Review

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Expansion and inflammation of white adipose tissue - focusing on adipocyte progenitors

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Abstract: Adipose tissue is an important organ in our body, participating not only in energy metabolism but also immune regulation. It is broadly classified as white (WAT) and brown (BAT) adipose tissues. WAT is highly heterogeneous, composed of adipocytes, various immune, progenitor and stem cells, as well as the stromal vascular populations. The expansion and inflammation of WAT are hallmarks of obesity and play a causal role in the development of metabolic and cardiovascular diseases. The primary event triggering the inflammatory expansion of WAT remains unclear. The present review focuses on the role of adipocyte progenitors (APS), which give rise to specialized adipocytes, in obesity-associated WAT expansion, inflammation and fibrosis.

Keywords: adipocyte progenitor; adipogenesis; adipose tissue; fibrosis; inflammation.

Introduction

The evolution in multicellular organisms requires an organ to store energy in times of food abundance and to provide nutrients during food shortage. White adipose tissue (WAT) represents such a key energy reservoir to convert free fatty acids (FFA) for storage as triglycerides (Kahn et al. 2019). Apart from energy metabolism, WAT plays important roles in thermal insulation and protection from mechanical stress. WAT is also the largest endocrine organ in the body, secreting numerous adipokines, hormones, cytokines, chemokines, growth factors, microRNAs and lipids to regulate energy homeostasis and immune responses (Scheja et al. 2019). While WAT represents the major constituent of adipose tissue in human, brown adipose tissue (BAT) is abundant in infants and small mammals primarily for energy dissipation and heat generation (Pollard et al. 2020). In adults, WAT is composed of white adipocytes, which store the triglycerides in unilocular lipid droplets. A small number of inducible/recruitable brown-like beige or brite adipocytes, which are multilocular and enriched with mitochondria, also exist in WAT (Wu et al. 2012). Selective activation of beige adipogenesis in WAT improves systemic glucose tolerance, insulin sensitivity and metabolic flexibility (Villanueva 2020).

The majority of adipocytes are originated from the mesoderm and organized into anatomically distinct depots, including subcutaneous and visceral WAT (Schoettl et al. 2018). The embryonic progenitors from the mesodermal sub-compartments unequally distribute into each adipose depot, contributing to the diversified adipocyte lineages that are affected by the developmental stage, age, gender, nutritional status, as well as the tissue microenvironment (Sebo et al. 2019). For example, the visceral WAT has divergent origins from those of subcutaneous WAT (Gesta et al. 2006). Even within a single WAT depot, the adipocytes are derived from different lineages (Merrick et al. 2019). As a result, adipocytes in WAT are highly heterogeneous and exhibit depot-specific ontogeny (Sanchez-Gurmaches et al. 2014). Adipocytes from the *transgelin* (*Tagln*) lineage are present in all WAT depots, whereas those from the *paired-related homeobox 1* (*Prx1*) lineage are found only in subcutaneous WAT (Sanchez-Gurmaches et al. 2015). Adipocytes derived from the mesothelium and marked by *Wilms tumor 1* (*Wt1*) expression exist only in the visceral WAT (Chau et al. 2014). The retroperitoneal WAT is derived from precursors expressing *myogenic factor 5* (*Myf5*) and *paired box gene 3* (*Pax3*), both of which are not essential for the development of mesenteric WAT (Sanchez-Gurmaches & Guertin 2014). The perigonadal WAT is partially dependent on *Pax3* and the

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zinc-finger protein 423 (*Zfp423*) (Jeffery et al. 2015; Schoettl et al. 2018). In summary, the heterogeneity of adipocytes influences the overall behavior of WAT and contribute to the development of obesity, insulin resistance, metabolic and cardiovascular diseases under obese conditions (Lee et al. 2019).

Diversified cellular composition in WAT

In addition to adipocytes, WAT contains different cellular populations, including mesenchymal stem cells (MSC), adipocyte progenitors (APS), pre-adipocytes, fibroblasts, endothelial cells, neutrophils, eosinophils, macrophages and lymphocytes. The cellular compositions of WAT are not static but altered by different pathophysiological conditions (Martyniak et al. 2017). The pluripotent MSC resided within WAT are referred to as adipose-derived mesenchymal stem cells (ASC) that play important roles in tissue regeneration, remodeling and homeostasis (Locke et al. 2009). ASC are able to differentiate into different lineages, such as adipocytes, cardiomyocytes, osteoblasts, chondrocytes and myocytes (Badimon et al. 2017). The International Federation for Adipose Therapeutics and Science (https://www.ifats.org/) has defined ASC based on the minimal cluster of differentiation (CD) surface markers, including $CD39^+CD44^+CD73^+CD90^+CD105^+CD45^-CD31^-$ (Bourin et al. 2013). The expression of the surface markers changes with division, thus different subpopulations of ASC exist in WAT and show distinct ability to grow, differentiate and regenerate (Badimon and Cubedo 2017). The very early ASCs required for adipocyte development and WAT expansion are marked by *Pref-1*, the preadipocyte factor 1 (Hudak et al. 2014).

Most of the adipocytes in WAT arise from APS that have been committed prenatally or in early postnatal life (Rosen et al. 2014). APS isolated from different WAT depots exhibit distinct patterns of gene expression and differentiation potential, thus affecting the capacity of adipogenesis and the susceptibility to insulin stimulation (Ghaben et al. 2019). White and brown adipocytes originate from different APS lineages (Giralt et al. 2013). Despite differences in pre-adipocyte commitment, the adipogenic differentiation involves a shared transcriptional cascade regulated by peroxisome proliferator-activated receptor (PPAR)-γ and CCAAT/enhancer-binding proteins (C/EBPs) (Farmer 2006; Gesta et al. 2007). Nevertheless, the cellular hierarchy that governs the commitment of ASC to APS and the subsequent differentiation of pre-adipocytes into white or brown adipocytes remains incompletely understood (Merrick et al. 2019).

Local inflammation, together with deregulated release of FFA to ectopic organs, such as liver and skeletal muscle, are the key events linking WAT dysfunction with obesity-associated insulin resistance and metabolic diseases (Lee et al. 2019). The cellular composition in WAT is significantly altered during the progression of obesity in a depot-specific manner (Gao et al. 2018; Lee et al. 2019; Schwalie et al. 2018). Accumulation of visceral WAT, referred to as central obesity, is positively associated with the development of insulin resistance and the increased risk of metabolic diseases (Ghaben and Scherer 2019). Visceral WAT contains a large population of immune cells that either inhibit or promote immune responses. Compared to subcutaneous WAT, chronic inflammation in visceral WAT results in more deleterious effects (Alvehus et al. 2010; Ibrahim 2010). Macrophage infiltration in visceral WAT contributes to systemic inflammation, insulin resistance and oxidative stress (Xu et al. 2003). In lean WAT, the $F4/80^+CD206^+$ M2 macrophages express arginase-1 and produce anti-inflammatory molecules, such as IL-10, to inhibit immune cell activation (Lumeng et al. 2007). In visceral WAT of obese individuals, the relative amount of proinflammatory $F4/80^+CD11c^+$ M1 macrophages increases, whereas that of regulatory T-cells (Treg) decreases, thus promoting chronic low grade inflammation (Kolodin et al. 2015; Weisberg et al. 2003). The presence of $CD8^+$ T-cells precedes the infiltration of macrophages in obese WAT (Nishimura et al. 2009).

Depot-specific differences in APS affect the susceptibility of WAT to chronic inflammation (Hwang et al. 2019; Joe et al. 2009). The increased production of monocyte chemoattractant protein (MCP)-1 and the activation of inflammasome signaling pathway in APS promote innate inflammatory responses in obese WAT (Kaplan et al. 2015). WAT inflammation *per se* also governs the differentiation and plasticity of APS (Badimon and Cubedo 2017). Pro-inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, suppress PPAR-γ expression thus inhibiting the adipogenic potential of APS (Cortez et al. 2013; Haylett et al. 2020). The complexity and heterogeneity of APS influence the plasticity and remodeling of WAT under different pathophysiological conditions. As adipocytes of different lineages exhibit variable responses to insulin stimulation, fatty acid uptake, lipolysis, lipogenesis and adipogenesis (Lee et al. 2019), to fully understand the complexity, heterogeneity and functionality of APS in different WAT depots is critical for uncovering the key mechanisms underlying the development of obesity and related metabolic abnormalities.

APS and WAT expansion

In response to excess energy supply, WAT undergoes massive expansion and remodeling, characterized by hyperplasia (increase in number) and hypertrophy (increase in size) of the adipocytes, extracellular matrix (ECM) accumulation, impaired angiogenesis, as well as inflammatory cell infiltration and activation (Figure 1). WAT expansion occurs via adipocyte hypertrophy or through the recruitment and differentiation of APS. The expansion of subcutaneous WAT is due primarily to hyperplasia, whereas that of visceral WAT occurs mainly by hypertrophy (Joe et al. 2009). WAT hyperplasia is generally more favorable than hypertrophy during adipose tissue remodeling, as small adipocytes show improved insulin sensitivity (Eriksson-Hogling et al. 2015; Shao et al. 2018). Hyperplasia requires the proliferation and differentiation of APS in WAT, which are positive for *stem cell antigen-1* (*SCA1*) and *CD34*, and negative for *CD45*, *CD31*, and/or *Ter119* [lineage (Lin) surface markers for endothelial cells, platelets, macrophages, white blood cells, osteoclasts and erythrocytes] (Rodeheffer et al. 2008). Obesity is associated with a diminished capacity for APS to self-renew and differentiate into adipocytes (Yamashita et al. 2007).

APS reside around the vasculature in WAT (Rodeheffer et al. 2008; Tang et al. 2008). Almost all $Lin^{-}SCA1^{+}CD34^{+}$ APS isolated from the stromal vascular fraction (SVF) of WAT are able to differentiate into adipocytes. However, the expression of the surface markers changes with division and differentiation, thus different subpopulations of APS exist in WAT (Berry et al. 2013; Macotela et al. 2012). There is no single set of consensus marker of APS, due largely to their heterogeneity. The complexity and heterogeneity of

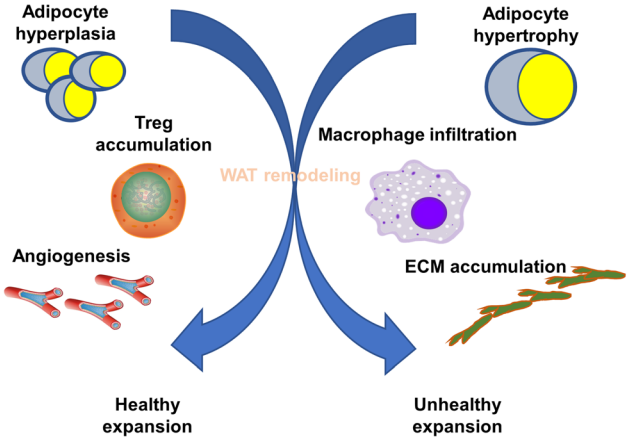

Figure 1: WAT expansion and remodeling. Different cellular components, including adipocytes, lymphocytes and macrophages, contribute to the healthy or unhealthy expansion of WAT.

APS influence the expansion of WAT under different pathophysiological conditions (Vishvanath et al. 2019). High self-renewal APS stimulates the production of well-functioning adipocytes through enhanced adipogenesis, rather than expanding the size of adipocytes with concomitant loss of function (Haylett and Ferris 2020). Compared to subcutaneous APS, the visceral APS are less committed to adipocyte differentiation due to a blockage of PPAR-γ expression (Macotela et al. 2012). In response to dietary obesity, however, enhanced adipogenesis occurs in visceral but not subcutaneous WAT (Jeffery et al. 2015; Kim et al. 2014).

In mice, a population of APS expressing *SCA1*, *CD34*, *CD29* and *platelet-derived growth factor receptor* (*PDGFR*)-*α* exhibits strong adipogenic potentials and contributes to the expansion of WAT upon long-term overfeeding (Miwa et al. 2018). However, this population of APS is not homogeneous, certain subpopulations co-expressing *PDGFRβ*, a mural cell marker (Z. Gao et al. 2018). Under normal conditions, the mature adipocytes do not express *PDGFRα* although its re-expression in disease states such as obesity could be important. PDGFRα expression precedes PDGFRβ in subcutaneous WAT, whereas the $PDGFR\beta^{+}$ population is derived from a separate APS lineage in visceral WAT (Vishvanath et al. 2016). PDGFRβ is expressed in mural cell progenitors to regulate their recruitment and expansion, and to modulate the innate or adaptive immunity (Olson et al. 2011). The $PDGFR\beta^{+}$ APS express high levels of adipogenic factors, such as *Ppary* and *Zfp423*, and reside adjacent to the endothelium in WAT blood vessels (Gupta et al. 2012; Tang et al. 2008). Mural cells, including pericytes and vascular smooth muscle cells, are heterogeneous and derived from mesoderm or neural crest. High-fat diet feeding induces $PDGFR\beta^{+}$ lineage recruitment to generate hypertrophic adipocytes. Increasing the adipogenic capacity of $PDGFR\beta^{+}$ APS through PPAR-γ overexpression results in healthy visceral WAT expansion, whereas the loss of mural cell PPAR-γ triggers pathologic visceral WAT expansion upon high-fat diet feeding (Shao et al. 2018). In subcutaneous WAT, beige adipocytes are induced from PDGFRα-high/PDGFRβ-low APS (Seki et al. 2016), whereas PDGFRβ induction and PDGFRα suppression favor white adipogenesis (Gao et al. 2018). The beige APS in subcutaneous WAT are marked as $Lin^{-}CD81^{+}PDGFRa^{+}SCA1^{+}$ (Oguri et al. 2020).

Among the $Lin^{-}CD29^{+}CD34^{+}SCA1^{+}$ APS isolated from the WAT SVF, a subpopulation of adipogenesis-regulatory (Areg) cells characterized by high expression of *CD142* and the *ATP-binding cassette subfamily G member 1* (*ABCG1*) suppress APS differentiation and adipocyte formation in a paracrine manner (Schwalie et al. 2018). Areg cells are

located perivascularly and more abundantly present in visceral than subcutaneous WAT, consistent with the higher adipogenic potential of the latter depot (Haider et al. 2019). In human WAT, several cell surface proteins are commonly reported to be expressed on APS isolated from SVF, including *CD34*, *CD29*, *CD13*, *CD44*, *CD73*, *CD90*, *CD142* and *CD9* (Cawthorn et al. 2012). Adipogenesis is also observed in cell populations expressing *CD36* and *mesenchymal stromal cell antigen-1 (MSCA)-1* (Esteve et al. 2015; H. Gao et al. 2017). The $Lin^-PDGFR\alpha^+CD29^+$ APS are identified to include $CD34^{high}$, $CD34^{low}$ and $CD34^-$ subpopulations, which possess similar proliferative and adipogenic capacities but different rates of lipid flux. Moreover, the APS with no CD34 expression display beige-like adipocyte properties (Raajendiran et al. 2019). Human adipose tissue also contains APS expressing PDGFRα and PDGFRβ, the balance of which determines APS commitment to beige or white adipocytes (Z. Gao et al. 2018). In human subcutaneous WAT, increased numbers of $Lin^-CD81^+PDGFR\alpha^+SCA1^+$ APS are associated with increased *de novo* beige fat adipogenesis and improved metabolic health profile (Oguri et al. 2020). In addition, $Lin^-PDGFR\alpha^+MyoD^+$ and other APS populations form distinct subtypes of beige adipocytes depending on the nature of browning stimuli (Chen et al. 2019). A better understanding of the mechanisms that define white or beige adipogenesis and the identities of different APS during WAT expansion represents a significant area of research.

APS and WAT inflammation

In WAT, different stages of obesity affect the infiltration and distribution of subpopulations of immune cells (Johnson et al. 2012). Macrophage accumulation in WAT is directly proportional to adiposity and contribute to systemic inflammation, insulin resistance and oxidative stress (McNelis et al. 2014; Weisberg et al. 2003; Xu et al. 2003). In lean WAT, the $F4/80^+CD206^+$ M2 macrophages express arginase-1 and produce anti-inflammatory molecules, such as IL-10, to inhibit immune cell activation (Kosteli et al. 2010; Lumeng et al. 2008). Early stages of WAT expansion are characterized by M2 macrophage polarization (Prieur et al. 2011). A delicate balance of the polarized macrophage populations maintains WAT expansion and function. In visceral WAT of obese individuals, the relative amount of proinflammatory $F4/80^+CD11c^+$ M1 macrophages increases, whereas that of Treg decreases, thus promoting chronic low grade inflammation (Feuerer et al. 2009; Lumeng et al. 2007).

Over 90% of macrophages in obese WAT are localized surrounding the dead adipocytes and form crown-like structures (CLS) (Weisberg et al. 2003). The macrophages found in CLS are positive for the M1 proinflammatory CD11c marker (Wentworth et al. 2010; Zeyda et al. 2010). The infiltrated macrophages initially function to clear adipocyte debris and enable healthy expansion of WAT. However, over time, the chronic inflammation often leads to reduced metabolic flexibility, long-term insulin and catecholamine resistance, abnormal WAT tissue remodeling and fibrosis (Reilly et al. 2017). Monocyte chemoattractant protein-1 (MCP-1) is a potent chemokine that recruits monocytes. Increased MCP-1 expression recruit $CCR2^+$ proinflammatory monocytes that differentiate into $F4/80^+CD11c^+$ macrophages in WAT (Kanda et al. 2006). Deficiency of MCP-1 protects mice from dietary obesity-induced WAT inflammation and insulin resistance (Kanda et al. 2006). Shortly after the initiation of high-fat diet, the $Lin^-CD29^+CD34^+SCA1^+CD24^-$ APS produce a high level of MCP-1 in visceral WAT (Kaplan et al. 2015). In human WAT, the $Lin^-CD34^+CD90^+$ APS with high surface expression of CD44 marks the MCP-1 producing APS (Kaplan et al. 2015).

Recent single-cell transcriptomic studies suggest that obese WAT contains multiple distinct populations of macrophages, the functional heterogeneity of which influences metabolic outcomes (Hill et al. 2018; Li et al. 2010). The Ly6c macrophages reside outside of CLS are adipogenic, whereas CD9 macrophages within CLS are lipid-laden and proinflammatory (Hill et al. 2018). Under obese conditions, a subset of $CD9^+CD63^+$ lipid-associated macrophages are prominently arising from circulating monocytes and positioned around the enlarged adipocytes to drive protective immune responses in WAT (Jaitin et al. 2019). The functional heterogeneity of macrophages in the obese WAT influence the different metabolic outcomes (Kraakman et al. 2015). Thus, to characterize the interactions between the subpopulations of macrophages and APS during the development of obesity will help to uncover the detailed cellular events triggering WAT inflammation and dysfunction.

Treg, characterized by $CD4^+CD25^+FOXP3^+$, are key players to inhibit WAT inflammation (Feuerer et al. 2009). They are generated in the thymus and enriched in the visceral WAT of lean mice (Cipolletta et al. 2015; Kolodin et al. 2015). The percentage content of Treg significantly decreases in the visceral WAT of obese mice (Deiuliis et al. 2011; Eller et al. 2011). High-fat diet induces a rapid increase of the proinflammatory Th1 cells, followed by a decrease in Treg in visceral WAT (Winer et al. 2009). Experimental ablation of Treg acutely reduces insulin sensitivity, whereas transfer of these cells improves insulin sensitivity

in animals changed with dietary obesity (Ilan et al. 2010; Wensveen et al. 2015). The differentiation, accumulation and function of Treg depend on IL-33, a critical immunomodulatory alarmin (Vasanthakumar et al. 2015). Genetic variations in IL-33 are linked to the development of obesity in humans, suggesting a role of this cytokine in the regulation of WAT inflammation (Angeles-Martinez et al. 2017; Hasan et al. 2014). IL-33 deficiency in mice results in increased WAT inflammation, whereas IL-33 treatment boosts the numbers and activity of WAT Treg (Vasanthakumar et al., 2015). IL-33 is required for Treg cell accumulation in visceral WAT through binding to its receptor IL-1 receptor-like 1, also known as IL1RL1 or ST2, which is highly expressed on Treg (Han et al. 2015; Kolodin et al. 2015).

IL-33-expressing cells are non-hematopoietic and located at the circumference of the adipose depot, presumably the mesothelium, or the interior of the depot in close association with blood vessels or neurons (Pichery et al. 2012). Over 90% of IL-33-producing cells are from $CD45^{-}CD31^{-}PDGFR\alpha^{+}SCA1^{+}$ population of APS in WAT (Spallanzani et al. 2019). However, as the $PDGFR\alpha^{+}SCA1^{+}$ cells are highly heterogeneous (Bernardo et al. 2013), the identity of the $IL\text{-}33^{+}$ cells in WAT remain contentious. Some APS in visceral WAT are derived from the mesothelium in the lateral plate mesoderm and show high expression of the mesothelial markers *Wt1, mesothelin (Msln) and uroplakin 3b (Upk3b)*, as well as the mesoderm gene marker *Tcf21* (Chau et al. 2014). Mesothelial cells characterized by $podoplanin(PDPN)^{hi}CD9^{+}PDGFR\alpha^{-}$ represent a distinct population of IL-33 expressing APS in visceral WAT (Mahlakoiv et al. 2019), which are regulated by Treg in a negative feedback loop (Spallanzani et al. 2019). APS-targeted ablation of IL-33 reduces visceral Treg accumulation (Li et al. 2020). To identify the cellular sources of IL-33 and the molecular mechanisms controlling the regulation of Treg by IL33-expressing APS are of critical importance for understanding the inflammation and remodeling process in WAT.

APS and WAT fibrosis

In advanced obesity, chronic inflammation and massive remodeling ultimately leads to unresolved tissue fibrosis of WAT (Marcelin et al. 2019). Inflamed and fibrotic WAT is deleterious for energy storage and endocrine function, resulting in altered local and systemic metabolic control (Longo et al. 2019). Fibrosis is a process involving the destruction of normal tissue by deposition of collagen-rich ECM. In response to high-fat diet treatment, adipocytes initially become hypertrophic and later hyperplastic (Jeffery et al. 2015; Wang et al. 2013). Hypertrophic adipocytes exhibit micro-hypoxia, ER stress, increased lipolysis and altered ECM remodeling (Halberg et al. 2009; Wensveen et al. 2015), which trigger adipocyte death and eventually prevent WAT to expand further (Cinti et al. 2005; Giordano et al. 2013; Gupta et al. 2012). Excessive deposition of ECM, especially the type I, IV and VI collagens, represents the physical constraints to WAT expansion (Chun et al. 2006). Moreover, fibrosis itself induces adipocyte dysfunction and promotes WAT inflammation. Abnormal remodeling characterized by reduced adipocyte size exists in regions of fibrotic WAT (Divoux et al. 2010). Targeting ECM remodeling improves glucose tolerance and insulin sensitivity (Khan et al. 2009).

Hyperactivation of the PDGFRα signaling in pericytes and adventitial cells located on the abluminal surface of capillaries and large vessels causes WAT fibrosis (Iwayama et al. 2015; Olson et al. 2009). The bipotent fibro/adipogenic progenitors in WAT are characterized by $CD31^{-}CD45^{-}CD34^{+}CD44^{+}PDGFR\alpha^{+}$ (Marcelin et al. 2017). Among this population of progenitors, those expressing CD24 actively proliferate to enlarge the pool of postmitotic $PDGFR\alpha^{+}CD24^{-}$ that differentiate into adipocytes (Rodeheffer et al. 2008), whereas those of $PDGFR\alpha^{+}CD9^{high}$ cells are highly fibrotic and represent an important source of both ECM production and proinflammatory factors (Marcelin et al. 2017). Activation of the $PDGFR\alpha^{+}CD9^{high}$ progenitors promotes WAT fibrosis and the development of insulin resistance (Olson & Soriano 2009). Upon the initiation of high-fat diet, there is a rapid switch of $PDGFR\alpha^{+}CD9^{low}$ to $PDGFR\alpha^{+}CD9^{high}$ cells, accompanied by collagen deposition and local insulin resistance. Obese patients with the highest metabolic deterioration also show the highest number of $CD9^{high}$ cells in their visceral WAT (Marcelin et al. 2017).

In visceral WAT depot of several mouse strains, the $Lin^{-}CD29^{+}SCA1^{+}CD34^{+}$ $PDGFR\alpha^{+}$ APS with $CD34^{high}$ expression are associated with hypertrophic growth, inflammation, ECM deposition, fibrosis and metabolic dysfunction (Buffolo et al. 2019). Moreover, the $CD34^{high}$ APS are $CD9^{+}$ and elicit paracrine function to inhibit the adipogenic differentiation of $CD34^{low}$ APS. These cells exhibit the potential to differentiate into vascular smooth muscle cells (Buffolo et al. 2019). Obesity induces the formation of $Sca1^{-}Sma^{+}ITGA5^{+}$ fibrogenic progenitor cells (FPC) in adipose tissue. CD9 and ITGA5 (CD49e) may function together to facilitate recruitment of FPC from the vascular compartment (Lin et al. 2018; Marcelin et al. 2017). In human WAT depots, distinct $Lin^{-}CD29^{+}$ APS subtypes with $CD34^{-}$ and $CD34^{low}$ are present and exhibit similar adipogenic properties, but

producing adipocytes with marked differences in their metabolic and thermogenic capacities as well as endocrine function. The subtypes with CD34^{high} are found as a firbo-adipogenic progenitor cells and exhibit increased fibrogenic potential (Raajendiran et al. 2019). The molecular events that shift the fate of perivascular progenitors from APS to FPC are poorly characterized but represent important area of intervention for protections against chronic obesity-induced fibrosis and metabolic dysfunction.

Mesothelial cells form a monolayer of the mesothelium that covers internal organs, and share a common developmental lineage with the mural cells (Rinkevich et al. 2012). Under certain circumstances, they undergo mesothelial-mesenchymal transition to acquire a myofibroblastic phenotype to secret inflammatory mediators and ECM components (Darimont et al. 2008; Mutsaers et al. 2015; Yanez-Mo et al. 2003). Single-cell sequencing revealed that one cluster of the PDGFRβ$^+$ stromal cells express mesothelial cell markers and are CD9^{high} (Hepler et al. 2018). Despite the information, the exact role of these cells in visceral WAT fibrosis remains unknown. Among the PDGFRβ$^+$ APS in visceral WAT, the Ly6c$^-$CD9$^-$PDGFRβ+ cells represent a distinct pool with a high adipogenic potential, whereas the Ly6c$^+$PDGFRβ$^+$ cells are fibro-inflammatory progenitors (FIP) (Shao et al. 2018; Vishvanath et al. 2016). Different from the Areg, FIP in visceral WAT suppress the differentiation of APS but activate immune cells, and exhibit a mesoderm-mural cell origin (Buffolo et al. 2019; Hepler et al. 2018). However, it remains unclear whether the PDGFRα$^+$ and PDGFRβ$^+$ progenitors represent the same or different fibrogenic niche for WAT remodeling. Identification of the adipogenic/fibrogenic progenitors for WAT remodeling is of clinical interest to limit adipocyte hypertrophy, fibrotic hyperplasia and the deleterious effects of obesity.

Summary

Obesity is driven by the massive expansion and chronic inflammation of WAT. With excess energy pressure, expandability and proper remodeling of WAT appear to be critical for determining the clinical outcomes. Under obese conditions, the pathological WAT remodeling is characterized by enlarged adipocytes, reduced adipogenesis, excessive macrophage accumulation, low-grade inflammation and fibrosis. APS have become a target of interest to control the homeostatic balances of WAT expansion, inflammation and fibrosis (Figure 2). APS in WAT not only function as a reservoir of precursors to replenish the mature differentiated adipocytes, but also act as important immunomodulators. The identification of specific markers

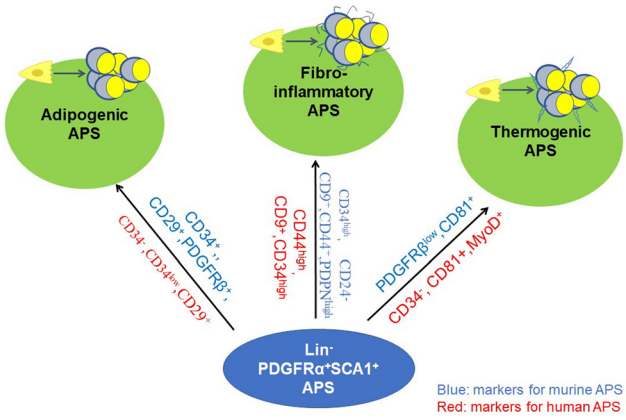

Figure 2: Diversified lineage and function of APS. Different surface markers are used to identify the adipogenic, fibro-inflammatory and thermogenic APS in WAT.

by single cell transcriptomic analysis allows tracking of the fate and function of APS within WAT. However, more studies are needed to delineate the different lineages of APS and the critical pathways controlling their activation and differentiation in order to uncover the key mechanisms underlying the development of obesity and related metabolic abnormalities. In particular, a deeper understanding of the multipotent capacity, heterogeneity and dynamic functions of APS in different WAT depots would lay the groundwork for developing new therapeutic strategies for obesity and associated metabolic diseases.

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