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Towards an understanding of the mechanoreciprocity process in adipocytes and its perturbation with aging

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Abstract

Adipose tissue (AT) is a complex organ, with multiple functions that are essential for maintaining metabolic health. A feature of AT is its capability to expand in response to physiological challenges, such as pregnancy and aging, and during chronic states of positive energy balance occurring throughout life. AT grows through adipogenesis and/or an increase in the size of existing adipocytes. One process that is required for healthy AT growth is the remodeling of the extracellular matrix (ECM), which is a necessary step to restore mechanical homeostasis and maintain tissue integrity and functionality. While the relationship between mechanobiology and adipogenesis is now well recognized, less is known about the role of adipocyte mechanosignaling pathways in AT growth. In this review article, we first summarize evidence linking ECM remodelling to AT expansion and how its perturbation is associated to a metabolically unhealthy phenotype. Subsequently, we highlight findings suggesting that molecules involved in the dynamic, bidirectional process (mechanoreciprocity) enabling adipocytes to sense changes in the mechanical properties of the ECM are interconnected to pathways regulating lipid metabolism. Finally, we discuss processes through which aging may influence the ability of adipocytes to appropriately respond to alterations in ECM composition.

Keywords

Adipocyte dysfunction; extracellular matrix stiffness; mechanical forces; mechanotransduction; adipose progenitor cells

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1. Introduction

Adipose tissue (AT) is a metabolically active endocrine and immune organ that is involved in the regulation of whole-body energy homeostasis and metabolism (Choe et al., 2016; Kershaw and Flier, 2004), enables adaptive thermoregulation (Gregory, 1989), and serves as a physical barrier to infection (Alexander et al., 2015; Zwick et al., 2018). Studies in both humans and animal models also suggest that AT is at the center of mechanisms and pathways involved in health span and longevity, with most anti-aging interventions, such as caloric restriction, impacting AT (Huffman and Barzilai, 2010; Palmer and Kirkland, 2016). Because of its multifunctional nature, a remarkable feature of AT is its ability to undergo dynamic remodeling in response to physiological challenges (e.g. embryonic development, puberty, pregnancy, and aging) and changes in nutrient deprivation and excess that occur throughout life (Choe et al., 2016). The remodeling of AT is the result of a highly complex and well-orchestrated set of events that entail quantitative and qualitative alterations in AT-resident cells, including adipocytes, adipose stem cells, and macrophages, along with balanced angiogenic and proinflammatory responses and an appropriate renovation of the extracellular matrix (ECM) (Sun et al., 2011). In individuals with excessive adiposity perturbations in processes related to AT remodeling can promote a “metabolically unhealthy phenotype” characterized by impaired AT expandability, increased adipocyte size, altered lipid metabolism, and local inflammation (Goossens, 2017). This phenotype promotes the development of systemic insulin resistance that is one of the most critical risk factors for chronic cardiometabolic diseases (Smith et al., 2019; Vishvanath and Gupta, 2019). A deep understanding of the biological processes and molecular mechanisms that are involved in AT remodeling is thus instrumental for the development of efficient interventions aimed to prevent the onset of metabolic complications associated with impaired AT expansion.

Mechanical forces have long been implicated in multiple biological processes at the molecular, cellular, and tissue level (Gooch, 2012). In physiological conditions, growth and remodeling occur in native tissues to maintain a preferred level of the mechanical state, called “mechanical homeostasis”, which requires, in part, assessment of ECM mechanics by the cells (reviewed by (Ambrosi et al., 2019; Humphrey et al., 2014). Aging, however, perturbs the ability of the cell to reestablish the homeostasis of the mechanical microenvironment in several physiological systems, including the musculoskeletal, cardiovascular, neuronal, and respiratory systems, thereby increasing the risk for many common chronic diseases (Epro et al., 2017; Levy Nogueira et al., 2016; Lieber et al., 2004; Sicard et al., 2018). The progressive changes in the cell’s biophysical properties occurring with aging have such a profound impact on the cellular function that they can predict the cellular biological age with more accuracy than classical biomarkers of aging, such as DNA repair, cellular metabolism, and cellular secretions (Phillip et al., 2017). In recent years, it has become increasingly evident that mechanical signals, such as those resulting from cell-matrix adhesions, play a crucial role also in AT biology (Alkhouli et al., 2013; Ruiz-Ojeda et al., 2019; Yuan et al., 2015). The mechanical behavior and properties of the AT as well as the effect of mechanical stress on adipose cells’ behaviors have been previously summarized (Oomens and Peters, 2014; Pope et al., 2016; Shoham and Gefen, 2012; Yuan et al., 2015). In this review, we will focus on key mechanosensory transduction

pathways in mature adipocytes and how they might be impacted by changes occurring with aging.

2. AT composition and anatomical distribution

AT is composed of lipid-laden mature adipocytes (~50% of cells) that are surrounded by connective tissue matrix, blood capillaries, nerve tissue, and stromal-vascular fraction (SVF) cells, including adipose progenitor cells (APCs), pericytes, lymphocytes, endothelial cells, and fibroblasts (Hausman and Dodson, 2013; Kershaw and Flier, 2004). Mature adipocytes are classified as white, brown, or beige/brite according to unique morphology, metabolic functions, biochemical features, and gene expression patterns (Park et al., 2014). White adipocytes compose the main parenchymal cells of white adipose tissue (WAT), which represents more than 95% of AT mass in adult humans. The primary role of white cells is to store neutral lipids (e.g. triglycerides and steryl esters) packed into a single large organelle called lipid droplet (LD) that occupies most of the cytoplasm (Konige et al., 2014). However, they also secrete pro- and anti-inflammatory adipokines, such as leptin, resistin, adiponectin, and omentin, which have crucial roles in satiety regulation and whole-body insulin sensitivity (Fasshauer and Bluher, 2015; Rabe et al., 2008). Anatomically, WAT is divided into subcutaneous WAT (sWAT) that is situated between muscle and skin, visceral WAT (vWAT) that is associated with internal visceral organs, and dermal WAT (dWAT) that underlies the reticular dermis (Driskell et al., 2014; Zwick et al., 2018). The distribution of sWAT and vWAT varies substantially among individuals and depends on several factors, such as nutrition, genetics, and sex (Kuk et al., 2009; Lee et al., 2013).

Unlike white fat cells, brown adipocytes are characterized by multilocular LDs, are richly vascularized, have abundant mitochondria (Park et al., 2014), and function prominently in thermoregulation by generating heat through the oxidation of available substrates (Harms and Seale, 2013). Moreover, brown adipocytes have a discrete localization, residing mainly in cervical-supraclavicular, perirenal/adrenal, and paravertebral regions around the major vessels in humans (Ravussin and Galgani, 2011), and share a common early gene expression profile with skeletal muscle cells (Timmons et al., 2007). Beige adipocytes, which are also called brite (brown-in-white), are phenotypically similar to brown adipocytes, but derive from WAT resident precursors or through reprogramming of mature white adipocytes in response to various activators, such as cold exposure or adrenergic stimulation (Harms and Seale, 2013; Shao et al., 2019).

The heat-generating feature of brown and beige adipocytes appears to have beneficial effects on both the reduction of body weight and insulin sensitivity (Harms and Seale, 2013; Peng et al., 2015). Moreover, more recent work demonstrated that perivascular AT (PVAT) displays characteristics of beige AT in humans (Efremova et al., 2020). PVAT is the fat located in close contact with the adventitial layer of most blood vessel walls, where it plays a crucial role in the regulation of vascular tone and remodeling by secreting several paracrine and endocrine mediators, such as adipokines and growth factors (Hu et al., 2020). There is growing evidence in animal studies that, during the development of obesity and with advancing age, beige-like adipocytes in PVAT can transition into white-like adipocytes that secrete factors causing constriction of blood vessels thereby leading to an increase

in blood pressure (Chang et al., 2020). Thus, the activation or maintenance of brown and beige adipocytes through pharmacological and lifestyle interventions can be an efficient therapeutic approach for the prevention of Type-2 diabetes (T2D) and hypertension (Chang et al., 2020; Harms and Seale, 2013; Mulya and Kirwan, 2016).

3. The role of ECM in AT growth

3.1. Dynamics of AT growth

In humans, AT first appears during the second trimester of pregnancy (Poissonnet et al., 1984) and progressively develops through multiple cell lineages that are heterogeneously and dynamically distributed (Sanchez-Gurmaches and Guertin, 2014). After birth, the most abundant fat is brown AT (BAT), which protects the newborn from the cold extrauterine environment (Lidell, 2018), but its prevalence and functionality decline with increasing age (Florez-Duquet and McDonald, 1998; Zoico et al., 2019). On the other hand, most of WAT growth occurs during childhood and adolescence through the generation of new adipocytes (adipocyte hyperplasia through adipogenesis) or an increase in the size of existing adipocytes (adipocyte hypertrophy) (Hager et al., 1977; Hirsch and Knittle, 1970; Knittle et al., 1979; Vishvanath and Gupta, 2019). Adipose lineage-committed preadipocytes and SVF-resident adipose-derived stem cells constitute the pool of regenerative cells from which new adipocytes are produced (Raajendiran et al., 2019). Although the number of total adipocytes per depot appears to be mostly stable throughout adulthood in weight stable individuals (Spalding et al., 2008; Strawford et al., 2004), recent lineage-tracing models in rodents have demonstrated that adult WAT expansion may result from both hypertrophy and hyperplasia during chronic states of positive energy balance (e.g. when energy intake exceeds energy expenditure) (exhaustively reviewed in (Ghaben and Scherer, 2019). Additionally, substantial evidence indicates that healthy WAT expansion, as seen in “metabolically healthy obese” people, correlates with increased adipogenic capacity and smaller adipocyte size (Smith et al., 2019; Vishvanath and Gupta, 2019). The mechanism of AT growth, however, varies according to sex and specific depots (Lee et al., 2013), with the expansion of vWAT in males occurring through adipocyte hyperplasia in both mice (Jeffery et al., 2015) and humans (Tchkonia et al., 2013a; Tchoukalova et al., 2010).

3.2. ECM remodeling regulates AT growth

A crucial step in AT expansion, as well as in its contraction after weight loss, is the controlled remodeling of the ECM that surrounds adipocytes (Liu et al., 2016; Ruiz-Ojeda et al., 2019; van Baak and Mariman, 2019). As comprehensively reviewed by (Ruiz-Ojeda et al., 2019), the ECM of the AT is composed of two main classes of macromolecules: soluble proteoglycans and fibrous structural proteins, including collagens, fibronectins, laminins, and elastins. Collagens comprise the most abundant proteins in ECM, with 20 subunits of 12 different types identified in rodent adipocyte ECM using proteomics techniques (Mariman and Wang, 2010). Of these, type VI collagen (COL6) is specific to AT (Khan et al., 2009), is more expressed in vWAT than sWAT (Mori et al., 2014), and is involved in AT inflammation (Gesta et al., 2016). However, the composition and supramolecular organization of the ECM differ not only in specific AT depots but also in developmental periods and the pathophysiological events taking place in the setting of a long-term positive

caloric imbalance (Liu et al., 2017; Mariman and Wang, 2010). For instance, it is well established that extensive ECM alterations occur during WAT growth through hyperplasia (Mariman and Wang, 2010). The formation of new adipocytes or adipogenesis is a tightly regulated process characterized by two essential phases (Ghaben and Scherer, 2019). The first phase consists of the proliferation and commitment of AT stem cells residing within the SVF in preadipocytes. This is followed by the differentiation phase during which preadipocytes accumulate a large amount of fat and become functional, insulin-responsive mature adipocytes (Ghaben and Scherer, 2019). As the fibroblast-like preadipocytes differentiate and assume the rounded form of the LD-rich adipocyte, cell shape is drastically altered (Mariman and Wang, 2010). To facilitate the change in adipocyte morphology, the ECM needs to transition from a fibronectin-rich stromal matrix to a laminin-rich basement membrane (Smas and Sul, 1995). This shift, which is regulated by insulin, energy metabolism, and mechanical forces (Mariman and Wang, 2010), is characterized by the replacement of the predominantly fibronectin-bound α5 integrin in preadipocytes to the laminin-bound α6 integrin in mature adipocytes (Liu et al., 2005). Furthermore, it requires the production and secretion of ECM components by local cells (e.g. adipocytes, fibroblast, adipocyte progenitors, and myofibroblast) and their degradation by enzymes belonging to either the fibrinolytic system or the matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]) (Datta et al., 2018; Ruiz-Ojeda et al., 2019). In this regard, it has been reported that, whereas the activity of MMP-2 and MMP-9 increases during adipocyte differentiation (Bouloumie et al., 2001), downregulation of TIMP-3 is necessary for the successful implementation of the adipocyte differentiation program (Bernot et al., 2010). It is also important to mention the critical role played by the membrane-anchored collagenase MMP-14 in ECM remodeling during adipogenesis. Unlike other MMPs, MMP-14 regulates not only the adipogenic collagenolytic turnover, but also the gene expression profile required for adipocyte differentiation by releasing the epigenetic constrains imposed by fibrillar type I collagen (Sato-Kusubata et al., 2011). Of note, more recent studies revealed that MMP-14 also digests COL6α3, one of the subunits of COL6, to generate endotrophin, a carboxy-terminally cleaved peptide of COL6α3 that enhances WAT fibrosis and inflammation during obesity development (Li et al., 2020). This work showed that, due to its multiple functions, overexpression of MMP-14 promotes healthy WAT expansion at early stages of obesity when collegenolysis is a necessary step to facilitate the change in adipocyte morphology. On the other hand, maintaining the expression levels of MMP-14 high at the late stages of obesity leads to massive WAT fibrosis and inflammation through the production of endotrophin (Li et al., 2020). Together, these findings highlight the complexity of the processes governing AT expansion and the importance of proper ECM remodeling.

3.3. Depot-specific perturbation of ECM remodeling during WAT expansion promotes a “metabolically unhealthy phenotype”

Given its pivotal role in AT biology, if ECM remodeling is perturbed because, for instance, an imbalance between degradation and replacement of structural components, WAT growth and plasticity can be compromised. This is supported by clinical observations of obese subjects, in whom adipocyte hypertrophy has been found associated with excess deposition of collagen fibers surrounding adipocytes, or pericellular fibrosis, in WAT (Dankel et al.,

2014; Divoux et al., 2010). Moreover, studies in humans have revealed that increases in WAT collagen gene transcripts and their content, mainly COL6, are associated with obesity-induced inflammation and insulin resistance (Michaud et al., 2016; Pasarica et al., 2009). On the other hand, COL6-deficient mice fed a high-fat diet (HFD) display reduced fibrosis in WAT and are metabolically healthier than control mice (Khan et al., 2009). Because of these findings, it has been proposed that the fibrous (or rigid) ECM may prevent the expansion of mature adipocytes by exerting mechanical forces onto the adipocyte plasma membrane that counteract the pressure exerted by enlarged LDs within the cell. This would limit the capacity for cell size storage and ultimately lead to adipocyte death and inflammation (reviewed in (Datta et al., 2018). This idea, however, has been challenged by work from Divoux and colleagues (Divoux et al., 2010) that found a negative correlation of vWAT fibrosis with circulating triglycerides in morbidly obese subjects, suggesting that vWAT fibrosis may instead play a beneficial role in metabolic complications of obesity by limiting adipocyte hypertrophy and promoting adipocyte hyperplasia (Divoux et al., 2010). Interestingly, this relationship was not observed in sWAT, arguing for differential consequences of the presence of fibrosis depending on fat depot (Divoux et al., 2010). Along the same lines, it has been reported that increased tensile strength exerted by excess collagen accumulation in vWAT promotes metabolically healthy obesity in women (Lackey et al., 2014). Furthermore, a study from Muir and collaborators (Muir et al., 2016) demonstrated that obese people without T2D had increased vWAT fibrosis, higher preadipocyte frequency (e.g. enhanced adipogenic capacity), and smaller mature adipocytes than obese diabetic patients. The contrasting findings highlighted here strongly suggest that the underlying processes linking WAT fibrosis and obesity-associated metabolic complications are considerably more complex than predicted. Nonetheless, the evidence collected so far provides solid ground to consider WAT fibrosis as a potential target for manipulation of regional adiposity and systemic metabolism.

3.4. ECM, mechanotransduction, and adipocyte fate and function

3.4.1. Cellular mechanotransduction – an overview—Proper cell behaviors, such as proliferation, differentiation, and survival, are influenced by the properties and composition of the ECM (Vogel and Sheetz, 2006). This is because cells can sense the mechanical properties of the ECM through mechanosensitive receptors or structures (mechanosensors) that, in turn, activate various mechanotransduction pathways (reviewed by (Gasparski and Beningo, 2015; Jansen et al., 2015; Lim et al., 2018; Paluch et al., 2015). Once activated, the mechanochemical pathways convey a signal from the cell membrane to the nucleus through the actomyosin-based cytoskeletal components, or stress fibers, which are directly connected to the nuclear lamina and can pass on stress and strain and thereby deform the nucleus (Buxboim et al., 2014; Swift et al., 2013). This ‘outside-in’ mechanotransduction signal leads to the reorganization of chromatin structures and changes in the expression of genes that ultimately promote the remodeling of the ECM (Mohammed et al., 2019). Reciprocally, cells can alter the composition and mechanical properties of the matrix by altering architectural aspects of the cytoskeleton, modulating cellular elasticity, or generating a concomitant actomyosin-mediated contractile response to applied forces (‘inside-out’ mechanotransduction) (Martino et al., 2018; Mohammed et al., 2019). Thus, a “dynamic reciprocity” exists between the cell and the ECM and it is through this relationship

that the cellular information can markedly impact the tissue microenvironment and the other way around (Xu et al., 2009). This close relationship enables cells to sense exogenous, physiological forces imparted upon them and restore mechanical homeostasis to maintain tissue integrity and functionality (Humphrey et al., 2014).

Several mechanosensors, such as integrins, G-protein coupled receptors, the glycocalyx, ion channels, and lipid rafts, have been identified so far (reviewed by (Gasparski and Beningo, 2015). Among them, there are the proteins of the focal adhesions (FAs), which are integrin-based transmembrane structures mediating the attachments of cells to the ECM (Kuo, 2014). FAs are very dynamic assemblies that consist of approx. 150 different structural and signaling proteins, including the mechanosensors talin, vinculin, and focal adhesion kinase (FAK), and serve as pivotal sites for both outside-in and inside-out mechanotransduction signals (Kuo, 2014). FA proteins are involved in activating and gathering integrins and linking integrins to F-actin filaments in response to force-induced conformational changes that expose cryptic peptide sequences that are otherwise hidden in the folded proteins (Lim et al., 2018). It is through FA proteins that cells can also exert F-actin cytoskeleton-mediated traction forces to sense their physical surrounding, such as matrix “stiffness” (e.g. the mechanical resistivity of the ECM), and respond to it (Paszek et al., 2005). Forces generated within the cytoskeleton produce active tension that is then applied to cell-ECM adhesions. As such, a tight relationship exists among FA assembly and growth, traction force transmission, and mechanosensing of ECM stiffness, such that perturbing one affects the other two (Wu et al., 2017).

It is well-recognized that alterations of matrix stiffness within or across a tissue have a profound effect on multiple aspects of cell behavior, including the lineage commitment of mesenchymal stem cells (MSCs) that are present in many adult tissues (Hadden and Choi, 2016). In this regard, remarkable are the experiments performed by Dupont and co-workers (Dupont et al., 2011) who demonstrated that changes in ECM stiffness regulate MSC differentiation commitment into either the adipogenic or osteogenic lineage through the transcriptional factors Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). They also reported that mechanosensing of ECM stiffness via YAP/TAZ is independent of the Hippo kinase cascade and that nuclear localization and activity of YAP/TAZ requires the activation of the Ras homologous (Rho)/Rho-associated kinase (ROCK) signaling pathway and tension of the actomyosin cytoskeleton (Dupont et al., 2011). Later work also showed that YAP regulates cell mechanics in response to ECM cues by controlling FA assembly (Nardone et al., 2017) and that the FA protein vinculin is necessary for the nuclear localization of TAZ and its inhibition of the adipocyte differentiation on rigid ECM (Kuroda et al., 2017).

Other crucial downstream intracellular mediators of mechanotransduction are members of the small guanosine triphosphatase (GTPases) of the Rho-family (Rho-family GTPases), which include Rac1, Cdc42, and Rho family member A (RhoA). The latter is a key signaling component regulating the assembly of ECM receptors, FA proteins, and the actomyosin cytoskeleton in response to mechanical forces (Chrzanowska-Wodnicka and Burridge, 1996). Like other members of the Rho-family GTPases, RhoA acts as a molecular switch, cycling between an active GTP-bound state and an inactive GDP-bound state. In

the active state, RhoA activates the kinase ROCK, which promotes actomyosin contractility by activating myosin via phosphorylation of the regulatory myosin light chain (MLC), and the formin protein mammalian Diaphanous, which stimulates actin polymerization (Chrzanowska-Wodnicka and Burridge, 1996). Apart from RhoA, Rac1 is also activated by ECM stiffness via a FAK- Cas-Rac1-lamellopidian signaling module that converts the external information encoded by ECM stiffness into stable intracellular stiffness and mechanosensitive cell cycling (Bae et al., 2014). Thus, changing the activities of Rho GTPases and/or their downstream effectors can severely alter cellular responses to substrate stiffness.

In recent years, it has become clear that members of the syndecan (SDCs) family, SDC1 and SDC4, are also involved in mechanosensing and mechanotransduction (Baeyens et al., 2014; Bellin et al., 2009; Chronopoulos et al., 2020; Huang et al., 2015; Jiang et al., 2020; Julien et al., 2007; Le et al., 2018) as well as obesity (De Luca et al., 2019; Kasza et al., 2014; Reizes et al., 2008). SDCs are type-I transmembrane glycoproteins belonging to the family of heparan sulfate proteoglycans that also include cell-surface glycosylphosphatidylinositol-anchored proteins (glypicans) and secreted proteoglycans found in basement membranes (agrin, collagen XVIII, and perlecan) (Sarrazin et al., 2011). Four SDC proteins, SDC1 to 4, are present in vertebrates, with SDC4 being distributed ubiquitously and the others having a tissue-specific expression pattern (Chakravarti and Adams, 2006). SDC4 is also the only mammalian syndecan that promotes focal adhesion assembly around pre-existing integrin clusters on fibronectin (Echtermeyer et al., 1999; Woods and Couchman, 2001). All SDCs are characterized by an extracellular domain (ectodomain) with attachment sites for glycosaminoglycan (GAG) chains (e.g. heparan sulfate and chondroitin sulfate) that mediate interactions with a wide array of ECM components, including fibronectin, laminins, and fibrillar collagens (Sarrazin et al., 2011). The ectodomain of all SDCs is constitutively released from the cell surface by proteolytic cleavage in a process known as ectodomain shedding that is mediated by matrix metalloproteinases (Manon-Jensen et al., 2013). Once released from the cell surface, the ectodomains may act as paracrine or autocrine effectors, or compete with cell surface receptors for the same ligand (Manon-Jensen et al., 2010). SDCs also contain a highly conserved transmembrane domain and a short cytoplasmic tail (Sarrazin et al., 2011). It is through their cytoplasmic domain, which includes binding sites for cytoskeletal proteins and protein kinases, that members of the SDC family can control cell behavior in synergy with the integrin-mediated signaling and/or independently of integrins (Morgan et al., 2007; Xian et al., 2010). Chaikof and collaborators were the first to report that mechanical stress promotes upregulation and shedding of SDC4 from vascular smooth muscle cells through differential activation of mitogen-activated protein kinase (MAPK) cascades (Julien et al., 2007; Li and Chaikof, 2002). A role for SDC4 as an initiator of cellular mechanotransduction without the direct extracellular binding of integrins was later revealed by Bellin and coworkers using NIH 3T3 fibroblasts (Bellin et al., 2009). Their study demonstrated not only that SDC4 can recruit FA proteins to sites of syndecan-specific cellular attachments, but also that mechanically induced SDC4 activation increases the phosphorylation of extracellular signal-regulated kinase (ERK) through the actin cytoskeleton (Bellin et al., 2009). More recently, an underlying mechanism for the role of SDC4 in cell mechanics, which, however, requires synergistic integrin activation,

has been reported by (Chronopoulos et al., 2020) who integrated biophysical, cell biology, and computational techniques for their study. Based on their findings, it appears that SDC4 responds to mechanical tension by inducing Rho-dependent adaptive cell stiffening *via* engagement of a phosphoinositide 3-kinase (PI3K)/kindlin-2/β1integrin axis as well as modulating YAP activation (Chronopoulos et al., 2020). Overall, these data imply a major function for SDC4 in mechanotranduction at the cell-matrix interface.

3.4.2. Mechanotransduction signals in adipocytes—Adipocytes may experience various physical forces *in vivo*, including shear stress and tensile and compressive forces (Lee and Kuo, 2013). These forces can lead to intracellular metabolic changes and the activation of mechanotransduction pathways that promote the formation of new adipocytes and the secretion of immune cell recruitment factors (Lee and Kuo, 2013). As previously reviewed and discussed by (Shoham and Gefen, 2012), studies in cell culture, animal models, and humans consistently suggest that, while static stretching enhances adipogenesis, dynamic (cyclic stretching and vibration) mechanical stimuli inhibit adipogenesis and reduces body fat. Despite this progress, the mechanotransduction pathways activated by the mechanical stimuli have not been fully characterized yet. As mentioned above (*see* ECM remodeling regulates AT growth sections), a change in cell shape marks the conversation of the fibroblast-like preadipocytes into the rounded form of the LD-rich adipocyte during the process of adipogenesis. Elegant work performed by Shoham and collaborators (Shoham et al., 2014), who used atomic force microscopy, interferometric phase microscopy, and finite element simulations to verify the experimental findings, demonstrated that the change in cell shape occurring during differentiation is accompanied by an increase in adipocyte stiffness that is triggered by the production and accumulation of lipids in LD. This, in turn, promotes changes in intracellular strain/stress distribution and in cytoskeletal rearrangements that, ultimately, lead to alterations in ECM composition (Shoham et al., 2014). In this regard, several studies have shown that activation of RhoA/ROCK signaling and the resulting less organized cytoskeleton and low tension is necessary for the induction of adipogenic differentiation in 3T3- L1 preadipocytes (reviewed by (Lee and Kuo, 2013). However, the role of RhoA/ROCK in AT is not only limited to adipogenesis but extends also to mature adipocytes. Long-lasting (72 hours) stretching of 3T3-L1 mature adipocytes grown on a collagen-coated silicon substratum up to 120% of initial diameter has been reported to promote Rho-kinase activation and stress fibers (Hara et al., 2011). Notably, the degree of mechanical stretching applied on the 3T3-L1 mature adipocytes corresponded to an ~ 20% increase in diameter of adipocytes (hypertrophic adipocytes) isolated from mice that were fed a HFD compared to mice fed a low-fat diet (LFD) (Hara et al., 2011). This increase in diameter of the adipocytes provided sufficient mechanical stress to elicit activation of the RhoA/ROCK signaling pathway, which, in turn, induced the expression of cytokines and chemokines, including monocyte chemoattractant protein-1 and tumor necrosis factor-α (TNFα) (Hara et al., 2011). On the other hand, inhibition of the RhoA/ROCK signaling pathway through pharmacological and genetic approaches led to mice with decreased adipocyte hypertrophy, reduced macrophage recruitment to AT, and lower gene expression of several adipocytokines despite being fed an HFD (Hara et al., 2011). Thus, lipid accumulation in adipocytes activates the Rho-Rho kinase signaling, partly, through the mechanical stretch. The critical role of ROCK signaling pathway in adipocyte function has

been further corroborated by studies using HFP-fed adipocyte specific *Rock1* mice, which revealed that ROCK1 regulates insulin signaling in the adipocyte (Lee et al., 2014).

Other candidates likely involved in mediating mechanotransduction signals in adipocytes are YAP and TAZ. As discussed in the previous section, nuclear localization of the transcriptional co-activators YAP and TAZ inhibits ECM stiffness-dependent differentiation of MSC into adipocytes (Dupont et al., 2011; Kuroda et al., 2017). On the other hand, adipogenesis is promoted when YAP and TAZ are re-localized to the cytoplasm on soft substrates (Dupont et al., 2011). However, recent research has also revealed that YAP/TAZ are activated by the proinflammatory adipokines TNFα and IL-1β in both human and mouse mature white adipocytes to promote adipocyte survival during WAT expansion (Wang et al., 2020). As argued by Wang and collaborators (Wang et al., 2020), activation of the YAP/TAZ signaling pathway in the adipocyte is likely induced to regulate the balance between adipocyte death and the formation of new adipocytes during obesity. In this regard, it is important to mention that computational modeling studies have revealed that large tensile strains generated by the production of LDs in mature adipocytes can be projected onto neighboring immature cells through the deformation of their plasma membrane (Ben-Or Frank et al., 2015). This finding is notable because it implies that adipocyte hypertrophy may influence the biomechanical microenvironment of neighboring cells in early-stage differentiation and thereby their fate (Ben-Or Frank et al., 2015).

The discovery that YAP/TAZ activation is induced by pro-inflammatory cytokines is also in line with previous evidence that an appropriate pro-inflammatory response at the level of the adipocyte, particularly activation of TNFα, is required for healthy WAT expansion and remodeling (Wernstedt Asterholm et al., 2014). The subtle balance between lipogenesis and lipolysis in adipocytes is critical for maintaining systemic energy homeostasis and insulin sensitivity and, therefore, it is highly regulated by numerous extracellular and intracellular stimuli (reviewed by (Luo and Liu, 2016). Elevation of TNFα levels, induced by β-adrenoreceptors (β-AR) stimulation (Orban et al., 1999), is a key step involved in the control of adipocyte lipid metabolism and lipolysis (Cawthorn and Sethi, 2008). TNFα can impair glucose uptake into adipocytes and inhibit the uptake of free fatty acids (Cawthorn and Sethi, 2008). Moreover, studies in human adipocytes revealed that TNFα promotes lipolysis through activation of ERK and elevation of the intracellular cyclic AMP (cAMP)-protein kinase A (PKA) pathway, which, in turn, leads to phosphorylation of perilipin-1 (PLIN1) (a protective coat protein until phosphorylated) and hormone-sensitive lipase (HSL), with consequent translocation of phosphorylated HSL from the cytosol to the LD (Zhang et al., 2002). TNFα can also destabilize the interaction between the insulin receptor and caveolin-1 (Cav-1) in mature adipocytes (Kabayama et al., 2007). Cav-1 is a component of caveolae, which are mechanosensitive membrane invaginations linking mechanotransduction pathways to actin-controlled changes in tension (Echarri and Del Pozo, 2015), and is found in high abundance in AT where it plays a role in insulin signaling through direct binding to the insulin receptor (Nystrom et al., 1999) and the modulation of lipolysis and LD formation (Cohen et al., 2004). Together, these observations strongly suggest that mechanical signals and molecular pathways regulating the balance between lipogenesis and lipolysis in adipocytes are highly interconnected. This idea is corroborated by evidence from studies performed by Pellegrinelli and collaborators (Pellegrinelli et al., 2014) who

used decellularized material of AT (dMAT) that were embedded in a peptide hydrogel to assess the impact of increased fibrosis on adipocytes. They reported that, when cultured with dMAT from obese individuals or subjected to compressive forces, adipocytes displayed reduced lipolysis and increased production of pro-inflammatory cytokines and fibrotic mediators. This phenotypic profile was induced by the activation of mechanosensitive molecules, such as integrins (Pellegrinelli et al., 2014). Along these lines, it has been further shown that β1 and β3 integrins interact with the insulin receptor in subcutaneous white adipocytes, and blunting their activity in the mature adipocyte through genetic inactivation of the Kindlin-2 protein, a regulator of integrin activation, results in lipodystrophy due to reduced insulin signaling (Gao et al., 2019; Ruiz-Ojeda et al., 2021).

A role in promoting adipocyte survival and maintaining insulin sensitivity during healthy AT expansion is also played by the mechanosensor molecule FAK. Studies in mice have revealed that knockout (KO) of *Ptk2* (encoding FAK1) specifically in adipocytes leads to animals with increased adipocyte cell death and inflammation as well as insulin resistance as a result of caloric excess (Luk et al., 2017). The mechanism behind these findings, which were replicated in the offspring of adipocyte-specific *Ptk2* KO mice crossed over genetically induced obese mice, involves increased activation of the p53 pro-apoptotic activity and decreased phosphorylation of ERK (Luk et al., 2017). It is well-established that death of adipocytes, resulting from apoptosis or necrosis, promotes macrophage infiltration and the formation of crown-like structures (CLS), which are composed of macrophages surrounding dead or dying adipocytes (Cinti et al., 2005) and are associated with AT inflammation and insulin resistance in obesity (Strissel et al., 2007). In this regard, we recently reported that deletion of the *Sdc4* gene in mice promoted sex-specific metabolic derangements associated with diet-induced obesity (De Luca et al., 2019). Specifically, HFD-fed *Sdc4* KO female mice, but not males, displayed increased levels of plasma total cholesterol, triglyceride, and glucose, as well as reduced whole-body insulin sensitivity. Additionally, they had increased adipocyte size, macrophage infiltration, and CLS in the vWAT (De Luca et al., 2019). The deletion of *Sdc4* was not specific to the adipocytes and it is, therefore, not possible to conclude that the effects on adipocyte size and macrophage infiltration are due to an adipocyte-mediated molecular mechanism. However, the results in mice echo our previous findings in *Drosophila melanogaster* showing that flies with decreased expression of the *Syndecan* gene in the fat body (the fly equivalent of mammalian adipose tissue and liver) had increased fat levels and reduced phosphorylation levels of prosurvival mediators, Akt and ERK (Eveland et al., 2016). Furthermore, cell culture studies have demonstrated that the SDC4 protein is expressed in mature white adipocytes and its synthesis and ectodomain shedding is regulated by insulin (Reizes et al., 2006). These studies also indicate that shed adipocyte syndecans associate with the lipoprotein lipase and stabilize its activity (Reizes et al., 2006). Together with the solid evidence that SDC4 acts as a cellular mechanosensory and mechanotransmitter (Chronopoulos et al., 2020), these observations suggest that SDC4 is involved in mechanotransduction and lipid metabolism in adipocytes. The reason behind the sex-specific effects of the *Sdc4* deletion in mice is still unknown, but it is important to point out that WAT displays a large number of significant differences in gene expression between the sexes in both mice (Yang et al., 2006) and humans (Gershoni and Pietrokovski, 2017). Among the sexually dimorphic genes identified in the mouse WAT, there are those encoding

actinins, cadherins, and calcium channel subunits (Yang et al., 2006), which are molecules involved in cell–matrix and cell–cell adhesions and, therefore, likely to functionally interact with SDC4 (Gopal et al., 2017). Moreover, elevated levels of *SDC4* gene transcription are often observed in estrogen receptor-positive breast cancer cells, suggesting that sex hormones may play a role in its regulation (Lendorf et al., 2011).

As depicted in Figure 1, the studies reviewed in this section suggest a critical role of adipocyte mechanotransduction signaling pathways in healthy WAT growth in normal physiological conditions. However, when the "mechanoreciprocity" that maintain tensional homeostasis is lost due to factors that perturb ECM remodeling and induce abnormal ECM deposition and stiffness, like obesity, genetics, and aging (*see* Aging, mechanotransduction, and adipocyte sections and Figure 2), then adipocyte cell death is promoted (Takao et al., 2019). This induces monocyte infiltration to manage tissue remodeling. If the inflammatory response is sustained, the chronic inflammation leads to massive fibrosis through excess collagen production mainly by the fibro-inflammatory stromal cells, with consequent unhealthy WAT expansion that, in turn, is associated with systemic insulin resistance (Smith et al., 2019).

4. Aging, mechanotransduction, and adipocyte

Aging is characterized by significant changes in the regional distribution of WAT that consist of a relative loss of sWAT, particularly from the limbs, and an accumulation of fat in abdominal sWAT and vWAT (Kuk et al., 2009). These fat distribution shifts are accompanied by an inadequate capacity to store lipids by hypertropic adipocytes and a subsequent conspicuous deposition of lipids in nonadipose tissues, which causes systemic lipotoxicity, a process that contributes to adverse metabolic and cardiovascular outcomes (reviewed by (De Carvalho et al., 2019; Palmer and Kirkland, 2016). The age-related loss of sWAT appears to occur through a decline in the function of APCs and their potential to differentiate into adipocytes as well as *via* a considerable accumulation of senescent cells (Palmer and Kirkland, 2016). Senescent cells are metabolically active cells that, however, are resistant to mitogenic stimulation (Shelton et al., 1999). While the growth arrest is achieved via either $p16^{INK4A}$ or the $p53/p21^{CIP1}$ pathway as key executers of cell-cycle arrest, the senescent phenotype is triggered by increased production of reactive oxidative species (ROS) followed by a chronically active DNA damage response (DDR), which promotes an irreversible cell cycle arrest by activating the $p53/p21^{CIP1}$ pathway (Tchkonia et al., 2013b). Senescent cells are also characterized by widespread changes in chromatin organization and gene expression that ultimately lead to the secretion of numerous pro-inflammatory cytokines, chemokines, and growth factors (a phenotype termed the "senescence-associated secretory phenotype" or SASP) (Tchkonia et al., 2013b). The number of senescent cells increases exponentially with age (Tchkonia et al., 2010) and signals from the ECM can induce cellular senescence (Choi et al., 2011). In addition, senescent cells participate in tissue remodeling through the release, accumulation, and modification of ECM components, including the production and secretion of multiple MMP proteins and fibronectin, and the recruitment of macrophages (Coppe et al., 2010; De Luca, 2019; Elder and Emmerson, 2020; Mavrogonatou et al., 2019). Although little is still known regarding the role of adipose tissue senescence in ECM quality/composition/stiffness, the enhanced senescence-induced secretion of MMPs and fibronectin

could produce ECM reorganization and changes in behavior of surrounding cells. For instance, adipogenesis in obesity requires an interplay between differentiating adipocytes, stromal cells, and blood vessels (Nishimura et al., 2007). The ECM plays an essential role in the crosstalk between APCs and endothelial cells in AT, with ECM components released by microvascular endothelial cells promoting preadipocyte differentiation (Varzaneh et al., 1994). This is particularly significant considering that the maintenance of the mechanical and mechanotransduction integrity of tissues rely on the interdependence between the cell-ECM traction force and the tension that it exerts at the cell-cell interface (Maruthamuthu et al., 2011). Thus, changes in ECM mechanical properties can directly impact the force levels at cell-cell adhesions and therefore modulate the strength of adhesion and influence intercellular dynamics (Tang, 2018).

As the APCs present in adipose SVF, mature adipocytes undergo senescence (Smith et al., 2021). Evidence suggests that adipocyte senescence results from a DNA damage response to elevated oxidative stress (Chen et al., 2015). Additionally, it has been reported that senescent endothelial cells in adipose SVF can induce senescence features in mature adipocytes through SASP (Barinda et al., 2020). Yet, the senescent characteristics of adipocytes and molecular mechanisms responsible for triggering the senescence program remain poorly understood. Recent data collected from an *in vitro* model of adipocyte aging revealed that, compared to young mature adipocytes, older adipocytes were characterized by not only an increase in senescence but also a higher expression level of profibrotic genes (Zoico et al., 2020). Notably, the ECM alterations were also accompanied by a significant decrease in expression of the *CAV1* gene (Zoico et al., 2020), suggesting that reduced levels of Cav-1 could contribute to adipocyte dysfunction with age.

As mentioned above, Cav-1 is a small integral membrane protein that is essential for caveolae formation in adipocytes (Pilch et al., 2011). Earlier studies in mice revealed that genetic deficiency of *Cav1* leads to an imbalance between degradation and replacement of collagen in WAT as a result of an increase in net collagen synthesis (Martin et al., 2012). Interestingly, this perturbation in ECM remodeling correlated with reduced lipolysis in adipocytes due to a decrease in the levels of the LD protein PLIN1 and increased susceptibility to cell death (Martin et al., 2012). Catecholamine-stimulated lipolysis is significantly reduced (50%) in healthy, nonobese elderly subjects compared to young subjects because of a declined function of the HSL complex (Lonnqvist et al., 1990). Given that translocation of HSL to the LD requires phosphorylation of PLIN1 (Sztalryd et al., 2003), which, in turn, is controlled by Cav-1 (Cohen et al., 2004), it is possible that the age-associated impairment in catecholamine-stimulated lipolysis is, in part, caused by reduced Cav-1 levels. Of note, studies in mice revealed that AT macrophages are also involved in the age-related reduction in adipocyte lipolysis by decreasing the bioavailability of norepinephrine and thereby its available concentration in adipocytes (Camell et al., 2017). Thus, this could further exacerbate the situation (Figure 2).

Evidence from both *in vitro* and *in vivo* studies has demonstrated that Cav-1 regulates mechanotransduction response to ECM stiffness through actin-dependent control of YAP (Moreno-Vicente et al., 2018). Loss of Cav-1 can also prevent caveolae formation in adipocytes (Razani et al., 2002) and the flattening and rapid disassembly of caveolae is

a process that enables cells to respond to surges in membrane tension occurring during mechanical stress (Sinha et al., 2011). Furthermore, it has been reported that Cav-1 deficiency promotes senescence in human fibroblasts *via* mitochondrial dysfunction and inactivation of SIRT1, which, in turn, leads to the activation of the p53/p21 pathway (Yu et al., 2017). Adipocytes respond to HFD by adopting a fibroblast-like phenotype characterized by enhanced expression of ECM, FA, and cytoskeletal-related genes, and reduced expression of genes involved in mitochondrial function (Jones et al., 2020). Thus, as illustrated in Figure 2, we propose that an age-related reduction of Cav-1 levels may not only lead to caveolae flattening but also to mitochondrial dysfunction-associated senescence, as seen in fibroblasts. At the same time, the age-related decline in APCs capacity to differentiate into adipocytes in sWAT promotes an increase in adipocyte hypertrophy (Palmer and Kirkland, 2016), with consequent cell stiffness augmentation. However, because of perturbation of ECM remodeling resulting from reduced Cav-1 levels and the adipocyte secretion of SASP factors, adipocytes lose their ability to restore mechanical homeostasis. The disrupted mechanoreciprocity response in the adipocyte eventually leads to cell death and macrophage infiltration. The situation is further exacerbated by the contribution of SASPs to chronic inflammation and profibrotic changes of fibroblast and other SVF cells that promote unhealthy expansion of sWAT (Smith et al., 2021) (Figure 2).

In addition to changes in WAT, a loss of brown and beige adipocytes also happens with advancing age (Zoico et. al, 2019). Activation of β-adrenergic receptors in response, for instance, to cold stress stimulates BAT thermogenesis in humans (Blondin et al., 2020; Gavrila et al., 2017). Moreover, it has been reported that actomyosin stiffness induced by β-adrenergic stimulation is required for the induction of thermogenic capacity in brown adipocytes through YAP/TAZ activation and translocation into the nucleus (Tharp et al., 2018). Thus, age-related changes resulting in altered mechanosensitive signals may also be partly responsible for the impairment of brown adipocyte regenerative capacity occurring with age.

5. Concluding Remarks

In conclusion, there is a large body of literature showing that the composition and mechanical properties of the ECM have an essential role in AT remodeling and healthy expansion. Most research so far has focused on the influence of matrix stiffness on adipogenesis, and we refer the interested readers to other excellent reviews on this topic (Mor-Yossef Moldovan et al., 2019; Pope et al., 2016; Yuan et al., 2015). In this review article, we sought to draw attention to the molecules and mechanisms of mechanotransduction involved in mature adipocyte function and fate. Although the experimental data is still very limited, current evidence suggests that the cellular pathways involved in the adaptative mechanoreciprocity process and lipid metabolism of adipocytes are highly interconnected and that their coordinated regulation is critical to preserve adipocyte function and survival under physiological conditions. Because of this, loss of mechanoreciprocity may result in adipocyte dysfunction and impaired AT expansion, which is intimately linked to the development of systemic insulin resistance, T2D, and cardiovascular disease (Smith et al., 2019; Vishvanath and Gupta, 2019). Most of our basic understanding of the effects of disruption of the mechanoreciprocity process in adipocytes

at the organismal level comes from *in vivo* studies using adipocyte-specific transgenic and KO mice models of genes related to mechanotransduction pathways (*see* Table 1). Molecular genetic studies have also reported significant associations of polymorphisms in ECM-related genes with human obesity and diabetes traits (Chun et al., 2010; Saravani et al., 2017), highlighting its clinical relevance. As such, future success in the prevention and treatment of these chronic diseases is, in part, dependent on a deeper understanding of the molecular mechanisms that regulate the mechanoreciprocity process in adipocytes. This includes our knowledge of the effects of aging on adipocyte ECM stiffness, which remains largely unknown due to the limited availability of techniques allowing the measurement of mechanical forces generated by adipocyte activities *in vivo*. The application of novel and more advanced tools, such as biocompatible and implantable optical fibers and waveguides (Choi et al., 2013; Nazempour et al., 2018), will likely be valuable in moving the field forward.

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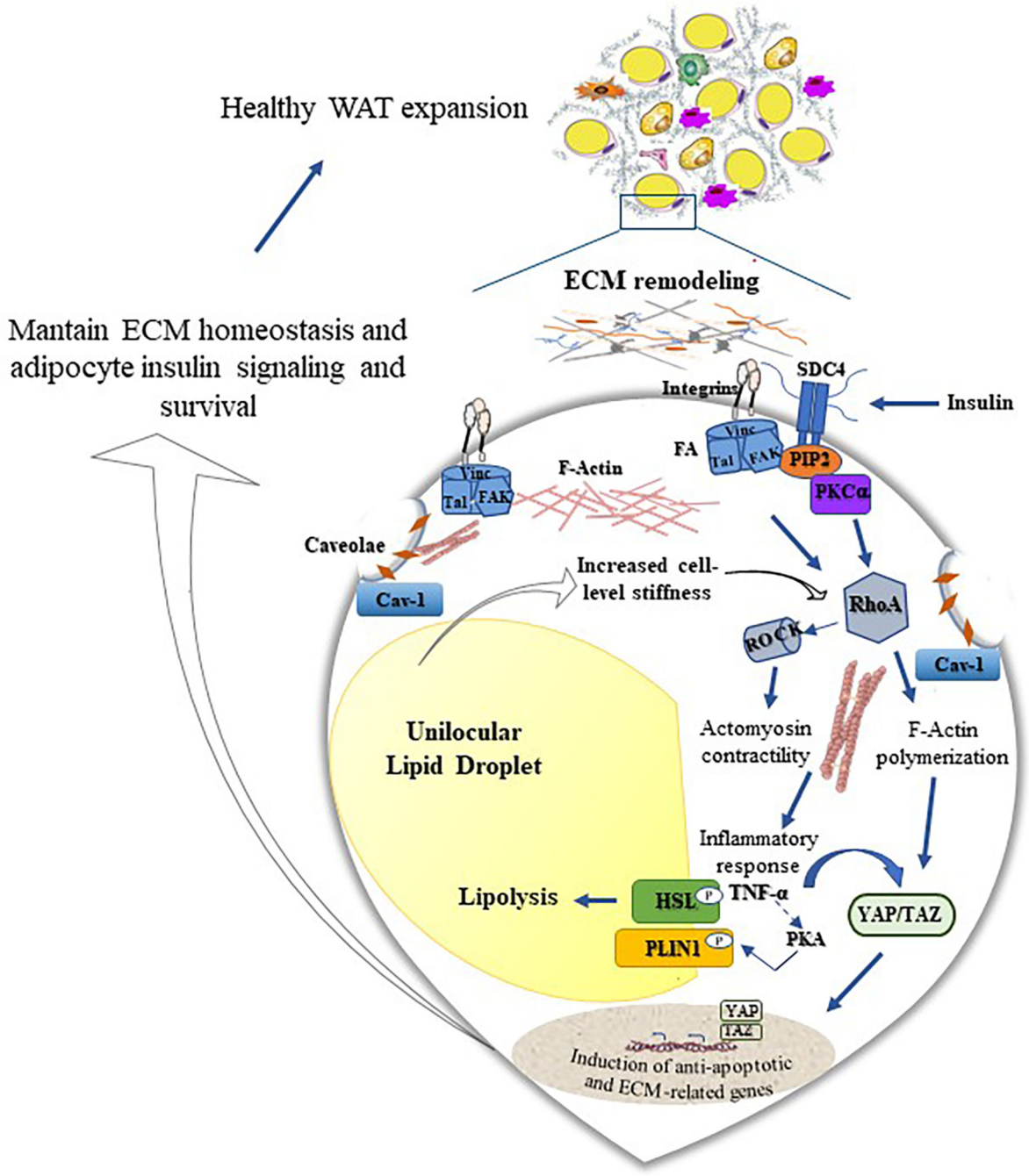

Figure 1. Schematic representation of the mechanosensing machinery in the adipocyte and its impact on white adipose tissue (WAT) expansion.

Mechanical properties of the ECM are sensed by the adipocyte via a range of membrane-bound mechanosensors, including integrins, syndecan 4 (SDC4), focal adhesion (FA) complex proteins, and Caveolin-1 (Cav-1), the principal component of caveolae in adipocytes. These mechanosensors dynamically regulate the transfer of extracellular/intracellular mechanical signals inside/outside the cell. ECM-mediated activation of the FA protein vinculin (Vinc), talin (Tal), and focal adhesion kinase (FAK) produces downstream signaling events regulating the activity of Rho family member A (RhoA). RhoA activation,

which is also mediated by increased cell-level stiffness and SDC4-induced phosphorylation of extracellular signal-regulated kinase, leads to activation of the Ras homologous (Rho)/Rho-associated kinase (ROCK) signaling pathway and a consequent increase in tension of the actomyosin cytoskeleton. This promotes the nuclear translocation of the transcriptional factors Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) resulting in transcriptional control of genes that sustain ECM homeostasis and adipocyte survival. The increased cellular tension also induces the expression of tumor necrosis factor-α (TNFα), which in turn, stimulates lipolysis through activation of cAMP-dependent protein kinase A (PKA) and its phosphorylation of perilipin-1 (PLIN1) and hormone-sensitive lipase (HSL). The interaction between phosphorylated PLIN1 and HSL allows HSL to translocate from the cytosol to the lipid droplet where it promotes lipolysis. Activation of lipolysis may, in turn, counterbalance the adipocyte hypertrophy-induced cellular tension.

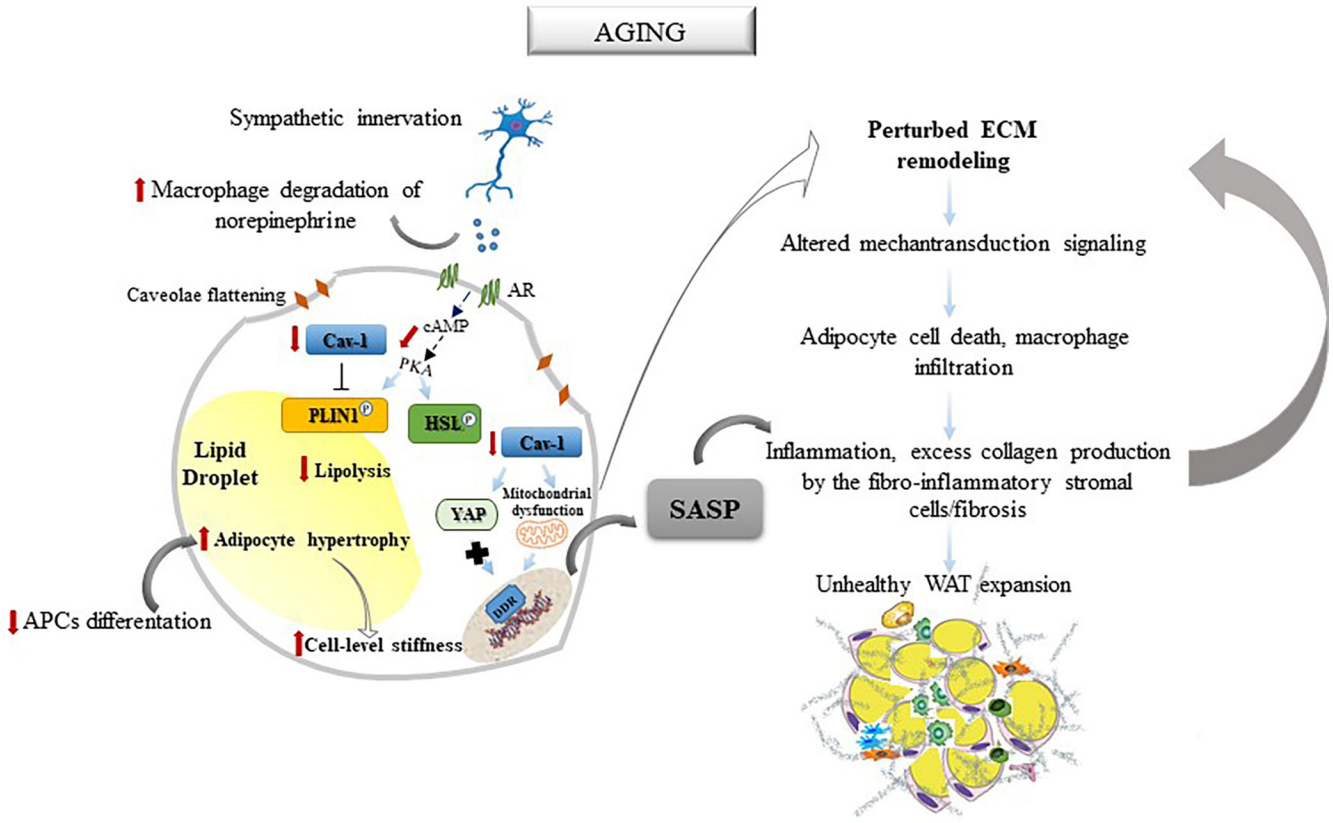

Figure 2. Schematic illustration of the hypothetical model through which aging may affect the mechanoreciprocity process in the white adipocyte cell.

Aging is characterized by reduced catecholamine-stimulated lipolysis caused by lowered bioavailability of norepinephrine by adipose tissue macrophages and decreased activation of the hormone-sensitive lipase (HSL)/perilipin-1 (PLIN1) complex. Age-related reduction of caveolin-1 (Cav-1) prevents caveolae formations in adipocytes and leads to an increase in net collagen synthesis. Moreover, reduced Cav-1 levels reduce actin-dependent mechanoregulation of Yes-associated protein (YAP) activity and induce mitochondrial dysfunction-associated senescence, which, in turn, promotes acquisition of a senescence-associated secretory phenotype (SASP). Together with the age-related decline in adipose progenitor cells (APCs) ability to differentiate into adipocytes and increased adipocyte hypertrophy and stiffness, these events disrupt the feedback loops that regulate extracellular matrix (ECM) composition and mechanical properties. This alters the adipocyte mechanotransduction signaling resulting in a vicious cycle that ultimately leads to adipocyte death, macrophage infiltration, and excess collagen production by the fibro-inflammatory stromal cells, an additional source of ECM perturbation. The senescence-associated secretory phenotype (SASP) produced by the senescent adipocyte contributes to the chronic inflammation and fibrosis that are responsible for the unhealthy expansion of the white adipose tissue (WAT).

Table 1.

Summary of mouse studies in which genes related to cellular mechanotransduction are altered in mature adipocytes

Target gene/protein	Adipocyte-Specific Mouse Model	Phenotypes of genetically altered mice vs control mice	References
Rhoa/Transforiming protein RhoA	HFD-induced obese transgenic mice overexpressing dominant-negative allele	Attenuated weight gain, adipocyte hypertrophy, and macrophage infiltration Lower serum free fatty acids Improved systemic insulin sensitivity Higher fasting glucose and insulin levels	Hara et al., 2011
Rockl/Rho-associated protein kinase 1	HFD-induced obese KO mice	No differences in weight gain, body composition, or biochemical parameters Improved systemic insulin sensitivity Enhanced adipocyte insulin signaling	Lee et al., 2014
Yapl and *Wwtrl*/Transcriptional coactivator YAP1 and TAZ	HFD-induced obese double KO mice	Attenuated weight gain No differences in fasting glucose levels Improved glucose tolerance Lipodystrophy Increased adipocyte death and macrophage infiltration Increased adipogenesis	Wang et al., 2020
Ptk2/Focal Adhesion Kinase 1	NCD-fed KO mice HFD-induced obese KO mice	No differences in total body weight Increased adipocyte death and macrophage infiltration Elevated fasting glucose levels and insulin resistance Hyperlipidemia Attenuated weight gain Enhanced adipocyte death, macrophage infiltration, and fibrosis Higher fasting glucose levels and insulin resistance	Luk et al., 2017
Fermt2/Kindlin-2	NCD-fed KO mice HFD-induced obese KO mice	Severe lipodystrophy, AT fibrosis and inflammation, adipocyte death Attenuated weight gain, smaller size, and reduced fat mass Adipocyte death, AT fibrosis and inflammation Higher fasting glucose levels, glucose intolerance, peripheral insulin resistance Hyperlipidemia and massive fatty liver	Gao et al., 2019 Ruiz-Ojeda et al., 2021
Itgbl/Integrin beta-1	HFD-induced obese KO mice	Reduced weight gain and fat mass No differences in fasting glucose and insulin levels and glucose tolerance	Ruiz-Ojeda et al., 2021

Abbreviations: HFD, High-fat diet; NCD, Normal chow diet; KO, knockout; AT, Adipose tissue