Adipose tissue macrophages

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Abstract

In obesity, adipose tissue macrophages (ATMs) are abundant immune cells in the adipose tissue and are known as inducers of metabolic inflammation that may lead to insulin resistance and immune disorders associated with obesity. However, much less is known about the ontogeny and physiological functions of ATMs in the lean adipose tissue. ATMs are present at birth and actively participate in the synthesis of mediators which induce lipolysis, mitobiogenesis and thermogenesis in adipocytes. Later in life ATMs limit the thermogenic competence of the adipocytes and favor lipid storage. ATMs respond to lipid overload of adipocytes in obesity with a sequence of pro-inflammatory events, including inflammasome activation and pryoptosis, as well as stimulation of nuclear factor kappa B and interferon response elements that evoke an uncontrolled inflammation. ATMs are life-long constituents of the adipose tissue, and hence signals that control ATM development and ATM-adipocyte interactions determine adipose tissue health.

Key words: obesity – adipose tissue – inflammation – macrophage

Brief history of adipose tissue macrophages

Adipose tissue macrophages (ATMs) are resident innate immune cells of the adipose tissue, that become abundant with the progression of obesity (Boutens and Stienstra 2016; Epelman et al. 2014; Glass and Olefsky 2012; Lee and Lee 2014; Li et al. 2013; Osborn and Olefsky 2012; Qiu et al. 2014; Röszer 2020d; Röszer 2022; Xu et al. 2003) (Fig. 1A). The presence of ATMs – termed as "fixed histiocytes" – in the adipose tissue is mentioned in a histology book from 1914 (Kopsch 1914), and a comparative histology textbook from the 1950s also mentions the existence of phagocytic immune cells in the amphibian adipose tissue (Ábrahám 1952). Accumulation of ATMs was first described in obese adipose tissue of mice in the 1960s (Hausberger 1966) and later ATMs were defined as phagocytosing myeloid cells that express CD11c and F4/80 antigen in mouse, and CD68 and IBA1 (ionized calcium binding adaptor molecule 1) in human, and various monocyte-macrophage proteins in other mammals (Röszer 2020d). Since adipose tissue is a specialized connective tissue, and since connective tissues harbor various immune cells, including macrophages, ATMs were considered as patrolling immune cells in the fat depots. Thus, initially ATMs were not assigned to a dedicated physiological function beyond immune surveillance. However, the central role of adipose tissue inflammation in metabolic syndrome and the clustering of obesity-associated immune pathologies become evident in the 2000s (Lumeng et al. 2007; Lumeng et al. 2008; Weisberg et al. 2003; Xu et al. 2003), that instigated a growing interest in understanding immune component of obesity.

The health impact of adipose tissue inflammation in obesity led to the rediscovery of ATMs in obese human adipose tissue in the early 2000s, catalyzing the rapid development of an ATM-centered paradigm of obesity-associated pathologies (Lumeng et al. 2007; Weisberg et al. 2003; Xu et al. 2003). ATMs are however appear in the lean adipose tissue as well, and

are constituents of the adipose tissue stroma in amphibia, rodents, ruminants, carnivora, primates and human (Akter et al. 2012; Ampem et al. 2016; Waqas et al. 2017b; Yu et al. 2019). ATMs secrete cytokines, lipid mediators, hormones and are sources of reactive oxygen species. Local and systemic effects of these ATM-derived biomolecules determine adipocyte functioning and systemic metabolism.

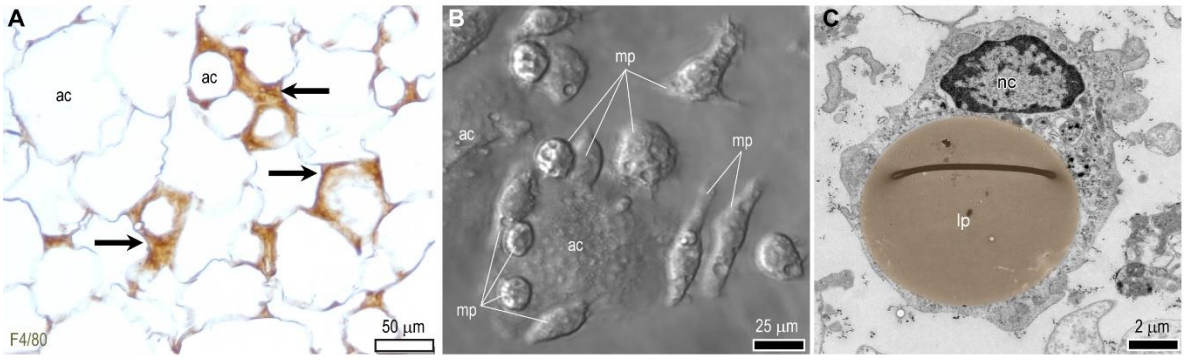

Figure 1. Obese adipose tissue in mouse. Adipose tissue macrophages (ATMs) are labeled with an antibody against the mouse macrophage marker F4/80 antigen. ATMs form crown like structures (indicated with arrows) around adipocytes (ac). (**B**) Apoptotic fat cells (ac) and macrophages (mp) *in vitro*. Such as in the adipose tissue, macrophages form clusters around the apoptotic fat cell and clear their remnants and lipid molecules. (**C**) Transmission electron microscopy of a mouse ATM, engulfing a large lipid droplet. nc: nucleus, lp: lipid droplet. For better visibility the lipid droplet is labeled with pseudo-color. Text and images are reprinted from (Röszer 2020d).

Adipose tissue macrophages: friend or foe?

ATMs are mostly known for their metabolically adverse effects that in obesity. Obesity is associated with a significant increase in ATM number and pro-inflammatory macrophage activation (Boutens and Stienstra 2016; Lumeng et al. 2007), that is concomitant with the development of chronic adipose tissue inflammation (Weisberg et al. 2003; Xu et al. 2003).

Inflammation impairs insulin sensitivity, deteriorates kidney and liver function, eventually, establishing a bad reputation for ATMs (Boutens and Stienstra 2016). There are several original articles and reviews, detailing the metabolic harm of ATMs residing in the obese adipose tissue. Historically, when the abundance of ATMs in the obese adipose tissue was shown, the so-called M1/M2 polarization model was the central paradigm of macrophage biology (Röszer 2020d). In brief, M1, or classical macrophage activation is elicited by lipopolysaccharides (LPS) and interferon gamma (IFNγ) in macrophages cultured *in vitro*. LPS is an activator of Toll like receptor 4 (TLR4), and IFNγ acts through its membrane receptor. Eventually, LPS and IFNγ stimulation of macrophages leads to the activation of nuclear factor kappa B (NFκB) and interferon regulatory factors (IRFs) controlled pro-inflammatory gene expression. This increases pro-inflammatory cytokine secretion and nitric oxide (NO) synthesis by macrophages. In turn, an interleukin-4 (IL-4) or interleukin-10 (IL-10)-induced, so-called M2, or alternative macrophage activation mitigates pro-inflammatory gene expression and favors an immune suppressive, pro-resolving or pro-fibrotic macrophage phenotype (Röszer 2020c). Initial studies indicated that ATMs of the obese adipose tissue express various M1 macrophage-associated cytokines, such as TNFα and IL-6, that ignite inflammation and impair insulin responsiveness (Röszer 2020d).

For about two decades, the mainstream of ATM studies corroborated the concept of a metabolically harmful M1 activation of ATMs (Boutens and Stienstra 2016; Glass and Olefsky 2012; Lackey and Olefsky 2016; Lumeng et al. 2008; Morinaga et al. 2015; Osborn and Olefsky 2012; Shapiro et al. 2011). Albeit obese adipose tissue is rich in ATMs that secrete pro-inflammatory mediators, the transcriptional landscape of ATMs and the *in vitro* activated M1 macrophages are distinct (Aron-Wisnewsky et al. 2009; Coats et al. 2017; Li et al. 2019; Lumeng et al. 2008; Morris et al. 2011; Russo and Lumeng 2018; Shaul et al. 2010), since ATM activation can be elicited by various pathogen recognition receptors apart from TLR4

and IFNγ receptors, that yields a pro-inflammatory macrophage phenotype (Röszer 2020d, a). Of note, adipocytes also express pro-inflammatory genes and have inflammasome activation in obesity (Giordano et al. 2013), and adipose tissue inflammation may be mitigated independently from macrophage activation (Nickl et al. 2021).

Nevertheless, obesity leads to a pro-inflammatory ATM activation and the underlying mechanism may be associated with a macrophage response to lipid-overloaded adipocytes and pro-inflammatory signals of other immune cells of the adipose tissue (Lindhorst et al. 2021). In obesity, adipocyte volume and adipocyte number increase, along with the apoptotic death of lipid-overloaded adipocytes (Fig. 1A). Weight loss due to caloric restriction and diet rich in short chain fatty acids reduce pro-inflammatory ATM activation (Eslick et al. 2022; Kováčiková et al. 2011), plausibly by eliminating the trigger – i.e., lipid overload of adipocytes – of a pro-inflammatory ATM activation.

ATMs, such as any other tissue resident macrophages, may engulf apoptotic fat cells and fat cell-derived apoptotic bodies (Fig. 1B). Indeed, ATMs form multinucleated syncytia, so-called crown-like structures around dying adipocytes in the obese adipose tissue (Amano et al. 2014; Boutens and Stienstra 2016; Epelman et al. 2014; Fuentes et al. 2010; Glass and Olefsky 2012; Lee and Lee 2014; Li et al. 2013; Osborn and Olefsky 2012; Qiu et al. 2014; Waqas et al. 2017a) (Fig. 1A). Apoptotic cell uptake promotes anti-inflammatory macrophage activation in most tissues, however, the uptake of apoptotic adipocytes triggers a pro-inflammatory ATM activation (Röszer 2021).

Under physiological conditions adipocyte differentiation is associated with an increase in the expression of survival factors, rendering the mature adipocytes long-lived cells (Sorisky et al. 2000). In mouse, lipid-storing “white” adipocytes are more resistant to apoptosis than the thermogenic “brown” adipocytes (Nisoli et al. 2006). Human abdominal subcutaneous preadipocytes are more resistant to apoptosis than are omental preadipocytes, and the distinct

fat depots contain at least two different adipocyte populations based on their resistance to apoptosis (Tchkonia et al. 2005). Adipocyte apoptosis and necrosis become prevalent under pathological conditions, such as cytokine-induced or congenital lipodystrophy (Birk and Rubinstein 2006; Domingo et al. 1999; Vogel et al. 2011), and in obesity.

Hypertrophic adipocytes undergo apoptosis or secondary necrosis in obese adipose tissue. Adipocyte death may be a response to lipid overload, mitochondrial damage and to inflammatory cytokines. Lipid overload in hypertrophic adipocytes can lead to the "spillover" of lipids into the cytosol, leading to so-called lipotoxicity and, ultimately, apoptosis (Prieur et al. 2010). Failure of fatty acid oxidation and oxidative phosphorylation initiates the mitochondrial pathway of apoptosis in adipocytes (Qian et al. 2020), and also triggers inflammatory cell death, termed pyroptosis (Giordano et al. 2013; Qian et al. 2020). Impaired lipolysis and hypertrophy are hence powerful triggers of adipocyte apoptosis (Osuga et al. 2000). Lipotoxicity also triggers apoptosis of adipose tissue stem cells in aged fat (Guo et al. 2007).

Adipocyte cell death is an inflammation-generating process, and is a prelude to a sequence of events leading to obesity-associated metabolic diseases (Lindhorst et al. 2021; Vandanmagsar et al. 2011; West 2009). It is plausible that the first wave of apoptosis of adipocytes during the development of obesity is well controlled by the ATMs, and they are able to maintain an M2-like activation state (Shaul et al. 2010), and remove excess lipids (Kosteli et al. 2010). However, the prevalence of damage-associated molecules and pro-inflammatory lipid species in the dying adipocytes – that are engulfed by the ATMs – can switch the function of ATMs towards the release of inflammatory cytokines and reactive oxygen species, probably due to NFκB, interferon regulatory factors (IRFs) and inflammasome activation. Moreover, the capacity of ATMs to clear apoptotic cells may be exhausted in

obesity (Luo et al. 2019), and the apoptotic or necrotic cell debris aggravates local inflammation.

ATMs are not the sole immune cells of the adipose tissue: indeed, there is a complex adipose tissue immune cell niche, that contains mast cells, innate lymphoid cells, natural killer cells, T cells and B cells. A pro-inflammatory ATM activation may initiate a cascade of intercellular signaling events within this immune cell niche, leading to an uncontrolled inflammation. In turn, immune cells of the adipose tissue release cytokines that further augment the pro-inflammatory ATM activation. This may result in adipose tissue inflammation (Boutens and Stienstra 2016; Coats et al. 2017).

It was initially thought that M2 activated (pro-resolving, anti-inflammatory) ATMs would be beneficial in obesity, by reducing adipose tissue inflammation and increasing insulin sensitivity (Röszer 2020d). It was also assumed, that the lean adipose tissue was rich in M2 ATMs (Rosen and Spiegelman 2014), albeit only a limited number of M2 marker proteins are expressed by ATMs in the lean state (Röszer 2020d). Moreover, number of M2 ATMs is limited by their removal by type I innate lymphoid cells (Boulenouar et al. 2017), and the abundance of M2 ATMs may cause adipose tissue fibrosis and worsen the metabolic impairment in obesity (Spencer et al. 2010). Fibrosis in the breast adipose tissue may increase the risk for tumor development and tumor aggressiveness (Kuziel et al. 2023). Pro-fibrotic ATMs in the perivascular fat layer also aggravate fibrosis in heart failure and increase the progression of coronary atherosclerosis (Fu et al. 2023). There are various negative feedback mechanisms (Zheng et al. 2015), including IL-4/STAT6 signaling itself (Arpa et al. 2009) that limit the abundance of M2 macrophages in tissues.

Single-cell sequencing data, and the growing body of studies using flow cytometry, macrophage-specific knockout models show that there are various ATM subsets, which show varying degree of M1 and M2 traits (Blaszczak et al. 2019; Huang et al. 2016; Li et al. 2019).

Depending on the state of the obesity, the ATM population may be dominated by M2 ATMs, a mixture of M1 and M2 ATMs and eventually can be dominated by M1, inflammatory, "metabolically activated" ATMs (Aron-Wisnewsky et al. 2009; Basinska et al. 2015; Chung et al. 2014; Coats et al. 2017). There are also depot-specific differences between ATM pools (Bigornia et al. 2012).

Immune-suppressive (often termed as M2) macrophages support tumor growth (Röszer 2020c), and accordingly, ATMs in the breast adipose tissue expressing M2 macrophage genes increase tumor progression (Li et al. 2023). Independent of obesity, an increased number of ATMs of the breast adipose tissue worsens breast cancer prognosis (Lin et al. 2021). It is also postulated, that ATM-derived cytokines, such as IL-6, IL-10, TGFβ, and mediators such as VEGF and enzymes such as metalloproteinases may support the development of malignant cell proliferation (Singh et al. 2022). ATMs thereby have more complex roles in adipose tissue functioning than inflammation control and interfering with insulin sensitivity.

The simplified concept of antagonistic M1/M2 ATM effects on systemic metabolism is further challenged by the role of pro-inflammatory signal mechanisms that are required for physiological adipose tissue development (Babaei et al. 2018; Sun et al. 2018) (Fig. 2A). ATMs stimulate thermogenic and fat catabolizing adipocyte activities after birth by releasing IL-6 and ablation of ATMs in newborn mice leads to the loss of thermogenic fat cells in the subcutaneous fat depot (Yu et al. 2019). Loss of thermogenic fat is associated with adiposity (Gyurina et al. 2023; Honecker et al. 2022; Sacks and Symonds 2013). Increased adiposity at the first year of life, and an early adiposity rebound before 5.5 years year of life increase the probability of obesity as a young adult (Carolan-Olah et al. 2015; Charney et al. 1976; Dietz 1994; Eriksson et al. 2003; Fall 2006; Geserick et al. 2018; Landgraf et al. 2015; Pietrobelli et al. 2017; Rolland-Cachera et al. 1984; Siervogel et al. 1991). Importantly, ATMs are already present in the fat depots after birth (Waqas et al. 2017b; Yu et al. 2019), concomitantly with the

abundance of thermogenic adipocytes in both mouse and human (Gyurina et al. 2023; Hoang et al. 2021). It is plausible that ATMs support thermogenic fat development in the early postnatal life (Fig. 2A).

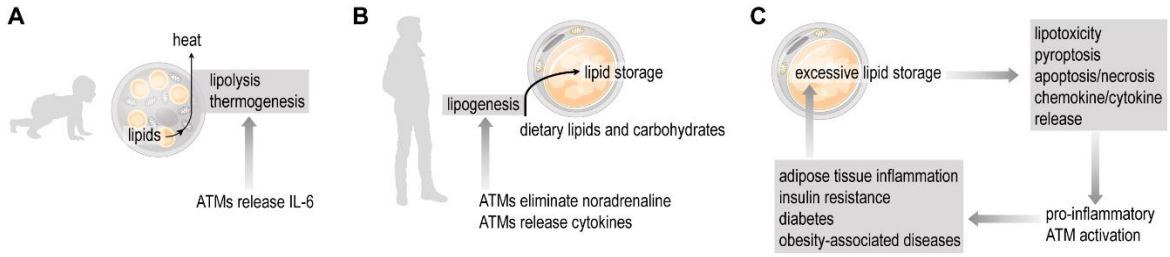

Figure 2. ATM functions under physiological and pathological conditions

(**A**) ATMs promote thermogenesis and lipolysis in the early postnatal development of the adipose tissue. (**B**) In the adult and aging adipose tissue ATMs support energy storage in neutral lipids. (**C**) In obesity the lipid-overloaded adipocytes induce a pro-inflammatory ATM activation that may induce adipose tissue inflammation, insulin resistance and obesity-associated pathologies. As a result, fat accumulation may further increase, initiating a vicious cycle.

Ontogeny of adipose tissue macrophages

Origin of ATMs is still poorly understood, despite an uncontrolled expansion of the ATM pool worsens obesity-associated diseases. In the visceral and subcutaneous adipose tissues – that are relevant in obesity – the number of ATMs may increase as a result of monocyte infiltration and local proliferation of ATMs (Amano et al. 2014; Haase et al. 2014; Waqas et al. 2017b). Hypertrophic adipocytes release chemotactic and pro-inflammatory signals, that stimulate bone marrow monocyte development and attract monocytes to the obese fat depots, eventually increasing the monocyte-derived ATM pool (Lumeng et al. 2007; Nagareddy et al. 2014). The

first wave of ATMs however develops from hematopoietic cells of the yolk sac – and probably of the fetal liver – and fetal ATMs persist in the newborn (Waqas et al. 2017b). ATMs retain the ability of self-replenishment and proliferate in response to interleukin-6 (IL-6) and neuropeptide FF (NPFF) (Röszer 2018, 2020b; Waqas et al. 2017a; Waqas et al. 2017b). NPFF is an appetite regulating hormone, that is released from the endocrine pancreas and from the hypothalamus (Waqas et al. 2017a). Later in infancy, the fetal ATMs are accompanied – and plausibly gradually replaced – by monocyte-derived ATMs (reviewed in (Röszer 2020b)). Interestingly, the interscapular brown adipose tissue, the largest thermogenic fat depot in rodents, is scarce in macrophages (Alcalá et al. 2017; Waqas et al. 2017b). ATMs of the breast may derive from circulating monocytes, or resident macrophages of the gland stroma (Linde et al. 2018). Origin of ATMs in the perivascular fat depots is still to be elucidated (Röszer 2020b).

Physiological functions of ATMs

In contrast to the abundance of studies on the metabolic harms caused by pro-inflammatory ATMs of the obese adipose tissue, only a small fraction of the ATM-related literature deals with ATM functions in the lean adipose tissue. In brief, ATMs appear to control the changes physiological functions of the developing adipose tissue. After birth, when the adipose tissue depots have an active lipolysis and thermogenesis, ATMs promote thermogenic “brown” or “beige” adipocyte development (Hoang et al. 2022; Yu et al. 2019) (Fig. 2A).

In adulthood and with aging, when fat storage becomes more relevant that thermogenesis and lipolysis, ATMs antagonize lipolysis and inhibit cold-induced thermogenesis (Camell et al. 2017; Pirzgalska et al. 2017) (Fig. 2B). It is generally assumed, that the lean fat contains anti-inflammatory ATMs, that express some markers of the M2 macrophages, such as arginase-1 and CD206. However, ATM-derived pro-inflammatory

signals are necessary for adipose tissue development, since a transient inflammatory signaling is essential for physiological adipogenesis (Chung et al. 2017).

It has been shown that elimination of ATMs with clodronate liposome uptake shifts subcutaneous adipose tissue development towards a fat storing state in newborn mice, suggesting that ATMs support the maintenance of the lean state (Yu et al. 2019). Mechanistically, ATMs synthesize platelet activating factor (PAF) that stimulates IL-6 release, that eventually activates the transcription of genes required for mitochondrial biogenesis and thermogenesis in neighboring adipocytes (Yu et al. 2019). This process is termed as adaptive thermogenesis, or adipocyte browning: a process that allows dissipation of energy stored in fat in form of heat. Albeit cold exposure increases the number of M2-activated ATMs (Hui et al. 2015), these ATMs do not affect adaptive thermogenesis (Fischer et al. 2017). In the aging adipose tissue, that stores fat rather metabolizing it, ATMs and macrophages in the sympathetic ganglia eliminate noradrenaline, a key signal of lipolysis and thermogenesis (Camell et al. 2017; Pirzgalska et al. 2017).

Safe disposal of apoptotic cells is another M2 function for ATMs, and obesity-inducing substances may also impair this function (Röszer 2017).The long life span of adipocytes however does not keep ATMs busy with this task. ATMs also release neuropeptide Y (Singer et al. 2013), and IGF-1 (Chang et al. 2016), suggesting an endocrine function for ATMs. However, that idea has not been corroborated by recent research. For instance, an initial finding on noradrenaline production of ATMs has been disproved by a more recent study (Fischer et al. 2017).

Albeit emphasis was given to the impact of ATM activation, and M1 macrophages were tagged as “metabolically harmful” and their M2 counterparts as “metabolically beneficial”, it is plausible that the metabolic effect of ATMs depends on specific enzymes they possess (e.g.,

enzymatic synthesis of PAF from dietary lipids and enzymatic degradation of noradrenaline), and signals (e.g., hormones) they release, rather to their activation state.

Expression of M1 and M2 markers are regulated by a wide range of signals such as hormones, lipid metabolites, fatty acids, cytokines, and microbial products (Röszer 2020a). Physiologically it appears that the effect of macrophage activating signals is antagonized by counter-regulatory mechanism. For instance, LPS released by the gut microbiota to the blood stream induce the expression of some M1 marker genes in ATMs under physiological conditions (Caesar et al. 2012). In turn, *Lactobacilli* may migrate into the adipose tissue, and mitigate a pro-inflammatory ATM activation (Huang et al. 2017). Moreover, ATMs and regulatory T cells produce IL-10 in the lean adipose tissue, which is a possible endogenous signal for suppressing an immune response in ATMs against gut microbiota (Liu and Nikolajczyk 2019; Russo and Lumeng 2018).

Blind spots in ATM biology

There are several unexplored aspects of ATM biology, especially in the therapeutic or diagnostic use of ATMs. Increased ATM number and inflammatory hyperactivation of ATMs are core traits that make ATMs potentially harmful for the systemic metabolism (Fig. 2C). Having pharmacological intervention for a targeted reduction of ATM number is however a yet to be achieved goal. It is known that bariatric surgery, regular exercise, and a diet rich in polyunsaturated fatty acids reduce ATM number and induce profound changes in the immune cell composition of the adipose tissue (Frikke-Schmidt et al. 2017). Weight loss due to caloric restriction induces a transient increase in ATM number in mice, that is followed by a steady reduction in ATM number (Kosteli et al. 2010). It appears that lipolysis and the eventual release of free fatty acids are the signals for the transient accumulation of ATMs (Kosteli et al. 2010).

The underlying mechanisms, such as the cell cycle regulation and life span of tissue macrophages are still incompletely understood. Moreover, we lack ATM-specific markers, that would allow a targeted elimination of the ATMs or a cell-specific drug delivery to ATMs.

Histopathology evaluation of adipose tissue specimens obtained with needle biopsy or removed during elective surgery may be used for the assessment of adipocyte size and number, adipocyte apoptosis, thermogenic and lipogenic potential of the adipocyte, number and activation state of ATMs may provide an accurate prognosis in obesity (Gyurina et al. 2023; Kováčiková et al. 2011). Adipose tissue-based personalized histopathology is however still not in use in clinical settings. As of technical limitations to study ATMs, it is worth to mention that we lack immortalized ATM cell lines, and methods for a lineage specific ablation of ATMs. Moreover, proper discrimination of monocytes, mast cells and ATMs is challenging due to the overlap of their marker proteins (Röszer 2020e). How ATMs respond to obesogenic signals of the environment (Ampem et al. 2019), or to viruses that can profoundly affect adipose tissue functioning (e.g., thermogenesis and lipolysis) (Atkinson 2007) are still largely unexplored aspects of ATM biology. And lastly, despite the enormous functional and developmental differences between the distinct fat depots of the human body (Cohen and Kajimura 2021), we lack an insight into depot-specific ATM functions. It is also plausible that ATMs have functions that are dependent on the developmental stage of the adipose tissue, thus ATMs may have distinct effects after birth, in adulthood and during aging (Röszer 2022).

Authorship

Conceptualization and writing: TR.

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