011).

In the absence of Smad3, the WAT switched its gene expression profile similarly to that of energy-burning BAT. BAT-selective mRNAs in body fat mass in skeletal muscle increased in Smad3 knockout mice. These changes we were also associated with increased levels of Uncoupling protein-1 (UCP-1) in skeletal muscle (Yadav and Rane, 2012) (Seale et al., 2009). The UCP-1-mediated uncoupling of mitochondrial energy generation serves as the key target of Smad3 deletion in these studies. Collectively, such metabolic changes favor energy expenditure and homeostasis that abrogates development of obesity.

Suppression of Smad3 can increase mitochondrial function, with increased mitochondrial DNA copy number and mitochondrial cristae in WAT (Yadav and Rane, 2012). These cristae-filled mitochondria are well-known phenotypic features of mitochondria in BAT (Cousin et al., 1992). In a complementary mechanism reported in murine models of obesity, TGF-β also increased $CD206^{+}$ M2-like macrophages in WAT that are causally linked to decreased browning of WAT and insulin resistance (Nawaz et al., 2017). In another study, Smad3 silencing reversed the inflammatory phenotype associated with obesity by increasing M2 macrophages to harness inflammation in WAT (Yadav et al., 2011). Collectively, the overwhelming evidence shows that downregulating Smad3 has a beneficial effect in preventing obesity.

TGF-β, through its regulatory effect on ATMs, also induces myofibroblast differentiation. TGF-β1 elicits a pro-angiogenic and remodeling phenotype in human ATMs that, in turn, activate adipose tissue progenitor cells in a paracrine fashion to differentiate into myofibroblasts (Bourlier et al., 2012). Other studies showed TGF-β induced adipose tissue progenitor cells to increase expression of collagen IV, and PAI-1, connective tissue growth factor (CTGF), and interleukin (IL)-6, thereby promoting a pro-fibrotic and inflammatory phenotype (Reggio et al., 2016) (Gottschling-Zeller et al., 2000) (Birgel et al., 2000). These observations suggest that TGF-β contributes to a dysfunctional adipose tissue in obesity, with impaired adipogenesis and amplified fibrosis and inflammation. In summary, downregulated TGF-β1/Smad2/3 signaling appears to be beneficial to metabolic homeostasis and health.

3. TGF-β1 in hypertension

Numerous studies identified hypertension as one of the major co-morbidities coupled with obesity (Gillum et al., 1982) (Witteman et al., 1989) (MacMahon et al., 1987) (Stamler, 1991) (Manson et al., 1990) (Denke et al., 1993) (Denke et al., 1994) (Aronow, 2017). Increased prevalence of hypertension parallels that of obesity, as men and women with a body mass index (BMI) greater than 30 kg/m^2 show up to 5 times greater risk of hypertension than leaner individuals (Rabkin et al., 1997). Evidence also shows that weight loss drastically reduces the risk of hypertension (Huang et al., 1998) (Hall et al., 2002) (Hall et al., 2003) (Stabouli et al., 2005) (Kotsis et al., 2005) (Aronow et al., 2011) (Jiang et al., 2016). Several lines of investigations have identified vascular dysfunction as the mechanistic link between obesity and hypertension.

Hypertension shows significant association with dysfunctional TGF-β1 signaling in several important effector cells (Gordon and Blobe, 2008).

TGF-β1 is a key signaling entity in various components of vasculature, such as vascular smooth muscle (VSM) cells, endothelial cells, and blood monocytes (Blobe et al., 2000) (Gordon and Blobe, 2008). For example, in atherosclerosis, VSM cells, endothelial cells, macrophages, and T-lymphocytes express TGF-β1 ligands and receptors, stimulating lipoprotein-trapping proteoglycans to increase lesion formation and macrophage stimulation while reducing VSM cell proliferation (Bobik et al., 1999). Though this would suggest progression of atherosclerosis, the relationship between TGF-β1 and vascular diseases remains complex. By functionally modulating these key cells of the circulatory system, TGF-β1 modulates diseases such as atherosclerosis and hypertension. The predominant TGF-β1-driven mechanisms in these cardiovascular diseases are increased vascular inflammation and vascular remodeling (Abe et al., 2001) (Xiao et al., 2012) (Feinberg et al., 2004) (Buday et al., 2010) (Fleenor et al., 2010) (Blobe et al., 2000). Vascular remodeling is prominent in hypertensive patients and is positively linked to TGF-β1 protein and mRNA levels in the vasculature (Gao et al., 2014) (Xu et al., 2019a) (Zabini et al., 2018). Obesity may contribute to vascular remodeling through a variety of mechanisms, such as leptin-induced collagen I, fibronectin, TGF-β, and connective tissue growth factor (CTGF) elevation (Martínez-Martínez et al., 2014a) that evoke inflammation, hypertension, and collagen deposition.

Since select *tgfβ1* polymorphisms upregulate TGF-β1 expression and these polymorphisms are linked to elevated mean arterial pressure and increased susceptibility to hypertension (Li et al., 1999), TGF-β1 may play a pivotal role in the pathogenesis of hypertension. Conversion of proTGF-β1 to mature TGF-β1 by furin convertases is a key step regulating the bioactivity of TGF-β1. Studies showed that vascular protein Emilin 1 binds to proTGF-β1 and inhibits this processing, and the deficiency of Emilin 1 causes arterial hypertension (Zacchigna et al., 2006). Some *in vitro* studies suggest TGF-β1 may play a beneficial role in the vasculature by inducing endothelial cell nitric oxide synthase (ecNOS) and inhibiting inducible NOS (iNOS) in macrophages (Inoue et al., 1995) (Vodovotz et al., 1993). Nitric oxide (NO) is an essential vasodilator produced throughout the body. Because iNOS is the inducible isoform of NO synthase, inhibition would reduce blood pressure as NO levels will remain stable (Oliveira-Paula et al., 2014). iNOS is known to overstimulate NO production seen in inflammation, while ecNOS is responsible for maintaining NO levels in homeostatic range. However, a vast majority of studies of human subjects show elevated TGF-β1 signaling is positively correlated with risk of hypertension. Importantly, in obese hypertensive patients TGF-β1 levels positively correlated with the BMI (Torun et al., 2007) (Porreca et al., 2002). Serum levels of leptin, a key adipokine elevated in obesity, and TGF-β1 were shown to be elevated in hypertensive subjects with higher BMI (Porreca et al., 2002). *In vitro*, leptin also increased TGF-β1 mRNA expression and release in human monocyte cultures, suggesting TGF-β1 at least partially mediates leptin-associated changes in obesity (Fig. 3) (Porreca et al., 2002).

Cardiac smooth muscle is another prominent tissue modulated by TGF-β1 in its role in hypertension. Obesity-associated myocardial fibrosis and diastolic dysfunction precipitate hypertension and heart failure. Increased TGF-β1 levels and myocardial fibrosis are reported in animal models of obesity (Biernacka et al., 2015). Studies showed that obesity-induced myocardial fibrosis was attenuated by inhibition of TGF-β1/Smad2/3 signaling using a dipeptidyl peptidase 4 inhibitor (DPP4i) that has been used in diabetes treatment (Hong et al., 2017).

3.1. TGF-β1 and pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH), a pulmonary vascular disease, manifests as hypertrophy and hyperplasia of VSM and endothelial cells. Obesity elevates the mean pulmonary arterial wedge pressure (PAWP), the measurement of the pressure sustained by arterial branches, a clinical parameter defining PAH (Maor et al., 2015). Patients with PAH showed reduced Smad3 expression in lung tissue, accompanied with marked VSM hyperplasia and hypertrophy (Zabini et al., 2018). Smad3 silencing in human pulmonary arterial VSM also enhanced proliferation, suggesting Smad3 deficiency as a key mechanism of PAH. In PAH patients, exercise-induced pulmonary arterial wedge pressure (PAWP) was proportionately increased with higher BMI (Maor et al., 2015). Adiponectin, a prominent adipokine released from adipose tissue, has anti-inflammatory and antiproliferative functions in various cell types (Li et al., 2007) (Shibata et al., 2005) (Yamaguchi et al., 2005). Adiponectin levels are decreased in obese subjects, therefore considered a key mechanistic link between obesity and metabolic syndrome. Evidence suggests that decreased adiponectin is causally associated with pulmonary hypertension in obesity (Summer et al., 2011). Adiponectin modulates AMPK that is a cellular energy sensor responding to AMP and ADP levels (Fig. 3). AMPK is phosphorylated and activated by adiponectin, setting in motion a signaling cascade aimed at metabolic homeostasis. Studies show that AMPK activation attenuates TGF-β1/SMAD4 signaling in kidney mesangial cells and lowers diabetic kidney disease (Seong et al., 2018) (Dugan et al., 2013) (Zhao et al., 2015) (Declèves et al., 2014). Although similar mechanisms are not reported in PAH or pulmonary VSM, a rodent PAH model showed that activation of AMPK/bone morphogenic protein (BMP)/Smad signaling inhibited pulmonary ASM cell proliferation (Luo et al., 2018). Nitric oxide, a pivotal regulator of vasomotor tone, along with NOS is also modulated by TGF-β1 and evokes arterial stiffening seen in hypertension, potentially causing endothelial dysfunction in pulmonary vessels (Inoue et al., 1995) (Vodovotz et al., 1993) (Bender et al., 2007) (Higashi et al., 2001).

4. TGF-β1 in renal disease

Obesity-related kidney disease is associated with hypertension and increased blood pressure can evoke glomerular damage and progressive renal fibrosis. The renin-angiotensin-aldosterone system (RAAS), originating from kidneys, also serves as a regulator of blood pressure. Multiple studies demonstrated that angiotensin II induces TGF-β1 expression and release in various tissues by transcriptional activation and latent-TGF-β1 complex processing (Fig. 3) (Kim et al., 1995) (Rosenkranz, 2004) (Chalmers et al., 2006) (Wolf, 2006) (Naito et al., 2004). Angiotensin II promotes TGF-β1 signaling through the p38 MAPK and c-Jun N-terminal kinases (JNK) pathways in human glomerular mesangial cells by inducing thrombospondin-1 (Naito et al., 2004). In obese subjects with type II diabetes, angiotensin II in plasma is increased, with rises in leptin levels along with body weight. This is negatively correlated with lipoprotein lipase level, posing a relationship between obesity and endocrine dysfunction that regulates the kidneys (Saiki et al., 2009). PAI-1, an inhibitor of fibrinolysis, also acts as a downstream effector in TGF-β1-induced renal fibrosis (Samarakoon et al., 2012). PAI-1 is increased during morbid obesity in human fat mass potentially due to increased TGF-β1 expression (Alessi et al., 2000). Evidence suggests that in rat mesangial cells, aldosterone increases PAI-1 mRNA and protein expression, while also increasing TGF-β1 expression and reactive oxygen species (ROS) levels independently, potentially inducing glomerulosclerosis via aldosterone production (Yuan et al., 2007). Another product of the RAAS system, angiotensin III, also increases mRNA levels of TGF-β1, PAI-1 and fibronectin in rat mesangial cells, promoting glomerulosclerosis (Fig. 3) (Ruiz-Ortega et al., 1998).

In multiple systems, AMP-activated kinase (AMPK) can link metabolic status to various signaling cascades. Activation of AMPK, a cellular energy sensor, inhibits TGF-β1 activity, reducing fibronectin levels and other markers of renal fibrosis (Dugan et al., 2013) (Seong et al., 2018) (Zhao et al., 2015). This is mediated by reduced Smad4 nuclear translocation (Fig. 3). Elevated AMPK activation also leads to reduced lipid vacuolization in proximal tubules and lowers infiltration of macrophages (Declèves et al., 2014). In summary, the profibrotic TGF-β1 signaling in renal fibrosis is regulated upstream by the RAAS in a MAPK-dependent manner. Further, PAI-1 acts as a downstream effector for TGF-β1, while AMPK, the energy sensing kinase, serves as a negative regulator of TGF-β1/Smad2/3 signaling.

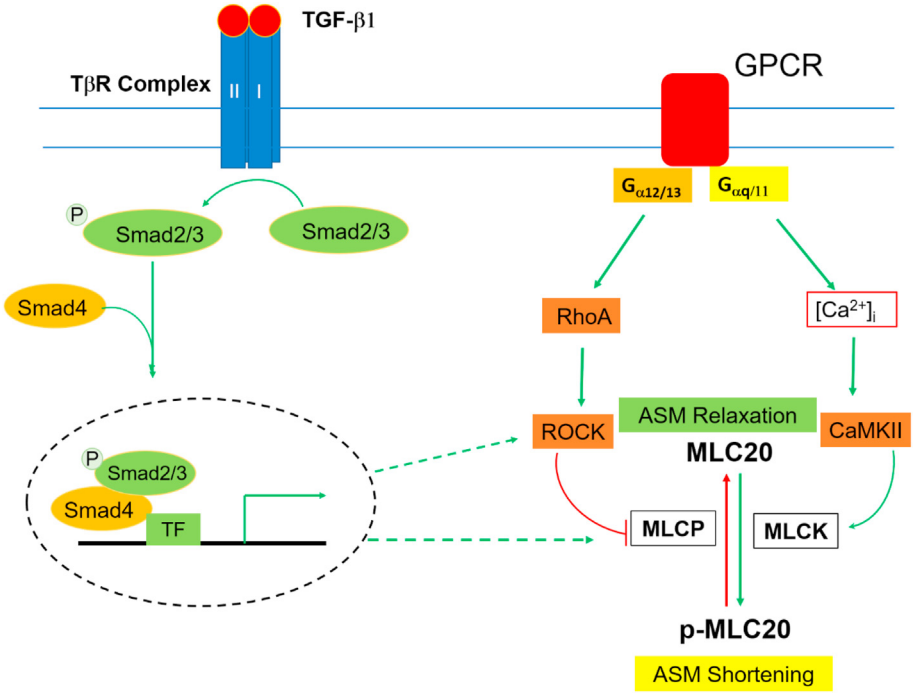

Fig. 4. TGF-β1 Amplifies Excitation-Contraction Coupling in Airway Smooth Muscle. Studies in our laboratory showed that in human airway smooth muscle (HASM) cells exposed to TGF-β1 amplified basal and agonist-induced HASM cell shortening in Smad3-dependent manner. In HASM cells, excitation-contraction coupling is characterized by agonist-induced phosphorylation of myosin light chain (MLC20). MLC phosphorylation is mediated by agonist-induced cytosolic Ca^{2+} and MLC kinase (MLCK) activity or Rho-activated kinase (ROCK)-mediated inhibition of MLC phosphatase (MLCP) activity. TGF-β1 amplified basal and agonist-induced ASM cell shortening in a ROCK-dependent manner. (CaMKII – Ca^{2+}/Calmodulin-dependent protein kinase II; GPCR – G Protein-coupled Receptor; MLC – myosin light chain; MLCK – MLC kinase; MLCP – MLC phosphatase; RhoA – Rho-small GTPase RhoA; TF – transcription factor; p-MLC20 – phosphorylated MLC20). (Modified from (136).

5. TGF-β1 and insulin resistance

Insulin resistance characterizes obesity and type 2 diabetes, with type 2 diabetes as a common co-morbidity associated with obesity (Al-Goblan et al., 2014). A proposed mechanism of obesity-induced diabetes involves chronic low-level inflammation, increased adipokines and activation of a nuclear factor kappa B (NF-κB)-mediated inflammatory phenotype in a variety of tissues (Wellen and Hotamisligil, 2005) (Fain et al., 2004).

Studies show that elevated TGF-β1 signaling increases the likelihood of developing insulin resistance. In humans and mouse models, TGF-β1 signaling promotes glucose-induced cell hypertrophy, reducing pancreatic islet β-cell function leading to insulin resistance (Wu and Derynck, 2009) (Yadav et al., 2011) (Rosmond et al., 2003) (Seong et al., 2018). Signs of altered TGF-β1/Smad signaling in diabetes mellitus is also reported in tissues outside the pancreatic islet β cells. For instance, genetic models of diabetic mice show increased TGF-β1 mRNA expression in glomerular and tubular compartments of the kidney promoting diabetic nephropathy (Hong et al., 2001). In support of these observations, Smad3 knockout mice manifest smaller adipocytes, reduced adipogenesis and protection against insulin resistance following high fat diet (HFD) (Tan et al., 2011). In humans, a genome-wide association study linked Smad3 with type 2 diabetes via multiple interconnecting pathways (Perry et al., 2009) (Tan et al., 2012). The direct role of Smad3 on development of type 2 diabetes was also shown in a Smad3 knockout mouse model, in which high-fat diet failed to induce obesity or insulin resistance (Tan et al., 2011).

Glucose-stimulated insulin secretion (GSIS) from pancreatic islet β cells modulates energy homeostasis. Interestingly, insulin gene expression is repressed by Smad3 while silencing of Smad3 derepresses the insulin promoter to restore GSIS in pancreatic β cells *in vitro* (Lin et al., 2009a) (Tan et al., 2011). In summary, multiple lines of evidence suggest that TGF-β1/Smad3 is central to mediating resistance and type 2 diabetes and requires Smad3-mediated regulation of gene expression in pancreatic β cells and skeletal muscle.

6. TGF-β1 and cardiomyopathies

Congestive heart failure (CHF) is characterized by cardiomyopathies, arrhythmias and reduced coronary circulation induce CHF, a common co-morbidity of obesity and metabolic syndrome (Rosenkranz, 2004) (Lavie et al., 2013) (Balaji et al., 2019). Cardiac muscle remodeling and fibrosis, common features of cardiomyopathy, are associated with hypertrophy that can eventually evoke heart failure. Elevated oxidative stress in obesity contributes in part to TGF-β1/Smad3 activation that mediates myocardial fibrosis (Richter et al., 2015). Elevated serum leptin in obesity, as previously described, also has a role in cardiac fibrosis in obesity (Porreca et al., 2002). Interestingly, HFD-induced obese rats manifest elevated leptin levels in cardiac tissue. Leptin has also been shown to increase along with fibrotic markers, like collagen I, fibronectin, CTGF, phosphorylated Akt, and superoxide radicals, together with increased TGF-β (Martínez-Martínez et al., 2014a, 2014b).

Similar to renal fibrosis, RAAS and TGF-β1 signaling together play pivotal roles in cardiac hypertrophy and cardiomyopathy. Angiotensin II-induced TGF-β1 in cardiac myocytes and fibroblasts, elicited myofibroblast formation and increased deposition of extracellular matrix (ECM) components such as collagen (Rosenkranz, 2004) (Schultz Jel et al., 2002) (Kawano et al., 2000). In a pressure overload hypertensive rat model, increased levels of TGF-β1 mRNA were associated with myofibroblast conversion; this pro-fibrotic event was abrogated by a TGF-β1 neutralizing antibody (Kuwahara et al., 2002). In addition to myocardial fibrosis, lipid accumulation in myocardial tissue (steatosis) occurs in obese subjects. Angiotensin II, by increasing TGF-β2, TGF-β receptor type I expression, and Smad2 phosphorylation, mediates myocardial steatosis and cardiomyopathy (Glenn et al., 2015). Further supporting the role of Smad3 in myocardial fibrosis, Smad3 haploinsufficiency in a leptin-resistant obesity model attenuated myocardial fibrosis, cardiac hypertrophy and oxidative/nitrosative stress (Biernacka et al., 2015).

Elevated myocardial TGF-β1 levels have been reported in left ventricular hypertrophy in obese patients, often seen with cases of prolonged hypertension (Parrinello et al., 2005) (Villarreal and Dillmann, 1992) (Boluyt et al., 1994). Obese hypertensive patients showed higher prevalence of left ventricular hypertrophy compared to lean patients, with the circulating TGF-β1 levels positively correlated with the BMI (Li et al., 2007).

7. TGF-β1 and asthma

Asthma, characterized by airway inflammation, remodeling and hyperresponsiveness is the predominant airway disease associated with obesity. Adult asthma prevalence is higher among obese individuals (Al-Alwan et al., 2014) (Beuther and Sutherland, 2007). Similarly, pediatric populations have the highest prevalence of asthma among obese children, with a higher risk in patients with a BMI greater than the 85th percentile (Rodríguez et al., 2002). The number of asthmatics in obese populations is greater at 11.1% compared to 7.1% in lean (in 2014) among individuals 20 and above. In support of the causative association of obesity and asthma, weight reduction reduced asthma severity and improved lung parameters in obese patients with asthma (Juel et al., 2012). Mechanisms underlying obesity-associated asthma include alterations in transient/inflammatory cells and structural cells of the lungs. For instance, studies in our laboratory showed that ASM cells obtained from obese lung donors showed amplified shortening in response to contractile agonists (Fig. 4) (Orfanos et al., 2018).

Multiple studies showed that the serum, tissue, and bronchoalveolar lavage (BAL) levels of TGF-β1 are increased in asthma (Bottoms et al., 2010) (Redington et al., 1997) (Vignola et al., 1997) (Koćwin et al., 2016) (Halwani et al., 2011) (Aschner and Downey, 2016). In moderate to severe asthma, TGF-β1 levels were increased due to a polymorphism in the C-509T variant on haplotype 1 on the TGF-β1 promoter (Pulleyn et al., 2001). Multiple genetic polymorphisms of TGF-β1 gene are reportedly associated with asthma pathogenesis in various study populations (Liu et al., 2018) (Yang et al., 2011) (de Faria et al., 2008) (Heinzmann et al., 2005) (Salam et al., 2007). In BAL from children, increased TGF-β1 levels induced reduction-oxidation (redox) dysfunction, with increased ROS formation in airway macrophages (Brown et al., 2012). Polymorphisms in a C-509T variant of the TGF-β1 promoter were associated with increased incidence of severe asthma in children predominantly in response to environmental pollutants (Salam et al., 2007). TGF-β2, often associated with epithelial cells, is increased in epithelial cells along with other pro-inflammatory cytokines in bronchial asthma, enhanced airway remodeling, and mucous secretion (Boxall et al., 2006) (Chu et al., 2004). TGF-β3 is primarily expressed in cells with mesenchymal origin and plays a role in development of lungs and associated anatomical structures (Dobaczewski et al., 2011). Similar to TGF-β2, TGF-β3 also increased mucin 5AC (MUC5AC) levels in bronchial epithelial cells and modulated autophagy (Zhang et al., 2018). In obese asthmatic pre-adolescent children, the promoter of TGF-β1 was shown to have increased DNA methylation in peripheral blood mononuclear cells, and while the clinical significance of this finding is unknown, this indicates potential negative regulation of TGF-β1 function in pediatric asthma (Rastogi et al., 2013). However, no other studies have examined the differences in the respiratory system in TGF-β1 activity between obese versus non-obese human individuals with asthma. Because of the mechanistic role TGF-β1 plays in various comorbidities of obesity, similar mechanisms can be explored to identify potential links that exist among obesity and inflammatory airway diseases. In summary, similar to other organ systems, TGF-β1 elicits pro-inflammatory and pro-fibrotic phenotypes in asthma (Al-Alawi et al., 2014).

7.1. TGF-β1 and airway inflammation

Airway inflammation is a salient feature of asthma. TGF-β1 expression as a Th2 cell mediator, along with other Th1 and Th2 inflammatory mediators, is elevated in bronchial asthma (Minshall et al., 1997) (Torrego et al., 2007) (Scherf et al., 2005). Levels of TGF-β are increased from both structural and inflammatory cells derived from the airways of asthma donors, and is induced by pro-inflammatory signaling pathways, including activation of NF-κB pathways (Torrego et al., 2007) (Lee et al., 2006) (Chu et al., 2000) (Ohno et al., 1996). The TGF-β pathway in the lungs can promote recruitment of immune cells such as eosinophils, neutrophils, macrophages, mast cells, and fibroblasts to induce initial inflammation and subsequent fibrosis (Minshall et al., 1997) (Lee et al., 2006) (Kelley et al., 1991) (de Boer et al., 1998). TGF-β1 also induces IL-8 production, expression of cyclooxygenase (COX)-2, and prostaglandin (PGE)-2 generation in human airway smooth muscle (HASM) cells, all indicators of airway inflammation (Fong et al., 2000). Along with increases in inflammatory cytokines and mediators, TGF-β1 is also a potent chemotactic cytokine, inducing migration of T-lymphocytes and monocytes during inflammation *in vitro* (Adams et al., 1991) (Wahl et al., 1987). Though TGF-β1 has been shown to induce inflammation, studies also show that even without significant airway inflammation, methacholine challenges can increase biomarker levels associated with airway remodeling in humans (Grainge et al., 2011). These data suggest that TGF-β1, independent of an airway inflammatory response, can evoke airway remodeling (Jeffery, 2001).

7.2. TGF-β1 and airway remodeling

Synthesis and deposition of ECM components are the key events in airway remodeling. TGF-β1 modulates synthetic and secretory functions of the airway structural cells, including epithelial cells, airway myocytes and fibroblasts. TGF-β1 induces collagen types I and IV mRNA and protein in murine lung fibroblasts to promote subepithelial fibrosis and deposition of ECM (Grande et al., 1997) (RR et al., 2020). TGF-β1 also promotes airway remodeling by potently inducing fibroblast-myofibroblast transformation (FMT), increasing ECM deposition, and prolonging myofibroblast lifespan (Wnuk et al., 2020) (Richter et al., 2001) (Zhang and Phan, 1999). Mammalian target of rapamycin (mTOR) activation by TGF-β1 reduces autophagy, leading to the pathogenesis of pulmonary fibrosis with excessive collagen deposition (Gui et al., 2018) (Gui et al., 2015). Because autophagy markers in hepatocytes have shown to be reduced in obesity and insulin resistant models, obesity can potentially lead to the onset of pulmonary fibrosis (Liu et al., 2009).

With increased airway remodeling, there is a reduction in lung function in asthma. As a profibrotic cytokine, TGF-β induces deposition of collagen into the reticular lamina of the lungs, thereby reducing lung function that is characterized by decreased forced expiratory volume (FEV_1), a measure of airway function (Minshall et al., 1997) (Tang et al., 2017). In parallel, TGF-β1 induced Forkhead Box P3+ (FOXP3) and Th17 T cell induction to modulate inflammatory responses (Bettelli et al., 2006) (Huang et al., 2017) (Andersson et al., 2008) (Shevach et al., 2008). TGF-β induces fibrosis, increasing ECM components in the lung, thereby reducing airway function.

ASM cells, in addition to playing a mechanical role, also have synthetic roles that contribute to immunomodulation and airway remodeling (Damera and Panettieri, 2011). An array of ECM components are secreted from ASM cells, with many of these induced by TGF-β. *In vitro*, TGF-β1 induced synthesis of collagen (I and IV), elastin, fibronectin, and biglycan from human ASM cells (Panettieri et al., 1998). ASM cell hyperplasia also contributes to airway remodeling and amplified airway reactivity in asthma. A variety of mitogenic signaling cascades, such as PI3K and MAPK, promote ASM cell proliferation with TGF-β1 modulating these mitogenic pathways. Fibroblast growth factor-2 (FGF-2), a mitogen of epithelial origin, acts through receptor tyrosine kinase (RTK) and elicits ASM cell proliferation *in vitro* (Schuliga et al., 2013). Findings from *in vitro* studies in human ASM cells suggest that TGF-β1-mediated proliferation is SMAD3-independent and PI3K-dependent. Furthermore, p38 MAPK acts as a negative regulator of TGF-β1-induced ASM cell proliferation (Xie et al., 2007). Evidence suggests that TGF-β1-induced rat ASM cell proliferation was attenuated by AMPK activation (Xie et al., 2007). TGF-β1-induced proliferation in this case was reportedly mediated through repression of miR-206 and subsequent induction of HDAC4 (Pan et al., 2018). AMPK is a key energy sensor and reported to be down-regulated in metabolic diseases such as diabetes mellitus (Dugan et al., 2013). These observations suggest that TGF-β1-induced ASM cell hyperplasia and airway remodeling are modulated by altered metabolic status in obesity.

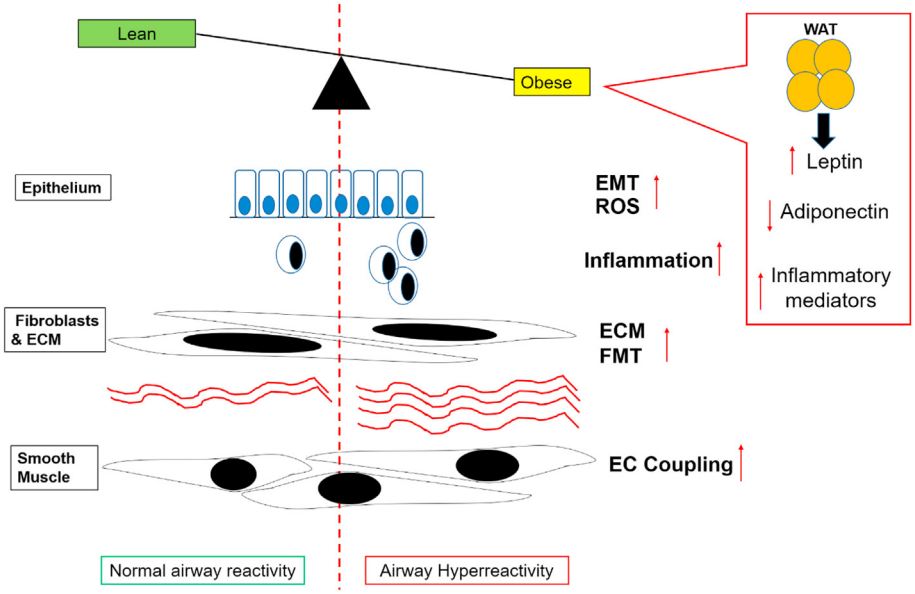

Fig. 5. Potential Mechanisms of TGF-β1 Role in Obesity-associated Airway Hyperreactivity. Obesity amplifies airway hyperreactivity in asthma, potentially through TGF-β1-mediated proinflammatory, profibrotic and mitogenic mechanisms summarized above. We posit that the 3 major airway structural components – epithelium, fibroblasts/ECM, and smooth muscle-are altered in obesity through TGF-β1-induced mechanisms. EMT, FMT, increased ECM deposition coupled with hyperplasia, increased inflammatory cell infiltration and elevated reactive oxygen species (ROS) are potentially the major pathophysiological mechanisms driving the AHR phenotype in obesity. The WAT in obesity potentially promote the pulmonary phenotype through endocrine regulation. (EC coupling – excitation-contraction coupling; ECM – extracellular matrix; EMT – epithelial-mesenchymal transition; FMT – fibroblast-myofibroblast transition; ROS – reactive oxygen species; WAT – white adipose tissue).

7.3. TGF-β1 and airway hyperresponsiveness

Airway hyperresponsiveness (AHR), inflammation and remodeling are the hallmarks of asthma. A comprehensive review by Ojiaku et al. examines the complex role of TGF-β1 in asthma pathogenesis (Ojiaku et al., 2017). Studies in our laboratory have also shown that TGF-β1 amplified excitation-contraction coupling (EC coupling) in human ASM cells and promoted AHR in Smad3-dependent manner (Fig. 4) (Ojiaku et al., 2018). It remains to be seen whether increased TGF-β1 signaling provides a mechanistic link between obesity and amplified airway hyperreactivity. However, the profibrotic and immunomodulatory functions of TGF-β1 in other systems linked to obesity suggest similar mechanisms may be at play in obesity-associated lung diseases.

Murine models are widely utilized in studying mechanisms of obesity-associated AHR (Park et al., 2019) (Jung et al., 2013) (Ge et al., 2013). Studies have yielded variable results on the role of TGF-β1 in obesity-associated AHR in mouse models. Obese mice sensitized and challenged with cockroach allergen showed increased levels of baseline TGF-β1 in their lung tissue and bronchoalveolar lavage fluid (BALF) (Ge et al., 2013). Inhibition of TGF-β1 in HFD obese mice attenuated AHR, which was accompanied by reduced airway inflammation, and lung tissue and perivascular fibrosis (Park et al., 2019). In a HFD-induced obesity mouse model, AHR, airway inflammation and goblet cell metaplasia were curtailed by anti-TGF-β1 antibody administration, while ovalbumin-induced AHR and inflammation were not diminished by anti-TGF-β1 antibody. An ovalbumin-induced AHR model in obese mice showed differentially higher AHR compared to the lean mice, with little effect on TGF-β1 mRNA levels (Jung et al., 2013). These findings support a notion that TGF-β1 has a mechanistic association with baseline AHR elicited by obesity, while allergen-induced AHR involves other mechanisms, potentially overriding the contribution of TGF-β1.

8. TGF-β1 and COPD

COPD, a chronic inflammatory lung disease, clinically manifests as breathlessness, cough, wheezing, and reduced expiratory volumes (Miravitlles and Ribera, 2017) (Devine, 2008) (Pauwels et al., 2001). Obesity increases the risk of COPD incidence (Lambert et al., 2017) (Franssen et al., 2008) (Cecere et al., 2011). Metabolic syndrome, characterized by hypertension, abdominal obesity and hyperglycemia, is highly prevalent among COPD patients (Cebron Lipovec et al., 2016). Though the exact mechanisms remain poorly defined, some metabolic pathways are implicated as potential candidates underlying the link between obesity and COPD. For instance, leptin is a prominent biomarker in obesity, where increased levels of leptin promote pro-inflammatory signaling characterized by activation of p38 MAPK, JNK, and NF-κB (Hsu et al., 2015). A study showed that leptin induced *cPLA2* gene expression by activating MAPK/NF-κB/p300 cascade. Given the non-canonical TGF-β1 activation of MAPKs and the ability of p38 MAPK to phosphorylate Smad3, this mechanism has the potential to amplify TGF-β1 signaling in obesity (Lee et al., 2007) (Furukawa et al., 2003). Additionally, redox imbalance in obese individuals, characterized by elevated ROS production, may also amplify airway inflammation in COPD, as is seen in obesity-associated diabetes and hypertension (Lee et al., 2003) (Hirosumi et al., 2002) (Hirosumi et al., 2002) (Zhang et al., 2003) (Xu et al., 2003).

COPD is often caused by smoking. Interestingly, TGF-β1 signaling is implicated in small airway fibrosis seen in COPD lungs. The epithelial-mesenchymal transition (EMT) in airways, a salient feature in smokers and COPD patients, is driven by TGF-β1/Smad2/3 signaling (Xu et al., 2009) (Sohal et al., 2010). Increased ROS level in COPD lungs is also thought to be inducing TGF-β1 expression to promote fibrosis (Barnes, 2019). However, investigations on TGF-β1 expression and activity (measured by Smad2/3 phosphorylation) in COPD airways reported variable findings, with some reporting increased signaling (Mahmood et al., 2017) (Di Stefano et al., 2018). In smoke-induced emphysema in a HFD rat model, adiponectin levels were decreased, potentially amplifying inflammation (Wang et al., 2016). In elderly smokers, an increase in dietary energy intake exacerbated COPD symptoms suggesting a link between positive energy balance and COPD pathology (Obase et al., 2011). Similarly, weight loss measures such as adopting balanced diet appeared to reduce clinical manifestations of COPD in smokers (Cochrane and Afolabi, 2004) (Scoditti et al., 2019) (van de Bool et al., 2014).

In COPD, TGF-β contributes to airway remodeling through a variety of mechanisms, including induction of Treg cells and associated *foxp3* mRNA expression (Zheng et al., 2018) (Yang et al., 2017) (Xu et al., 2019b) (Chu et al., 2016). However, obesity reduces circulating and lung resident FOXP3+ Treg cells, amplifying airway inflammation (Ramos-Ramírez et al., 2020). The net effect of these signaling events potentially induces remodeling and inflammation, contributing to amplified COPD pathology in obese patients. In addition to amplified inflammation, ROS levels also are elevated in HASM cells of COPD patients due to upregulated NADPH oxidase (NOX)-4 activity (Hollins et al., 2016). Pulmonary

vasculature, as seen in PAH, also undergoes remodeling, compromising pulmonary function in COPD (Calabrese et al., 2006) (Kranenburg et al., 2006) (Barberà et al., 1994) (Magee et al., 1988). Since vascular remodeling is also a common feature in various comorbidities of obesity, one can expect to see an amplified vascular pathology and PAH in obese COPD patients (Bender et al., 2007) (Higashi et al., 2001) (Kim et al., 2008). Through these shared pathological features, obesity contributes to clinically amplified COPD.

9. Conclusions

Obesity and associated co-morbidities have reached epidemic proportions globally. Understanding the mechanisms of the major obesity-related disorders is important to design preventative and therapeutic measures. The proinflammatory and pro-fibrotic cytokine TGF-β1 appears to play important roles in numerous aspects of the metabolic syndrome. Generally, an amplified TGF-β1 signaling is characteristic in these diseases, suggesting downregulating TGF-β1 activity will restore metabolic homeostasis. The major mechanisms underlying TGF-β1's involvement in many obesity-related disorders are remodeling, fibrosis and ECM deposition. The primary molecular mechanism involved in the role of TGF-β1 role in these diseases is transcriptional regulation of target genes by Smad2/3/4, with some involvement of miRNA and redox balance regulation. The key regulators of metabolism, such as adipokines and AMPK, recruit TGF-β1 signaling cascades in a variety of cell types to manifest obesity-related pathology. The mechanisms of obesity-associated inflammatory lung diseases, asthma and COPD, are only partially understood. In light of evidence that TGF-β1 act as a key modulator of metabolic diseases in other systems, future novel therapeutics could target TGF-β1 signaling pathways to improve clinical outcomes in chronic diseases especially asthma and COPD (Fig. 5).

CRediT authorship contribution statement

Joanna Woo: Conceptualization, Writing - original draft, Writing - review & editing. **Cynthia Koziol-White:** Conceptualization, Writing - review & editing. **Reynold Panettieri:** Conceptualization, Writing - review & editing, Funding acquisition. **Joseph Jude:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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