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Review

Role of extracellular matrix remodelling in adipose tissue pathophysiology. Relevance in the development of obesity

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Summary. Adipose tissue responds dynamically to alterations in nutrient excess through adipocyte hypertrophy and hyperplasia, followed by increased angiogenesis, immune cell infiltration, extracellular matrix (ECM) overproduction, and thus, increased production of proinflammatory adipokines during the progression of chronic inflammation. Adipose tissue remodelling is an ongoing process that is pathologically accelerated in the obese state in large part mediated by ECM proteins and proteases. The ECM is subject to major modifications by adipocytes and other cell types that are infiltrated in the adipose tissue, such as macrophages and vascular cells. In obesity, unusual expression of ECM components and fragments derived from tissue-remodelling processes can influence immune cell recruitment and activation, actively contributing to inflammation. ECM turnover requires a tightly regulated balance between the synthesis of the components and their proteolysis, mainly by fibrinolytic systems and matrix metalloproteases (MMPs). In this review, we discuss the key cellular steps that lead to adipose tissue remodelling and the main molecular mechanisms and mediators in this process. We highlight the importance of hypoxia and angiogenesis in the adipose remodelling process, as well as the cross-talk between adipocytes, macrophages and ECM components.

Key words: Adipose tissue, Extracellular matrix, Angiogenesis, Hypoxia, Collagens, Metalloproteinases

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Introduction

Obesity constitutes a pathological condition resulting from an imbalance between energy intake and energy expenditure (Haslam and James, 2005). However, the pathophysiology of obesity is complex, in large part because of the heterogeneous nature of the disease (Frühbeck, 2006). The prevalence of obesity is increasing at an accelerating and alarming rate world-wide, reaching 35.5% among adult men and 35.8% among adult women in 2009-2010 in the United States (Flegal et al., 2012). Obesity is closely linked to the development of insulin resistance, cardiovascular disease and a wide array of other pathophysiological consequences, including non-alcoholic fatty liver disease, hyperlipidemia, arthritis, asthma and certain forms of cancer (Calle and Kaaks, 2004; Kahn et al., 2006; Moore, 2010; Apovian and Gokce, 2012). Body mass index (BMI) is the most used diagnostic tool in the current classification system of obesity, frequently used as an indicator of body fat percentage (BF). However, in spite of its wide use, BMI is only a surrogate measure of body fat and does not provide an accurate measure of body composition (Gómez-Ambrosi et al., 2012). Noteworthy, obesity is defined as a surplus of body fat accumulation, with the excess of adipose tissue really being responsible for most obesity-associated comorbodities.

Adipose tissue is an active endocrine organ which is key in the regulation of whole body energy homeostasis (Frühbeck et al., 2001; Ahima, 2006; Galic et al., 2009). Adipose tissue consists of adipocytes, a principal cellular component, surrounded by supporting connective tissue that is highly vascularized and innervated, and contains macrophages, fibroblasts, adipocyte precursors, and

various cell types included in the stromovascular fraction (Cinti, 2001; Hausman et al., 2001; Nishimura et al., 2007). Adipose tissue releases a variety of proteins termed adipokines, which exert numerous metabolic and vascular effects (Trayhurn and Wood, 2005; Catalán et al., 2009b; Balistreri et al., 2010). Notably, obesity alters the production of adipokines, increases the synthesis of acute-phase reactants and activates the production of pro-inflammatory signalling pathways, involved in the development of metabolic diseases (Gregor and Hotamisligil, 2011; Horng and Hotamisligil, 2011). During the past years the direct participation of membrane proteins such as aquaporin 7 (Frühbeck, 2005; Frühbeck et al., 2006) and caveolin 1 (Frühbeck et al., 2007; Catalán et al., 2008) in the regulation of intermediary metabolism has gained preponderance. Recent attention is currently being directed towards extracellular matrix (ECM) components.

A positive energy balance leads to an increased lipid storage in fully differentiated adipocytes, resulting in enlarged fat cells, which once they have reached a maximum size lead to further adipose tissue enlargement by increasing the number of adipocytes (hyperplasia), which relies on progenitor cell proliferation (Björntorp, 1974; Hirsch and Batchelor, 1976; Frühbeck et al., 1995; Prins and O'Rahilly, 1997). These changes are related to the development of a well-designed supportive ECM with specific structure and composition to adapt to the dramatic alterations of cell shape with adjustment to the need for adipose tissue remodelling and expansion in obesity (Halberg et al., 2008; Mariman and Wang, 2010). Therefore, the ECM is not just an inert supporting material for the cells. On the contrary, the ECM is a complex and dynamic assemblage of interacting proteins and polysaccharides that regulate cell functions in response to both endogenous and exogenous stimuli (Slater, 1996). The ECM is voluminous and highly insoluble, typically composed of proteins, often with signalling functions (Hohenester and Engel, 2002). The ECM components affect cell behaviour through controlling transmembrane signalling, the speed of various molecules through the ECM, as well as the access of growth factors, hormones and neurotransmitters to the cell surface (Hynes, 2009). Variations in the relative quantity of each matrix factor and the way they are combined determines the cell-specificity of the ECM (Nakajima et al., 1998). Adipose tissue is a type of connective tissue whose ECM components are poorly characterized. Both adipocytes and non-adipose cells of the stromovascular fraction contribute to the synthesis and turnover of ECM components (Lee et al., 2010). Although the composition of the ECM is key in the regulation of multiple biological functions such as cell proliferation and differentiation, migration or apoptosis, its structure, ensuring tissue architecture, is also clearly an important factor. The ECM of adipose tissue is composed of the same proteins as found in other cell types, proteoglycans and fibrous proteins being the two main classes of proteins in the adipose ECM (Mariman and Wang, 2010).

Adipose tissue remodelling and expandability hypothesis

The concept of adipose tissue remodelling refers to a combination of matrix synthesis and degradation, with the deposition of specific proteins in response to physiological requirements for growth and expansion or tissue repair, and pathological processes such as inflammation, aging or disease (Lee et al., 2010). Remodelling of adipose tissue ECM plays a pivotal role not only in tissue architecture, but also in adipogenesis and further processes essential for the development of obesity.

The adipose tissue expandability hypothesis links the inability to store a surplus of energy in the form of triglycerides in the adipocyte to the appearance of obesity-associated disease, in particular with insulin resistance (Virtue and Vidal-Puig, 2010). The hypothesis states that adipose tissue expansion is required to store energy efficiently and avoid lipids accumulating in ectopic depots in skeletal muscle, heart, liver and pancreas. An accumulation of lipid in non-adipocyte cells may cause lipotoxic insults and cardiometabolic derangements, including insulin resistance and inflammation. However, in spite of an increased adiposity not all obese patients necessarily develop comorbidities related to ectopic fat deposition in key metabolic organs. In fact, some obese individuals do not exhibit impaired glucose tolerance, hypertension or dyslipidemia concomitantly to the enlarged fat mass, thereby being designated as metabolically healthy obese (Blüher, 2010; Karelis, 2011). In this sense, recent studies have reported that metabolically healthy obese individuals had 54% less fat accumulation in the liver and lower muscle fat infiltration compared to obese subjects with proven circulating metabolic alterations (Stefan et al., 2008; Fabbrini et al., 2009; Messier et al., 2009; Primeau et al., 2011). Adipose tissue expands by either hypertrophy or hyperplasia or both (Arner et al., 2009). The size of adipocytes is of great importance (Medrikova et al., 2012), with adverse metabolic consequences of obesity being accompanied by fat cell hypertrophy (Bays et al., 2008; Arner et al., 2009). In this context, different studies have shown that insulin resistance and increased risk for developing type 2 diabetes correlate with adipocyte size (Weyer et al., 2000, 2001; Lundgren et al., 2007). Small adipocytes are more insulin-sensitive and store more fat than larger ones, thereby limiting the ectopic accumulation of lipids and also regulating expression levels of the inflammatory cytokines such as tumor necrosis factor (TNF)-α.

The mechanisms that determine adipose tissue expandability are not known but the capacity to remodel the ECM and to adequately increase capillary vascularization to enable oxygen and nutrient supply are

necessarily involved (Hardy et al., 2012). In early stages of adipose tissue development, adipogenesis is tightly associated with angiogenesis (Lijnen, 2008) and the ECM can either promote or inhibit angiogenesis (Spencer et al., 2011). In this sense, adipose tissue stiffness is of great importance, because if the ECM surrounding adipocytes does not allow an adequate expansion, adipocytes may be more susceptible to necrosis (Khan et al., 2009). In this sense, although adipose tissue remodelling is a process pathologically accelerated in obesity, not all adipose tissue expansion is associated with pathological changes (Sun et al., 2011).

Angiogenesis and hypoxia in adipose tissue expansion

The growth of blood vessels (a process known as angiogenesis) is associated with and essential for the growth and repair of every organ (Carmeliet, 2005). An imbalance in this process contributes to the pathogenesis of numerous disorders. The remodelling of the ECM is critical in all phases of the angiogenic process, involving a proteolytic activity provided mainly by the fibrinolytic (plasminogen-plasmin) cascade and matrix metalloproteinases (MMPs) (Daquinag et al., 2011).

Angiogenesis as a hallmark in obesity development

Adipose tissue is highly vascularized with an extensive capillary network surrounding each adipocyte, ensuring an adequate exposure to nutrients and oxygen (Crandall et al., 1997) (Fig. 1). The microvasculature is indispensable for the expansion of newly formed adipose tissue, not only as a result of its ability to prevent hypoxia, warranting blood access to adipocytes, but also as a potential source of the adipocyte progenitors, since these cells can derive from the microvasculature of the tissue (Tang et al., 2008). In addition to its need for metabolite transport, the blood capillary network also contributes to immunity and inflammation (Rutkowski et al., 2009). In this regard, angiogenesis inhibition reportedly reduces adipose tissue mass (Daquinag et al., 2011). Specifically, treatment with different angiogenic inhibitors significantly decreased body and adipose tissue weights in genetically obese leptin-deficient mice (Rupnick et al., 2002; Liu and Meydani, 2003; Brakenhielm et al., 2004). A number of recent reports also confirm the initial observation that disruption of adipose tissue neovascularization can prevent the onset of obesity in both genetic and diet-induced obesity models, offering a novel therapeutic option for the treatment of obesity and related metabolic disorders (Cao, 2010). A close examination of developing adipose tissue microvasculature revealed that angiogenesis often precedes adipogenesis; the expansion of adipose tissue is associated with active angiogenesis, whereas inhibition of angiogenesis prevents adipose tissue enlargement (Crandall et al., 1997; Kolonin et al., 2004; Cao, 2007). Thus, a dynamic cross-talk between adipocytes and endothelial cells supposedly takes place in the development and maintenance of adipose tissue via numerous paracrine factors associated with angiogenesis, as well as direct cell-to-cell interactions (Planat-Benard et al., 2004; Ledoux et al., 2008).

Adipose tissue produces and secretes many different types of proangiogenic factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), the two key angiogenic factors produced by adipocytes (Frühbeck, 2004; Lijnen, 2008). VEGF is a key physiological and pathophysiological regulator of angiogenesis (Ledoux et al., 2008). Notably, the VEGF system is generally accepted to account for most of the angiogenic activity in adipose tissue (Lijnen, 2008). Previous studies indicate the involvement of the VEGF family in the expansion of adipose tissue in relation to the need for increased vascularization (Gómez-Ambrosi et al., 2009). In this sense, serum VEGF concentrations have been positively correlated with BMI and visceral fat area and with subsequent decreases in circulating VEGF levels following weight loss (Miyazawa-Hoshimoto et al., 2003; Gómez-Ambrosi et al., 2009). Moreover, VEGF enhanced expression of MMP-3 (Miyazawa-Hoshimoto et al., 2003).

Other important adipose tissue-derived factors with proangiogenic effects include MMPs, plasminogen activators and cathepsins. Adipose tissue also produces endogenous antiangiogenic factors, such as adiponectin, thrombospondin (TSP)-1, TSP-2, ADAM and ADAMTS family members (Lijnen, 2008). Thus, the regulation of angiogenesis in adipose tissue depends on the local balance between proangiogenic and antiangiogenic factors. The potential of the main pro- or anti-angiogenic components is sometimes context-dependent and varies

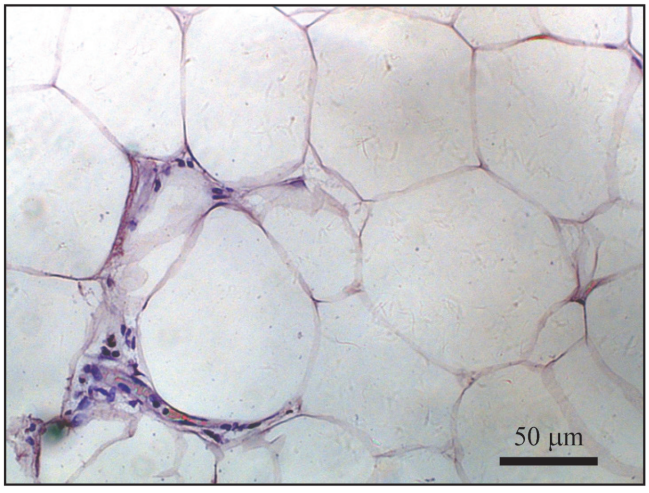

Fig. 1. Human omental white adipose tissue with hematoxylin-eosin staining. Mature visceral adipocytes with variable size surrounded by a blood vessel and a fibrotic depot composed by macrophages and extracellular matrix components can be observed.

according to the different fat pads (Christiaens and Lijnen, 2010). The ECM is a highly important modulator of angiogenesis (Ucuzian et al., 2010). Type IV collagen is a major basement membrane component that has been implicated in promoting the lengthening of neovessels and also preventing their regression (Bonanno et al., 2000). Furthermore, the degradation of type IV collagen releases several antiangiogenic proteins. Previous studies have found that collagen V led to a decrease in angiogenesis, whereas collagen I and III had no effect (Spencer et al., 2011), while a role in the disruption of endothelial adherence to vascular structures has been put forward (Fichard et al., 1995).

Hypoxia and extracellular matrix remodelling

The increased adipocyte size requires oxygen to diffuse over broader areas, implying that hypertrophic fat cells survive with less oxygen supply than is adequate (Halberg et al., 2009). In this context, obesity-associated adipose tissue hypoxia with a decreased capillary density has been suggested by several groups in both human (Fleischmann et al., 2005) and rodent (Rausch et al., 2008) adipose tissue. However, no significant relationship between CD31, an endothelial marker, or hypoxia-inducible factor (HIF)-1α and either BMI or insulin sensitivity has been reported (Spencer et al., 2011). This discrepancy may rest with the fact that evidence of hypoxia has been observed if morbidly obese subjects are studied or the visceral adipose tissue that is more pathogenically related to insulin resistance is examined.

In the presence of hypoxia, cells must respond by coordinated expression of numerous genes to ensure adaptation. The well-characterized key regulator of the adaptive response to alterations in oxygen tension is HIF-1, a transcription factor that consists of an oxygen-sensitive α subunit and a constitutively expressed ß subunit (Wang and Semenza, 1995). In oxygenated cells, the HIF-1α subunit is rapidly destroyed by a mechanism that involves ubiquitination. This process is suppressed by hypoxia whereby HIF-1α escapes from the oxygen-mediated degradation and is subsequently stabilised to form a dimer with HIF-1ß in the nucleus (Jaakkola et al., 2001), resulting in transcriptional activation of a wide variety of genes that stimulate erythropoiesis, angiogenesis, glucose metabolism, cellular growth, and apoptosis (Semenza, 1999; Hosogai et al., 2007). The major effect of HIF-1α is the induction of an angiogenic response through binding to the hypoxia response element of target genes, such as VEGF and angiopoietin 2. The impact of hypoxia on gene expression in adipocytes seems to be central in the inflammatory response observed in obesity (Wood et al., 2009). Hypoxia is reportedly associated with an increased expression of the transcription factor NF-κB and the TNF-α gene promoter in 3T3-L1 adipocytes, as well as with a decreased expression of adiponectin, an anti-inflammatory adipokine (Ye et al., 2007). Consistently, adipose tissue hypoxia has been shown to be attenuated during weight loss induced by calorie restriction in a murine model, suggesting an improvement in oxygenation of the tissue (Ye et al., 2007).

Microarray analysis has also revealed the involvement of several pathways and crucial biological processes modulated by hypoxia in Simpson-Golabi-Behmel syndrome (SGBS) preadipocytes and human adipocytes, including glucose utilization, lipid oxidation and cell death, consistent with low O_2 tension underlying adipose tissue dysfunction in obesity (Geiger et al., 2011; Mazzatti et al., 2012). Moreover, the role of hypoxia and HIF-1α in the regulation of the expression of collagens has been further highlighted (Schipani, 2010). An activation of collagen synthesis, mainly collagen I in periarterial smooth muscle cells, an accumulation of syndecan-4 in lung cancer cells or the stimulation of the production of galectin-1 by hypoxia have been described (Koike et al., 2004; Case et al., 2007; Jean et al., 2011). Hypoxia also facilitates the production of fibronectin in fibroblasts and may also affect integrin biology (Milner et al., 2008; Keely et al., 2009). Simultaneously, hypoxia can also influence ECM degradation through production of MMPs (Lolmede et al., 2003). Finally, using a transgenic model of overexpression of a constitutively active form of HIF-1α, it was shown that HIF-1α induces adipose tissue fibrosis leading to further adipose dysfunction (Halberg et al., 2009; Khan et al., 2009). Fat pads from transgenic mice exhibited an accumulation of extracellular matrix proteins. This is in line with different cell culture studies that have demostrated that hypoxia increases the expression of collagen I, fibronectin, and tissue inhibitor of metalloproteinases (TIMP1) (Falanga et al., 1993, 2002).

Involvement of extracellular matrix components in the adipose tissue remodelling process

Previous research of ECM structure in adipose tissue found a network of collagen fibres around adipose cells (Napolitano, 1963). Currently, it is known that adipose tissue ECM components include structural proteins (collagens) as well as various classes of adhesion proteins, such as fibronectin, laminin, elastins and proteoglycans (Scherer et al., 1998; Divoux and Clément, 2011). Multiple types of collagen are found in adipose tissue including I, IV, V, VI, VII, VIII and IX. Among these, collagen VI is highly enriched in adipose tissue (Scherer et al., 1998; Pasarica et al., 2009). However, it should be noted that adipocyte differentiation is accompanied by specific modifications in the network structure. *In vitro* studies have shown a decrease of fibronectin synthesis during adipocyte development, whereas basement membrane molecules, including collagen IV, laminin and heparan sulfate seem to increase during adipocyte differentiation (Pierleoni et al., 1998; Nakajima et al., 2002). In this regard, the differentiation of 3T3-F442A cells is accompanied by a

decreased cytoskeletal-protein synthesis (ß and γ-actin, vimentin, α and ß-tubulin and fibronectin) together with an increased biosynthesis of lipogenic enzymes, suggesting that cytoskeletal changes may influence the new gene expression needed for adipogenesis (Spiegelman and Farmer, 1982; Spiegelman and Ginty, 1983).

Adipose extracellular matrix components in obesity

Previous studies have also demonstrated increased expression of some ECM proteins in obesity and insulin resistance (Pasarica et al., 2009; Spencer et al., 2010). Thrombospondin (TSP)-1 exists as both a component of the extracellular matrix and as a soluble molecule (Bornstein, 2001), being a major regulator of transforming growth factor (TGF)-ß activity, a well-known endogenous angiogenesis inhibitor (Crawford et al., 1998). Increased TSP1 expression has been reported in adipose tissue of murine obesity models (Voros et al., 2005) and it has also been shown that TSP1-deficient mice exhibit improved glucose tolerance and insulin sensitivity (Li et al., 2011). In humans, TSP1 has been associated with BMI, markers of inflammation and insulin resistance (Varma et al., 2008). Collagens, specifically collagen VI (COL6), are highly upregulated in adipose tissue of obese and diabetic *db*/*db* mice (Khan et al., 2009). In this sense, it has been recently described that collagen VI-null *ob*/*ob* mice have a better metabolic profile compared with control mice and are protected against the development of high-fat diet-induced obesity (Khan et al., 2009). In humans, COL6 expression increases with BMI independently of diabetes and is accompanied by adipose tissue inflammation (Pasarica et al., 2009). Collagen V (COL5) expression is increased in adipose tissue of obese subjects compared to lean volunteers and is inversely associated with insulin sensitivity (Spencer et al., 2011). COL5 abundantly surrounds adipose vessels as well as fibrotic areas. Regarding elastin, its expression is decreased in obese subjects and in adipocytes cocultured with M2 macrophages (Spencer et al., 2011).

Osteonectin, or Secreted Protein Acidic and Rich in Cytsteine (SPARC) is a matricellular protein involved in the modulation of cell-matrix interaction by its binding to structural matrix proteins, such as collagen and vitronectin (Brekken and Sage, 2000). SPARC regulates the expression of collagen type I and TGF-ß1 and the activity of growth factors, such as VEGF and fibroblast growth factor (FGF)-2 (Francki et al., 1999; Motamed, 1999; Brekken and Sage, 2000). Adipocytes secrete SPARC and its expression is strongly elevated in several models of experimental obesity (Tartare-Deckert et al., 2001). Another ECM molecule described in adipose tissue is tenascin C (TNC). TNC is a large, extracellular matrix glycoprotein that belongs to the DAMPs family (Midwood et al., 2011). Little or no TNC is found in most healthy adult tissues, but its expression is specifically induced and tightly controlled in response to tissue injury (Udalova et al., 2011). *TNC* is also reportedly overexpressed in human preadipocytes after stimulation with secreted factors from activated macrophages (Keophiphath et al., 2009). TNC is frequently co-expressed with MMPs (Jones and Jones, 2000). Genes essential for collagen production, such as TNC and procollagen I, III, VI are upregulated in adipose tissue of obese diabetic mice fed a high-fat diet rich in saturated and monounsaturated fatty acids (Huber et al., 2007). Osteopontin (OPN) can be added to the group of adipose ECM proteins. OPN is an acidic glycoprotein involved in ECM remodelling and other processes, including immunity, inflammation or neoplastic transformation (Rangaswami et al., 2006). The expression of *OPN* in omental adipose tissue is increased in overweight/obese patients (Gómez-Ambrosi et al., 2007) and in patients with colon cancer (Catalán et al., 2011b). YKL-40 (also known as human cartilage-glycoprotein 39 or chitinase 3-like 1) is a 40 kDa secreted glycoprotein involved in extracellular matrix remodelling (Shao et al., 2009). Increased visceral adipose tissue gene expression levels of *YKL40* in obese patients with type 2 diabetes, as well as an association with variables of insulin resistance and inflammation, have been recently described (Catalán et al., 2011a) (Fig. 2).

An excessive deposition of ECM proteins contributes to the formation of fibrotic depots, probably related to a chronic inflammation state in the tissue (Wynn, 2007). In this sense, the analysis of the transcriptomic signature of the subcutaneous adipose tissue in obese subjects revealed a significant up-regulation of genes related to ECM constituents and a strong interrelationship with inflammatory processes (Henegar et al., 2008). Moreover, long-term energy restriction downregulated genes encoding several procollagens, other extracellular matrix proteins such as osteonidogen, fibrillin 1 or fibrillin 2, cell adhesion molecules including sarcoglycan δ, or proteins involved in ECM turnover, MMP-11 and 12 in mice (Higami et al., 2006).

Proteolysis of extracellular matrix components in obesity

To remove excess extracellular matrix and allow adipocyte hypertrophy, proteolytic activity mainly by the fibrinolytic and MMPs systems are required (Lijnen, 2008, 2009). The fibrinolytic system is composed by plasminogen, an inactive proenzyme that can be converted into the active enzyme, plasmin. Plasmin degrades fibrin into soluble fibrin degradation products (Lijnen, 2009). Two distinct plasminogen activators, namely, tissue-type plasminogen activator (t-PA) and urokinase type plasminogen activator (u-PA) have been identified. A nutritionally-induced obesity model in t-PA- and u-PA-deficient mice revealed that while t-PA knockout mice showed higher body weight and subcutaneous fat depots accompanied by higher adipocyte diameters, the deletion of uPA had no effect on

this model of nutritionally-induced obesity (Morange et al., 2002). Plasminogen activator inhibitor (PAI)-1 is the predominant inhibitor of the fibrinolytic system and is a main determinant of fibrinolytic activity (Alessi et al., 2007). Elevated PAI-1 concentrations are a hallmark of visceral obesity but its production may be attributed to the stromal compartment of human adipose tissue, mainly by the macrophages infiltrating adipose tissue (Bastelica et al., 2002; Fain et al., 2004).

MMPs comprise a large family of structurally related Zn^{2+}-dependent proteolytic enzymes. MMPs are responsible for remodelling ECM by the degradation and turnover of connective tissue and basement membrane proteins, such as collagen, proteoglycans, and elastin as well as several circulating and cell surface components, thereby regulating cell behaviour in numerous ways (McCawley and Matrisian, 2001; Sternlicht and Werb, 2001). MMPs have been classified into subgroups on the basis of their structure, substrate specificity, and cellular localization. These subgroups are collagenases, gelatinases, stromelysins, membrane-type MMPs (MT-MMPs), and other MMPs (Chavey et al., 2003). MMPs can be controlled at the protein level by the activation of their endogenous inhibitors, TIMPs, representing a family of at least four 20-29 kDa secreted proteins that reversibly inhibit MMPs (Gómez et al., 1997). The ECM is not simply an extracellular scaffold, it also acts as binding reservoirs of biologically active molecules such as growth factors and cytokines that are released once the ECM is degraded. Hence, degradation of ECM components by MMPs can alter cellular behavior and phenotypes. In this regard, the proteoglycan decorin acts as a reservoir for TGF-ß and its degradation by various MMPs makes TGF-ß available to carry out its biologic functions (Imai et al., 1997). Several studies evidence that MMPs play important roles in obesity-mediated adipose tissue remodelling (Catalán et al., 2009a; Unal et al., 2010; de Meijer et al., 2012). MMP-9 expression in adipose tissue is increased with obesity and insulin resistance and is increased in adipocytes in response to co-culture with macrophages (Unal et al., 2010). Upregulation of the expression of MMP-2, -3, -12, -19 and -14 in adipose tissue from genetically obese *ob/ob* and diet-induced obesity mice has been found, whereas that of MMP-7 was downregulated (Maquoi et al., 2002; Chavey et al., 2003; de Meijer et al., 2012). Reportedly, circulating levels of MMP-2 and -9 are increased in obese patients, which may reflect abnormal ECM metabolism (Derosa et al., 2008). In this sense, the activity of MMP-2 and the MMP-9/lipocalin-2 complex are significantly increased in obese patients and positively correlated with gene expression levels of OPN, a protein involved in matrix remodelling (Catalán et al., 2009a). MMPs also play a key role in the control of adipogenesis during the fat mass enlargement that takes place in obesity. The inhibition of MMP activities during the initial stages of differentiation can block adipogenesis, suggesting that MMP-2 and MMP-9 may be necessary mediators of adipocyte differentiation of 3T3-L1 cells (Bouloumie et al., 2001; Croissandeau et al., 2002).

Cathepsin K (CTSK) is a typical cysteine protease that can degrade several matrix constituents, displaying collagenase and gelatinase activities (Chapman et al., 1997). The gene expression levels of *Ctsk* are increased in adipose tissue in a variety of murine experimental models of obesity (Chiellini et al., 2003). Moreover, *Ctsk* knockout mice fed a high-fat diet showed a partial

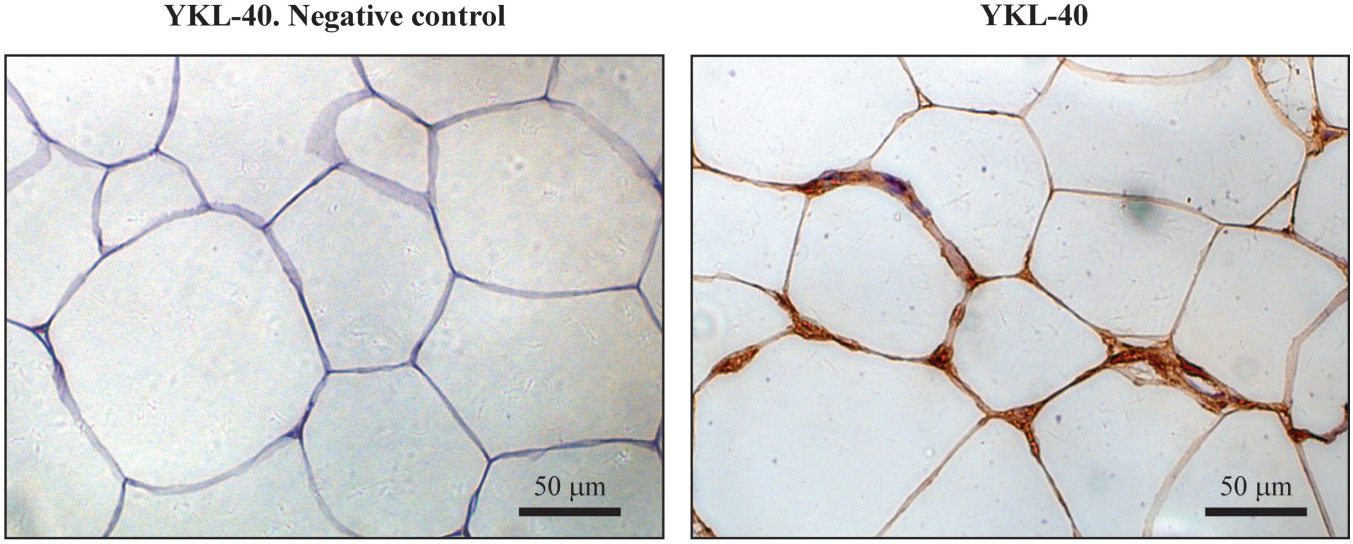

Fig. 2. Immunohistochemistry of YKL-40 in human omental adipose tissue. A strong positivity (brown staining) was observed for YKL-40 in both fully mature adipocytes and cells of the stromovascular fraction. No immunoreactivity was found without the primary antibody (negative control).

resistance to the development of dyslipidemia (Funicello et al., 2007). In humans, CTSK was up-regulated in the adipose tissue of obese subjects with a positive correlation with BMI (Xiao et al., 2006). The deficiency or inhibition of CTSK leads to fibronectin accumulation, suggesting that CTSK plays an important role in adipogenesis, possibly via degradation of fibronectin (Yang et al., 2008).

The crosstalk between adipocytes, macrophages and extracellular matrix

Obesity gives rise to a state of chronic, low-grade inflammation that leads to insulin resistance and type 2 diabetes (Xu et al., 2003; Gómez-Ambrosi et al., 2006; Frühbeck, 2008; Gregor and Hotamisligil, 2011). There is evidence demonstrating a marked infiltration of adipose tissue by macrophages as well as their participation in the inflammatory pathways, suggesting the interplay between adipocytes and nonadipocytes as a contributor to adipose tissue pathology (Weisberg et al., 2003; Wellen and Hotamisligil, 2003; Lumeng et al., 2007). For the infiltration of macrophages, a proteolytic cleavage of basement membrane molecules, including the endothelial basement membrane components type IV collagen or laminin α5, is required (Pipoly and Crouch, 1987; Heck et al., 1990). In this sense, in addition to their roles in innate immunity, macrophages are also involved in programmed tissue remodelling (Lang and Bishop, 1993). It has been described that in adipose tissue, macrophage-induced angiogenesis is essential for subsequent adipogenesis, at the same time as being required for the growth of mouse epididymal adipose tissue (Cho et al., 2007). Furthermore, macrophage production of MMPs is associated with adipocyte enlargement and adipose tissue expansion (Hu et al., 2010). Moreover, the expansion of adipose tissue can lead to multiple consequences, including adipocyte death, increased chemokine production or dysregulation in fatty acid fluxes, with macrophages being involved in these processes (Sun et al., 2011).

ECM fragments as chemoattractants

There is increasing evidence suggesting that ECM molecules or cleaved bioactive peptides can influence

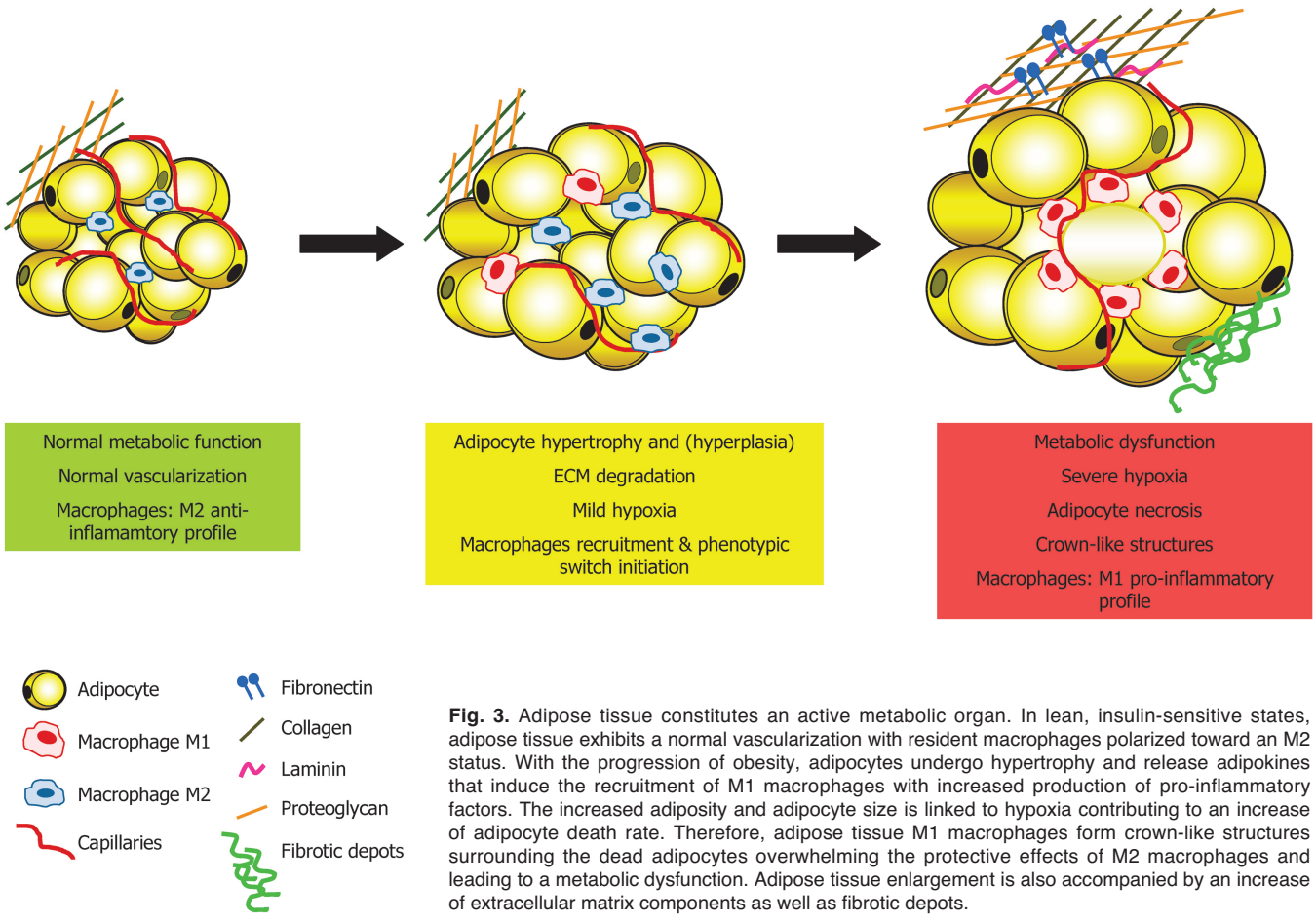

Fig. 3. Adipose tissue constitutes an active metabolic organ. In lean, insulin-sensitive states, adipose tissue exhibits a normal vascularization with resident macrophages polarized toward an M2 status. With the progression of obesity, adipocytes undergo hypertrophy and release adipokines that induce the recruitment of M1 macrophages with increased production of pro-inflammatory factors. The increased adiposity and adipocyte size is linked to hypoxia contributing to an increase of adipocyte death rate. Therefore, adipose tissue M1 macrophages form crown-like structures surrounding the dead adipocytes overwhelming the protective effects of M2 macrophages and leading to a metabolic dysfunction. Adipose tissue enlargement is also accompanied by an increase of extracellular matrix components as well as fibrotic depots.

immune cell activation, differentiation and survival (Korpos et al., 2009; Sorokin, 2010). ECM derived peptides such as collagen types I and IV, elastin, fibronectin or laminins, reportedly have chemotactic activity for inflammatory cells recruiting macrophages (Adair-Kirk and Senior, 2008). Furthermore, cell surface receptors are also responsible for inflammatory cell chemotaxis to ECM fragments (Duca et al., 2007). Recent studies have broadened our understanding of collagens as chemoattractant molecules. An acetylated peptide that results from the cleavage of type I collagen by MMP-8 or MMP-9 shares structural homology to CXC chemokines and mimics the chemotactic effects of CXC-chemokine ligand 8 (CXCL8) (Weathington et al., 2006). Elastin-degradation products by elastase and MMP-12 digestion generated at diseased sites are potent chemoattractants for monocytes, the precursors of the macrophages (Senior et al., 1980; Hunninghake et al., 1981). Fragments of hyaluronan increase the expression of MMP-12, PAI-1 and stimulate the production of several cytokines by macrophages in mice (Horton et al., 1999). In reponse to fibronectin-derived fragments, an increased secretion of the proteases MMP-9 and -12, as well as pro-inflammatory cytokines such as IL-1, -6 and TNF-α, has been reported (Marom et al., 2007; Adair-Kirk and Senior, 2008). Therefore, the remodelled ECM of inflamed tissues affects the propagation of the inflammatory response and the development of obesity comorbidities.

Adipocyte death

Hypertrophied adipocytes are the target of multiple cytotoxic stimuli that activate inflammatory cascades mediating, in part, stress-induced cell death (Ventura et al., 2004). Moreover, a positive association between adipocyte size and death has been found (Strissel et al., 2007). Adipocyte death frequency is dramatically increased in advanced obesity with a focal convergence of macrophages surrounding sites of necrotic-like adipocyte death designated crown-like structures. Thus, necrosis of adipocytes is an important modulator of obesity-associated macrophage responses in the homeostatic remodelling program that promotes adipose tissue expansion in response to energy surfeit (Cinti et al., 2005; Strissel et al., 2007).

The obesity-driven phenotypic switch in macrophages to a pro-inflammatory profile

Later stages of adipose tissue remodelling are associated with phenotypic changes in macrophage subsets. Adipose tissue macrophages undergo a phenotypic switch from an antiinflammatory M2 state to a proinflammatory M1 polarization state, losing their protective capacity in the process (Lumeng et al., 2007). M2 and M1 macrophages present different gene expression characteristics; while M2 expresses IL-10 or arginase, M1 expresses TNF-α, IL-6 or iNOS, increasing the inflammatory profile and contributing to insulin resistance (Lumeng et al., 2007). Proinflammatory macrophages also release cytokines such as TGF-ß, TNF-α and IL-1ß with profound alterations in the ECM turnover (Sorokin, 2010). TGF-ß causes matrix deposition by promoting expression of ECM genes and suppressing the activity of genes such as MMPs (Leask and Abraham, 2004), while IL-1ß upregulates the expression of several MMPs (Woessner, 1991). IL-17 has been reported to selectively stimulate the expression of MMPs in fibroblasts. IL-17 is indirectly capable of attracting both monocytes and neutrophils to the inflammatory focus (Qiu et al., 2009). MMP-9 expression is regulated by TNF-α and INF-γ with the ability of inducing the migration of mast cells through matrix proteins (Di Girolamo et al., 2006). Persistent inflammation leads to accumulation of abnormal ECM components.

Lipid flux in the accumulation of macrophages in adipose tissue

Apart from impaired insulin signalling, adipose tissue mass enlargement, together with adipocyte hypertrophy, are accompanied by different metabolic consequences such as increased endoplasmic reticulum stress and higher rates of basal lipolysis (Duncan et al., 2007). Macrophages filled with lipid are also characteristic of adipose tissue obtained from obese individuals, suggesting an adaptive response by taking up the excess of free fatty acids (FFA) resulting from adipocyte lipolysis (Kosteli et al., 2010). Weight loss leads to an increase in the infiltration and accumulation of lipids in macrophages (Kosteli et al., 2010). During weight loss, the increase of lipids is transient (Frühbeck and Gómez-Ambrosi, 2003). However, in obesity, the chronic elevation in lipolysis and local FFA concentrations provides a constant signal for macrophage accumulation without a significant initial increase in inflammation that nonetheless subsequently results in chronic stimulation, leading to local inflammation and M2 to M1 phenotype polarization.

Conclusions

Adipose tissue plays an active role in energy balance by regulating lipid storage, as well as in metabolic homeostasis via the secretion of a large number of adipokines that influence a variety of physiological and pathophysiological processes. The adipose ECM is capable of modulating cellular behaviour and phenotype, binding specific cytokines and growth factors and, finally, organizing the adipose architecture that facilitates cell migration and cell-cell interactions. The ECM of adipose tissue is a functionally relevant regulator of adipose tissue physiology and also an important site of modulation of systemic metabolism. Obesity may be viewed as a chronic, low-grade inflammation state associated with substantial

modulation of adipose tissue structure, involving adipogenesis, angiogenesis, and ECM remodelling (Fig. 3). The ability to mimic or inhibit some of the ECM functions or proteolytic events would provide novel means to manipulate the development of the inflammatory response in obesity. Thus, specific constituents of the adipose ECM environment may provide potential targets for pharmacological intervention for the treatment of obesity-related metabolic disorders.

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