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Adipose tissue macrophages: phenotypic plasticity and diversity in lean and obese states

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Abstract

Purpose of review—Proinflammatory adipose tissue macrophages (ATMs) contribute to obesity-associated disease morbidity. We will provide an update of the current state of knowledge regarding the phenotypic and functional diversity of ATMs in lean and obese mice and humans.

Recent findings—The phenotypic diversity of ATMs is now known to include more than two types requiring an expansion of the simple concept of an M2 to M1 shift with obesity. Potential functions for ATMs now include the regulation of fibrosis and response to acute lipolysis in states of caloric restriction. Novel pathways that can potentiate ATM action have been identified, which include inflammasome activation and the response to lipodystrophic adipose tissue. Studies provide a new appreciation for the ability of ATMs to respond dynamically to the adipose tissue microenvironment.

Summary—ATMs play a key role in shaping the inflammatory milieu within adipose tissue, and it is now apparent that ATM heterogeneity is acutely shaped by the adipose tissue environment. To account for the new findings, we propose a new nomenclature for ATM subtypes that takes into account their diversity.

Keywords

adipose tissue macrophages; inflammation; obesity

Introduction

Obesity contributes to systemic insulin resistance and metabolic disease partly because of chronic activation of inflammatory pathways in expanding visceral adipose tissue [1,2]. The cellular mediators of obesity-induced inflammation include an array of leukocytes which reside within fat and accumulate during obesity. However, quantitatively, adipose tissue macrophages (ATMs) are the predominant leukocyte population in fat [3,4•]. A significant number of ATMs are present in lean, metabolically normal humans and rodents [5,6•]

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implying that not all ATMs are inherently proinflammatory and deleterious to metabolic function. Current evidence indicates that ATMs undergo both quantitative increases in fat and qualitative changes in their activation state to promote inflammation during obesity [5,7•].

Here, we discuss the phenotypic heterogeneity of ATMs in both lean and obese states and describe how obesity tilts the balance toward a proinflammatory environment in fat. We define ATMs as macrophages in adipose tissue that co-express F4/80 and CD11b in mice or F4/80 and CD68 in humans [4•,8]. New findings will be highlighted that provide an insight into how ATM populations are dynamically regulated by signals unique to the adipose tissue environment. Taking the latest data into account, we propose a new nomenclature for ATMs that captures their diversity in both mice and humans.

The M2 to M1 'phenotypic switch' of adipose tissue macrophages with obesity

To facilitate immune function and maintain tissue homeostasis, macrophages adapt a wide range of activation states that can be classified within the M1/M2 model of macrophage polarization [9]. 'Classically activated' M1 macrophages are programmed for microbicidal activity and produce nitric oxide and proinflammatory cytokines (e.g., TNF-α and IL-12) in response to inflammatory stimuli such as lipopolysaccharide (LPS) and interferon-γ. By contrast, Th2 cytokines (e.g., IL-4 and IL-13) generate 'alternatively activated' M2 macrophages, which attenuate inflammatory responses to maintain tissue homeostasis. It is important to note that these polarization states are extremes of a spectrum, and macrophages display many intermediate phenotypes *in vivo* that are strongly influenced by the tissue microenvironment [9,10].

When examining the entire population of ATMs in visceral fat, we and others have found evidence that obesity alters the phenotype of ATMs from an M2 to an M1 polarized state in mice [5,7•,11•,12•]. In lean mice, resident ATMs express markers of M2 macrophages [CD206 (mannose receptor), MGL1 (macrophage galactose type C-type Lectin/CD301a/CLEC10A), and *Arg1*] and are interspersed between adipocytes in all adipose tissue depots [13,14•]. The beneficial function of these resident ATMs in nutrient metabolism was demonstrated by the observations that PPARγ-deficient and PPARδ-deficient mice, which have impaired M2 polarization, are more susceptible to diet-induced inflammation and insulin resistance [15–17].

With obesity, $CD11c^+$ ATMs are recruited to fat in a C–C chemokine receptor 2 (CCR2)-dependent manner [18] and cluster around dead adipocytes to form crown-like structures (CLS) [19]. $CD11c^+$ ATMs have increased the expression of many M1 genes relative to $CD11c^-$ ATMs (e.g., *Il1b*, *Il6*, and *Nos2*) [4•,5,7•,11•,20]. The importance of this ATM subtype has been supported in human studies where $CD11c^+$ ATMs are associated with glucose intolerance and metabolic syndrome [4•,21•]. In addition, ablation of $CD11c^+$ cells improved insulin sensitivity and attenuated inflammation in obese mice [22].

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The increased ratio of $CD11c^+$ ('M1') to $CD11c^-$ ('M2') ATMs during obesity tips the balance toward a proinflammatory environment in fat and is a central feature of the M2 to M1 'phenotypic switch'. It should be noted that some studies present evidence that this model is inaccurate and argue that ATMs have either mixed activation states or states that are not consistent with a strict M1 or M2 phenotype [23••,24•,25]. Overall, we feel that the M1/M2 model remains a good starting point from which to tease apart ATM biology. Many factors may contribute to differences between studies including differences in ATM definitions, ATM isolation techniques and conditions, flow cytometry protocols, and the reliance on quantitative RT-PCR as the sole measure of ATM activation state.

Adipose tissue fibrosis and $CD11c^+CD206^+$ adipose tissue macrophages

The diversity of ATM subtypes has been expanded by recent studies suggesting that $CD11c^+$ ATMs may be further subdivided based on the expression of M2 macrophage surface markers CD206 and MGL1 [4•,24•]. The identification of lipid-laden $CD11c^+CD206^+$ ATMs in mice supports the concept that some ATMs may fall in the middle of the M1/M2 continuum [4•,12•]. The gene expression profile of $CD11c^+MGL1^{mid}$ ATMs in mice suggests that these ATMs upregulate M2 genes involved in tissue remodeling and repair [24•]. In humans, both $CD86^+CD206^+$ and $CD150^+$ (M2c) ATMs were found in fibrotic areas in visceral fat [14•]. *In vitro* studies also suggested that adipocyte-derived signals could induce a profibrotic, M2 gene signature in human macrophages.

These observations align with the growing body of evidence that suggests dysregulation of the extracellular matrix (ECM) around adipocytes is a feature of obesity. ECM deposition strongly influences the flexibility of adipocytes to store lipids [26,27]. Divoux *et al.* [28••] noted significant fat depot-specific differences in fibrosis in obese humans. Visceral fat had more fibrosis than subcutaneous fat and the amount of fibrosis negatively correlated with adipocyte size and triglyceride content. Interestingly, omental (visceral) fat contained hypercellular fibrotic regions containing large quantities of ATMs as well as mast cells. Whether these cells cooperate and communicate to promote inflammation as seen in other settings (e.g., pulmonary disease [29]) will have to be further explored. Collectively, these new studies highlight the need to further understand how different ATM subtypes regulate the remodeling of the ECM within adipose tissue.

Adipose tissue macrophage accumulation in response to lipolysis

Another example of how ATMs may interact with the adipose tissue microenvironment comes from new data linking ATM accumulation and adipocyte lipolysis. With obesity, adipocytes become insulin resistant resulting in dysregulated lipolysis and free fatty acid release [30]. By being juxtaposed to dysfunctional adipocytes, ATMs are poised to respond to acute and chronic changes in lipolysis during obesity. Supporting this view is the finding that acute lipid infusion in lean, healthy adults induced production of proinflammatory plasminogen activator inhibitor-1 (PAI-1) in ATMs [6•].

In obese mice, Kosteli *et al.* [31••] found that caloric restriction or an overnight fast induced significant demand lipolysis, leading to the rapid and transient accumulation of ATMs. This is consistent with a previous report indicating that β-adrenergic-induced lipolysis increases

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ATM content in fat [32]. Interestingly, the ATMs that are recruited to fat during short-term caloric restriction (3–7 days) in mice were not associated with any clear change in inflammation [31••]. However, another study found that 3 weeks of caloric restriction in mice reduced the inflammatory profile of adipose tissue and decreased *Tnfa* and *Il1b* gene expression in $CD11c^+$ ATMs [7•]. These changes were independent of quantitative decreases in either $CD11c^+$ or $CD11c^-$ ATMs. These studies reveal a surprising degree of phenotypic plasticity for ATMs and suggest that lipolysis associated with calorie restriction activates a unique type of immune response.

Collectively, these findings suggest that dysregulated lipolysis *per se* may not completely explain inflammatory activation of ATMs during obesity. It has yet to be established whether lipolysis-induced changes during caloric restriction in ATMs are mechanistically similar or different from the processes that govern ATM accumulation with chronic high fat diet feeding, at least in mice. Establishing whether these rapid changes in macrophage recruitment and phenotype occur in human obesity with caloric restriction or fasting are a clear next step, although 3 months of surgical-induced weight loss has already been shown to decrease the ratio of $CD40^+$ (a putative M1 marker) to $CD206^+$ (M2) ATMs [33].

Adipose tissue macrophage triglyceride metabolism: friend or foe?

The close association between triglyceride-laden $CD11c^+$ ATMs and dead adipocytes suggests that ATM function may be coupled to lipid metabolism and/or lipid scavenging. Lipidomic analysis of lipid-rich ATMs from leptin-deficient (*ob*/*ob*) mice demonstrated that obesity increases the abundance of cytotoxic lipid species (e.g., free cholesterol, short-chain fatty acids, and saturated triglycerides) in ATMs and decreases the accumulation of protective lipids, such as long chain and polyunsaturated triglycerides [12•]. This study raises the hypothesis that accumulation of lipotoxic species in ATMs during obesity promotes inflammation, and suggests that altered lipid metabolism in ATMs may be important for the ‘phenotypic switch’.

On the contrary, Koliwad *et al.* [34•] suggested that increasing macrophage triglyceride storage improves metabolism. Overexpression of diacylglycerol acyltransferase 1 (DGAT1) in macrophages was sufficient to protect mice from high fat diet-induced insulin resistance and adipose tissue inflammation and limits M1 activation by palmitate. *Dgat1* expression was shown to be regulated by anti-inflammatory PPARγ, suggesting a coupling between macrophage triglyceride storage mechanisms and an anti-inflammatory state. Combining these data with the identification of GPR120 as an ω-3 fatty acid receptor that can shift macrophages from an M1 to an M2 profile ([35] and [36] in this review), perhaps more attention should be placed on how lipids attenuate macrophage inflammation. Further studies are required to resolve these potentially competing views of macrophage lipid response and storage.

Inflammasome activation and intracellular ceramides

In addition to lipids, dying adipocytes may produce other signals to trigger an innate immune response. ‘Danger signals’ from stressed or dead cells mobilize macrophages to contain the tissue damage [37]. The Nod-like receptor (NLR) family of pattern recognition

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receptors participate in this process and trigger the cryptopyrin/Nalp3 inflammasome in macrophages to activate caspase-1 and induce IL-1β and IL-18 production [38].

Caspase-1 activity and IL-1β expression in adipose tissue are both increased in obese mice, whereas *Nalp3*-deficient and *Casp1*-deficient mice are resistant to high fat diet-induced inflammation [39••,40•]. Although ATM number was unaltered in obese *Nalp3*$^{-/-}$ mice, pro-inflammatory gene expression (e.g., *Tnfa* and *Ccl20*) was decreased and *Arg1* and *Il10* (M2 genes) expression was increased in visceral fat [39••]. This suggests that the NALP3 inflammasome promotes an inflammatory phenotype in ATMs. Like many other molecular pathways, a direct effect of inflammasome activation on adipocyte function cannot be excluded, as caspase-1 deficiency alters adipogenesis and adipocyte insulin sensitivity [40•].

In-vitro studies also identified a link between ceramide accumulation and the induction of caspase-1 activity in macrophages [39••]. This is particularly interesting given that the anti-inflammatory effects of adiponectin have been shown to involve increased ceramidase activity and reduced ceramide accumulation in multiple tissues [41•]. Fully understanding the links between ceramide-mediated inflammasome activation, obesity-induced inflammation, and metabolic dysfunction will require further dissection.

Does the M1/M2 paradigm faithfully describe adipose tissue macrophage heterogeneity?

Although the M1/M2 paradigm and the ‘phenotypic switch’ model are useful starting points for understanding ATM biology, the recent findings presented above indicate that this model may not be sufficient to describe the biology of ATMs in all contexts. Further complicating things is the lack of overlap between M1/M2 definitions in murine and human macrophages [42]. In addition, the identification of the classical myeloid dendritic cell (mDC) marker CD11c on ATMs calls into question whether these ATMs are macrophages or dendritic cells [43,44]. It should be noted that this problem is not unique to this field as the distinction (or lack there of) between macrophages and dendritic cells is of significant debate among immunologists even in well defined lymphoid tissues [45,46].

On the basis of the unique niche and properties of ATMs relative to other tissue macrophages, we propose a new nomenclature system for ATMs with the hope that this will improve communication between investigators and help advance the field. Our proposed nomenclature for human (Table 1) and mouse (Table 2) ATMs captures the known diversity of ATMs *in vivo*, but also provides room for the discovery of additional ATM subtypes and activation states and frees the field from the known limitations of the M1/M2 paradigm. This classification scheme relies on the objective measures of surface marker expression, tissue localization, and lipid content. In this section, we provide an overview of the four best characterized types (type 1a, type 1b, type 2, and type 3) of ATMs thus far identified in mice and humans.

Type 1 ATMs (formerly M1 ATMs) express CD11c, localize to CLS in obese mice, and have increased lipid content. Many, but not all, ‘classical’ M1 genes are upregulated in type 1 ATMs relative to other subtypes. Kinetic studies have shown that type 1 ATMs

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accumulate rapidly in fat relative to other ATM subtypes [13] and that their recruitment is CCR2 dependent [18]. However, it is currently unclear whether the decreased accumulation of type 1 ATMs in *Ccr2*$^{-/-}$ mice is because of the inability of monocytes to sense its ligand monocyte chemoattractant protein 1 (MCP1/CCL2) secreted by fat or because of the lack of circulating monocytes in these mice which is attributed to defects in monocyte egress from the bone marrow [47].

Type 1 ATMs in both mice and humans can be further subdivided based on the absence (type 1a) or presence (type 1b) of M2 surface markers CD206 and/or MGL1. Although both types localize to CLS, type 1a and type 1b ATMs have unique gene expression patterns and potentially have different functions [4•,24•]. In humans, CD40 [33] and CD86 [14•] may also be markers of type 1a ATMs.

Type 2 ATMs (formerly M2 ATMs) express low levels of CD11c, but express high levels of CD206 and/or MGL1. Type 2 ATMs are the dominant ATM population in lean mice and localize outside of CLS in obese adipose tissue. This subtype accumulates little lipid during obesity [12•]. Relative to type 1 ATMs, type 2 ATMs have slower rates of recruitment to fat [13,24•] and are not dependent upon either CCR2 or MGL1 for trafficking to fat in mice [5,48]. Although some variability exists in the literature, murine type 2 ATMs generally express higher levels of *Arg1* and *Ym1* than do type 1a and type 1b ATMs. CD150 [14•] and the scavenger receptor CD163 [25,33] may also be a marker of type 2 ATMs in humans; however, only CD206 is a validated M2 marker in human macrophages [42].

In mice, a third population of ATMs (type 3) that does not express either CD11c or CD206/MGL1 has been reported [11•]. Like type 1 ATMs, type 3 ATMs localize to CLS and have high lipid content but express *Ym1* and *Arg1* and proinflammatory cytokines such as IL-1β. In the only study characterizing them, type 3 ATMs were reported to be the dominant ATM subset in obese mice, which differs from many other reports.

Additional ATM subtypes may exist that are not currently captured in our scheme. For example, by surface markers, ATMs from lipodystrophic mice are predominantly type 1 ATMs [23••]. However, expression profiling demonstrated unique properties of lipodystrophic ATMs compared with ATMs from obese mice. These ATMs may ultimately deserve characterization as a distinct subtype (e.g., type 4 or 5), but further details about their phenotype are required.

Conclusion

Our understanding of the inflammatory mediators that influence adipose tissue biology and insulin sensitivity continues to increase at a rapid pace. This is taking place concurrently with efforts to fully characterize the interactions that occur between cellular components of adipose tissue. The unique adipose tissue environment in which ATMs reside dynamically alters their function as an inflammatory effector population in fat. Therefore, the original model of the ‘phenotypic switch’ in ATMs, which was once restricted to the M1/M2 paradigm, must continue to be expanded as new ATM populations are functionally characterized and as new regulators are identified. We hope that this review underscores the

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complex heterogeneity of ATMs and that the proposed nomenclature will advance the development of new models to explain how the various ATM populations contribute to the progression of obesity-induced inflammation and metabolic dysfunction.

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Key points

- The phenotype of ATMs is augmented by acute and chronic changes that occur within adipose tissue, which include fibrosis, weight loss, and lipid flux from adipocytes.
- Metabolic cues such as adipocyte lipolysis and ‘death signals’ can promote ATM recruitment and activation.
- New ATM subtypes have been identified that require an expansion of the original model of the M2 to M1 ‘phenotypic switch’ of ATMs during obesity.
- A new nomenclature system for ATMs is proposed to improve communication between investigators and help advance the field.

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Table 1

Adipose tissue macrophage subtypes in humans

	Type 1a ATMs	Type 1b ATMs	Type 2 ATM
Surface markers	$CD11c^{+}CD206^{-}(CD86^{+}CD40^{+})$	$CD11c^{+}CD206^{+}$	$CD11c^{-}CD206^{+}(CD150^{+})$
Change with obesity	↑	↑	↓ or =
Gene expression	*Cd11a*	*Cd86*, *Cd1c*, *H2Ab1*	*Cd34*, *Cd163*
Secretion	n.d.	↑ IL-1β, IL-6, IL-10, TNF-α, CCL3 (vs. type 2)	n.d.
Localization	CLS	CLS	Interstitial
References	[14•,33]	[4•,14•]	[4•,14•,33]

ATMs, adipose tissue macrophages; CLS, crown-like structures; n.d., no data; ↑, increased; ↓, decreased; =, unchanged.

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Table 2

Adipose tissue macrophage subtypes in mice

	Type 1a ATMs	Type 1b ATMs	Type 2 ATMs	Type 3 ATMs
Surface markers	$CD11c^{+}CD206^{-}MGL1^{-}$	$CD11c^{+}CD206^{+}$ $MGL1^{mid}$	$CD11c^{-}CD206^{+}MGL1^{hi}$	$CD11c^{-}CD206^{-}$
Change with obesity	↑	↑	↓ or =	↑
Gene expression	*Tnfa*, *Il6*, *Nos2*, *Ccr7*	*Il12*, *Arg1*	*Arg1*, *Mgl1/2*, *Il10*, *Ccl8*, *Cx3cl1*, *Ccl2*	*Arg1*, *Chi3l3*, *Ccr2*, *Cx3cr1*, *Ccr1*, *Ccr9*
Localization	CLS	CLS	Interstitial	CLS
Recruitment kinetics in obesity	Fast	n.d.	Slow	n.d.
Lipid content	High	High	Low	n.d.
References	[11•,12•,13,24•]	[12•,24•]	[11•,12•,13,24•]	[11•]

ATMs, adipose tissue macrophages; CLS, crown-like structures; n.d., no data; ↑, increased; ↓, decreased; =, unchanged.