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Macrophage ontogeny and functional diversity in cardiometabolic diseases.

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Summary

Macrophages are the dominant immune cell types in the adipose tissue, the liver or the aortic wall and they were originally believed to mainly derived from monocytes to fuel tissue inflammation in cardiometabolic diseases. However, over the last decade the identification of tissue resident macrophages (trMacs) from embryonic origin in these metabolic tissues has provided a breakthrough in the field forcing to better comprehend macrophage diversity during pathological states. Infiltrated monocyte-derived macrophages (moMacs), similar to trMacs, adapt to the local metabolic environment that eventually shapes their functions. In this review, we will summarize the emerging versatility of macrophages in cardiometabolic diseases with a focus in the control of adipose tissue, liver and large vessels homeostasis.

Introduction

Cardiometabolic diseases (CMDs) remain the largest cause of death worldwide. They are multifactorial diseases influenced by a number of metabolic risk factors as well as immune cell activation, including macrophages. Therefore, understanding the mechanistic role of macrophages has always been imperative in the cardiometabolic field in order to uncover effective ways to reduce CMDs burden.

Macrophages are ubiquitously present across organs and play key roles in both health and disease [1]. Tissue-resident macrophages (trMacs), that develop during embryonic or early postnatal stages, can be distinguished from the macrophages that derived from monocytes upon inflammation [1]. However, such classification is sometimes oversimplified depending on the tissue and pathological state studied. Macrophages are plastic cells that can adopt a wide range of phenotypes depending on their environment. Indeed, the impact of tissue environment on resident macrophage heterogeneity *in vivo* has been previously proposed [2–4] and has only recently been thoroughly documented [5,6]. Divergent gene expression landscapes across different trMacs clearly support the idea of local macrophage plasticity at the steady state [5–7]. However, the transcriptional and molecular basis underlying such diversity is still not fully understood, and we are only starting to better appreciate the relationship between the tissue environment and trMac phenotypes. In addition, during pathological states, macrophages, whether they are tissue-resident or recruited monocyte-derived cells, can also respond to additional stimuli that further imprint diversity on macrophages. In metabolic tissues, the nutrient environment has emerged as a driver of macrophage reprogramming during CMDs, modulating their key effector functions. As a result, the maintenance of tissue homeostasis may be perturbed depending on the pro- or anti-resolutive functions macrophages adopt to face their environment.

In this review we will discuss recent progress regarding how macrophage subsets and their plasticity impact on tissue function and remodeling. These findings will be illustrated in the context of cardiometabolic diseases, in which macrophage effector and metabolic functions are exquisitely intertwined to face and adapt to their environment.

Adipose tissue macrophages in obesity.

The white adipose tissue (WAT) has a central role in metabolic adaptation to nutritional cues because of its ability to store energy as triglycerides. The unprecedented growth of obesity and metabolic disease worldwide associated with a low-grade inflammation has focused attention on the immune cells that comprise the stroma vascular fraction (SVF) of this dynamic endocrine organ [8]. Indeed, the majority of the pro-inflammatory cytokines produced in the obese adipose tissue are secreted from the SVF, including adipose tissue macrophages (ATMs).

Origin and diversity of adipose tissue macrophage subsets in obesity.

At the steady state, a major trMac population closely associated with the blood vasculature inhabit the visceral WAT [9], but their origin and maintenance mode (monocyte input versus self-renewal) still remain poorly defined. A study conducted in *Xenopus laevis* suggested adipose trMacs were from embryonic origin and capable to self-renew by proliferating locally [10] (**Figure 1**). Nevertheless, while WAT trMacs have been sparsely studied, ATMs as a whole have retained much attention for the last two decades. The original observation of the recruitment and infiltration of circulating monocytes into obese WAT, which exacerbates the inflammatory burden, led to the hypothesis that ATMs originated from bone marrow myelopoiesis [11–13] (**Figure 1**). A recent study reported that diet-induced obesity fueled tissue inflammation not only by enhancing monocyte recruitment but also by triggering

epigenetic modulation and NLRP3-dependent activation of bone marrow (BM) myeloid progenitors to promote monocyte production [14]. These findings are most likely linked to the metabolic requirement of myelopoiesis [15,16] that not only provide intermediate metabolites necessary to generate and modify epigenetic marks [17] but also to prime and activate the NLRP3 inflammasome [18,19]. Thus, monocyte mobilization and their recruitment to the obese WAT favors monocyte-derived macrophages (moMacs) accumulation [20], but trMacs contribution to the ATM pool is still not well understood. Beside monocyte recruitment, the ATM pool may also expand by proliferation [21]. Enhanced expression of MCP-1 in obese adipose tissue is also a key driver of monocyte recruitment as evidenced in *Mcp1*-deficient mice [22] as well as in mice deficient for *Ccr2* [20]. Importantly, both *Mcp1*- and *Ccr2*-deficient obese animals had improved insulin sensitivity and hepatosteatosis [20,22]. Similar improvements in insulin sensitivity were observed after ablation of CD11c⁺ myeloid cells [23] or after limiting monocyte recruitment to adipose tissue in high-fat diet fed *Itgam*-deficient mice [24]. Nevertheless, recent studies have challenged the causality of these associations by showing that high-fat diet-fed *Ccr2*-deficient mice co-housed with their littermate controls did not show improved insulin sensitivity despite reduced circulating monocytes [25,26]. One potential explanation could be attributed to the role of CCR2 in promoting infiltration of colonic pro-inflammatory macrophages upon high-fat diet feeding that perturbs intestinal permeability, microbial antigen leakage and subsequent insulin sensitivity [27]. Overall, while ATMs are key drivers of obesity-induced metabolic alterations, their origin and function are still not fully understood.

Newly recruited adipose tissue macrophages and their zonation to ‘crown-like structures’ in obesity.

An elevated ratio of pro-inflammatory macrophages to anti-inflammatory/pro-resolving macrophages was originally described in obese WAT, which could contribute to the pro-inflammatory milieu and serve as a spatiotemporal signal to the accumulation of distinct ATM subtypes [28,29]. Intriguingly, ATMs surrounding dead adipocytes, which form ‘crown-like structures’ (CLS), are thought to be a major source of pro-inflammatory mediators [30–32] (**Figure 1**). These observations contrast with *in vitro* experiments showing that clearance of apoptotic debris by macrophages (i.e. efferocytosis) contributes to resolution of inflammation [33]. However, it could reflect the inefficiency of macrophages to handle the large amount of lipids and other metabolites released by dying adipocytes in the obese WAT environment [34]. The frequency of adipocyte death in WAT increased from 0.1% at baseline to 16% after 12 weeks of high-fat diet and coincided with increased MCP-1 levels, a key driver of monocyte recruitment, and insulin resistance [32]. Elevated IL-6 and IL-10 levels in CLS could also contribute to ATM accumulation by increasing their proliferative potential [35].

Single-cell RNA sequencing (scRNAseq) recently extended our ability to better characterize immune cell diversity and uncover disease-associated leukocyte subsets. Notably, scRNAseq was performed on CD11b⁺ Ly-6C⁻ ATMs before or after 12 weeks of diet-induced obesity [36] as well as on CD45⁺ immune cells in the SVF fraction of WAT after 6, 12 and 18 weeks of diet-induced obesity [37]. As expected, there was a dramatic increase in the proportion of macrophages after high-fat diet in these two studies [36,37]. A CD9⁺ CD63⁺ ATM subset accumulated in CLS of high-fat diet-fed mice and was associated with a strong lipid metabolism and phagocytosis transcriptomic signature, leading to their designation as ‘lipid-associated macrophages’ (LAMs) [36,37] (**Figure 1**). LAMs were further characterized by the expression of ‘triggering receptor expressed on myeloid cells 2’ (*Trem2*) and whole-body knockout of this lipid receptor prevented the appearance of this ATM subset in obesity and reduced the formation of CLS [37]. In addition, *Trem2*-deficient mice exhibited massive

adipocyte hypertrophy upon high-fat diet feeding and exacerbated metabolic complications associated to obesity [37]. The presence of TREM2⁺ ATMs was also observed in human visceral adipose tissue and correlated with body mass index (BMI) [37]. A similar population of ‘phagocytic macrophages’ was further increased following 2 weeks of caloric restriction post high-fat diet feeding [38], supporting a role of these ATMs in clearing lipid and adipocyte remnants to restore adipose tissue homeostasis. These scRNAseq studies have paved the way to understand ATM biology and we entered an exciting era that should pinpoint the relative contribution of each different subsets to WAT homeostasis.

Metabolic rewiring of adipose tissue macrophages in obesity.

There is increasing evidence that ATMs can be re-programmed by their environment, especially by the presence of metabolic stressors such as saturated fatty acids (SFAs) [39]. SFAs may arise from the diet or from uncontrolled adipose tissue lipolysis during obesity. While excessive lipolysis could have a pro-inflammatory effect on ATMs, adipocyte lipolysis is needed to avoid cell toxicity and death. Indeed, hormone sensitive lipase (*Hsl*)- and adipose triglyceride lipase (*Atgl*)-deficient mice, in which adipose tissue lipolysis is reduced, exhibited a dramatic increase in CLS that was associated with increased adipocyte lipid storage and death [30,40]. Thus, since dying adipocytes are surrounded by macrophages as mentioned above, one could speculate that dead adipocytes clearance participates to macrophage lipid loading during obesity. A recent study also identified that lipid-filled vesicles secreted from adipocytes, which contain triglycerides, phospholipids and cholesterol, were a dominant driver of ATM inflammation [41]. This work highlights an early metabolic and inflammatory event involving the paracrine communication between adipocytes and ATMs (**Figure 1**). This study complements recent and earlier works on the role of extracellular vesicle or mitochondrial transfer as a mean of communication between adipocytes and surrounding stromal cells [42,43]. Free fatty acid released by adipocytes through lipolysis could also communicate at distance with monocyte and alter their metabolic and inflammatory activities during obesity as recently observed upon fasting [44] (**Figure 1**). Thus, different routes can be used by SFAs to reach ATMs.

The way macrophages handle and metabolize lipids has been reviewed elsewhere [45,46], and this is tightly coupled to a program of lysosome biogenesis in obesity [47]. A direct genetic evidence that lipid handling by ATMs drives metabolic inflammation during obesity has been provided by studying mice deficient for the fatty acid synthase (*Fasn*) in macrophages [48]. This led to the attenuation of chronic inflammation and limited macrophage accumulation in the obese adipose tissue [48]. Interestingly, inhibition of fatty acid synthesis impaired membrane cholesterol order in ATMs, limiting their inflammatory response [48] most likely by interfering with Toll-like receptor 4 (TLR4) ability to enter lipid raft [49]. *In vitro*, SFAs induced JNK activation and inflammation were only effective in TLR4-primed macrophages [50]. Such priming altered cellular metabolism and membrane lipid composition, allowing cells to efficiently respond to SFAs [50]. This could create a vicious cycle as TLR4 can enhance the toxicity of SFAs [51]. Consequently, mice lacking JNK signaling in macrophages were markedly protected against diet-induced insulin resistance [52]. Altogether these findings suggest a specificity of metabolic pathways that promote macrophage lipid overload and the subsequent initiation of ATM inflammation.

Emerging accessory function of ATMs in the control of thermogenesis.

Apart from lipid storage, beige subcutaneous (scWAT) and brown adipose (BAT) tissues can dissipate chemical energy as heat notably by increasing uncoupling protein 1 (UCP1) activity [53]. Heat production and energy burning in scWAT and BAT can be induced by the activation of sympathetic neurons upon cold exposure (i.e, simulation of norepinephrine

release) or artificially by β 3-adrenergic stimulation. β 3-adrenergic stimulation is associated with a strong remodeling of the WAT immune landscape [54]. Intriguingly, compared to cold challenge, β 3-adrenergic stimulation is more effective at inducing UCP1 expression in visceral WAT [55], where it is accompanied by a strong inflammatory response and CLS formation [54], likely due to moMacs accumulation. Although the physiological relevance is not fully understood, CLS formation is associated with the release of lipid metabolites and other chemoattractants that are required for WAT browning by potentiating the proliferation and differentiation of adipose progenitors [56]. Interestingly, adrenergic signals have also been reported to mobilize hematopoietic progenitors from the bone marrow and favor myelopoiesis [57–59]. The underlying mechanisms within the bone marrow niche are complex but most likely involved a reduced interaction between CXCL12 (SDF-1) and CCL2 and their respective receptors CXCR4 and CCR2 expressed by monocytes [60,61]. However, whether these mechanisms could contribute to moMacs accumulation and thermogenesis upon β 3-adrenergic stimulation remains elusive (**Figure 2**). Regarding cold-induced thermogenesis, it remains unclear whether it remodels the macrophage pool. At least, the requirement of monocyte recruitment via CCR2 and alternative activation via IL-4R α as potential mechanisms leading to the biogenesis of thermogenic fat has been debated [62–64]. Nevertheless, it was recently uncovered that a subset of trMacs is tightly associated with the peripheral nervous system [65,66], which could impact on nonshivering thermogenesis [67,68]. Mechanistically, these macrophages can regulate the sympathetic tone by at least two independent mechanisms (**Figure 2**). First, macrophage expressing PlexinA4 can limit sympathetic tone-mediated BAT thermogenesis by repulsing Sema6A-expressing sympathetic axons to locally control neuronal density [69]. A recent report also suggested that sympathetic neuron-associated macrophages can locally reduce norepinephrine (NE) availability through its uptake and subsequent degradation, which represents an alternative mechanism of thermogenesis regulation [70]. Overall, macrophages could be harnessed to fuel adipose tissue thermogenesis, facilitating fat burning and limiting obesity-associated comorbidities.

Liver macrophages in non-alcoholic fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) encompasses two major clinical phenotypes, non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). While NAFL has a limited impact on overall health, progression to NASH and its evolution towards cirrhosis and even hepatocellular carcinoma in some cases is life-threatening [71,72]. Steatosis, ballooning and inflammation, sometimes accompanied by fibrosis, are the key features typifying the development of NASH. While obesity contributes to NASH onset, NASH is now recognized as an independent risk factor for cardiovascular diseases. Thus, there is a strong interplay between the 3 pathological states of cardiometabolic disease.

Hepatic injury during NASH is associated with the accumulation and activation of immune cells, including macrophages. However, while trMac inhabit the steady state liver, liver macrophage become more diverse during disease, and we are only starting to better appreciate such complexity and how this could impact on disease onset and progression.

Origins and roles of liver macrophage subsets during NASH.

KCs are the liver trMac population located in hepatic sinusoids, at the interface between the liver parenchyma and the blood circulation. Recently, a second liver trMac subset, located in the liver capsule was described [73]. While KCs develop during embryogenesis and maintain in the adult independently from the circulating monocyte pool [74–78], capsular Macs seem constantly replenished by monocytes [73] (**Figure 3**).

Although embryonic KCs (emKCs) self-renew to maintain on the long-term, they can be replaced by monocyte-derived cells following their non-physiologic depletion [79–81]. Such monocyte-derived KCs (moKCs) eventually adopt a phenotype very similar to their emKCs counterparts [79–81] (**Figure 3**). EmKCs depletion studies allowed to probe the sequence of moKCs generation and how liver stromal cells, especially liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs), provided the cues necessary for KC specification at the enhancer and transcriptomic levels [80,82]. Indeed, as an example, the Notch ligand DLL4 produced by LSECs and HSCs [82] was critical to activate the emKC lineage-determining factor LXR α [80], recently described to control homeostatic emKC survival [83], and forge KC identity [80,82].

Upon hepatic injury, as occurring during NASH, circulating blood monocytes are recruited to the liver parenchyma where they can differentiate into macrophages and participate to the liver macrophage pool (**Figure 3**). We and others recently described liver macrophages diversity in mouse models of NASH [84–86]. Single cell RNAseq analysis of liver leucocytes revealed distinct macrophages populations in NASH [84,85]. First, it highlighted a population of KC with low *Timd4* expression [84,85], similar to the vast majority of moKCs generated following emKCs depletion [80–82], suggesting moKCs were present during NASH. We came to a similar observation by fate-mapping monocytes and uncovering their participation to the KC pool during NASH [86]. We also provided evidence that emKCs were enriched in genes associated with lipotoxicity during NASH and were more prone to cell death [86]. Conversely, protecting emKCs from cell death limited moKCs generation during NASH [86]. Such KC diversity was also revealed by flow cytometry. Cell surface markers specific for KCs, such as CLEC4F, VSIG4, TIMD4 and CLEC2, were instrumental to isolate KCs during NASH. Among those markers, we used CLEC2, the most rapidly induced KC-specific marker during monocyte to moKC differentiation [81], which proved efficient to selectively identify emKCs but also and above all moKCs in contrast to VSIG4, CLEC4 and TIMD4 [86]. Overall, CLEC2 better capture KCs in their diversity as compared to other classical KC markers. When compared at the transcriptional level, moKC were more inflammatory than emKCs and did not acquire the full gene spectrum associated with emKCs accessory functions, notably erythrophagocytosis [86]. We also compared the functional impact of moKCs versus emKCs on NASH initiation and observed that mice mostly carrying emKCs were limited in their ability to safely store hepatic triglycerides, leading to increased liver injury [86] (**Figure 3**). Thus, while they replenished the KC pool, moKC are not as protective as their emKC counterparts.

In addition, scRNAseq revealed that macrophages characterized by the expression of *Spp1*, *Itgax*, *Gpnmb*, *Cd9* and *Trem2* (among other markers), which resemble to the lipid-associated macrophages (LAMs) described in obesity [37], accumulated during NASH [26,84,85,87]. LAMs are derived from monocytes, dominate in number the inflammatory infiltrate observed in steatohepatitis and were localized in crown-like structures [26]. However, their impact on NASH, as a definite cell type, remains to be determined. Previous studies made use of *Ccr2*-deficient mice that lack monocyte-derived cells, including moKCs and LAMs, and revealed these mice were protected from NASH [88]. Along these lines, cenicriviroc, a dual CCR2/CCR5 inhibitor currently under evaluation for the treatment of NASH in humans, was shown to limit NASH development in mice and especially fibrosis [89–91]. In addition, osteopontin (encoded by *Spp1*) has been shown to promote NASH development and fibrosis [92,93]. However, since cholangiocytes are the main source of osteopontin in the liver [94] and 20% of LAMs are osteopontin positive at most [84], the functional impact of LAMs-derived osteopontin on NASH pathology and associated fibrosis remains to be validated. By contrast, TREM2, one of the typical LAM markers (**Figure 3**), seems protective in diet-induced obesity [37], but also liver diseases [95,96]. Thus, as LAMs can express genes known

for their opposite effect on NASH physiopathology, further study will be needed to better appreciate how they impact on liver injury during NASH.

As mentioned above, CLEC2 was instrumental to identify KCs whatever their origin and stage of differentiation [86]. CLEC2 was further recognized as a marker allowing moKCs identification in their very early differentiation phase [84], when they are very similar in phenotype to LAMs. At this stage, depending on the gating strategy used, part of moKCs can be found in the LAM gate. Along these lines, we reported that moKCs, when compared to emKCs, were enriched in genes used to define LAMs (*Cd9*, *Itgax*, *Gpnmb*) [86]. In addition, several LAMs markers were also induced by emKCs, albeit to a lesser extent than moKCs, during NASH [86]. Thus, the LAM signature seems to encompass diverse macrophage subsets during NASH and could be viewed as a metaflammation (“metabolic inflammation” [8]) signature.

Zonation of liver macrophages.

In the steady state liver, KCs, which reside in liver sinusoids, were shown to have a preferential tropism toward portal veins (PVs) rather than central veins [97]. KCs concentrate around PVs in response to a chemokine gradient depending on CXCL9, produced by LSECs, and its receptor CXCR3 on KCs [97]. Mechanistically, periportal CXCL9 expression depended on the gut microbiota and its sensing through Myd88 signaling in LSECs [97].

Such proximity to the portal regions suggests KCs may have an important role in the communication axis operating between the gut and the liver. Indeed, KCs may impact on liver homeostasis by sensing and responding to mediators and metabolites present in the portal circulation and that eventually reach the liver. It was indeed previously reported that KCs internalize bacteria-derived metabolites released in the portal circulation [98]. More recently, microbiota-derived D-lactate was shown to control KC ability to capture and kill blood-borne pathogens [99]. Finally, altering KCs tropism to portal regions impaired bacterial clearance by the liver and the host ability to combat infection [97]. All together, these studies highlighted the importance of microbiota-derived signals in the control of KCs zonation and function, which in turn were critical to efficiently clear bacteria and fight against infection.

During NASH, moKCs were shown to localize to hepatic sinusoids, similar to their emKCs counterparts. Whether KC subsets tropism towards PVs and ability to capture and kill bacteria are altered in NASH livers still remain to be evaluated. By contrast to KC subsets, monocyte-derived LAMs were present in the parenchyma [84,85] and enriched in regions of high desmin⁺ HSC density [84]. This suggests LAMs are involved in a crosstalk with HSCs that this might alter HSCs fibrogenic functions and impact on liver fibrosis (**Figure. 3**). Thus, liver macrophage subsets seem to occupy specific anatomical niches depending on their origins and this might be crucial for their regulatory functions.

Metabolic regulation of liver macrophages.

So far, little is known regarding the cellular metabolic features of KCs during homeostasis and disease. LXR α was recently described as a key transcription factor controlling both KC specification and survival at the steady state and during NASH [80,83,85]. LXR α is a nuclear receptor known to control lipid homeostasis in macrophages and its ligands include oxysterols and desmosterol [100]. Thus, in the lipid-rich environment of the liver, cholesterol-derivatives sensing by LXR α is crucial to maintain KCs survival and identity.

KCs are well known to efficiently break down old and damaged red blood cells [101]. Iron is an essential component of erythrocytes that KC must need to handle and safely metabolize for detoxification at the steady state. Interestingly, a transient population of moMacs that resemble moKCs was shown to participate to red blood cells ingestion after intravenous injection of senescent erythrocytes [102]. The differentiation of this moKC subset depends on

the antioxidant transcription factor Nrf2 and expresses high level of the iron-regulated transporter ferroportin 1 (FPN1, encoded by Slc40a1) that can recycle iron towards hepatocytes [102]. Whether KC-mediated erythrophagocytosis impacts NASH pathogenesis has not been studied yet.

Overall, our understanding of the cellular metabolic fluxes that control KC maintenance and functions remain to be studied.

Macrophages in Atherosclerosis.

The pathogenesis of atherosclerosis begins with the accumulation and retention of cholesterol derived from lipoproteins within the vascular subendothelium [103]. This initiates a local inflammatory response dominated by macrophages.

Origin of atherosclerotic plaque macrophage subsets in atherosclerosis.

The inflammatory response was originally restricted to macrophage defective lipid handling or an imbalance between pro-inflammatory “M1” macrophages and anti-inflammatory “M2” macrophages [100,103–105]. Indeed, a key function of atherosclerotic plaque macrophages (APMs) has been attributed to their ability to handle lipids and clear apoptotic or even necrotic debris in a hypoxic and oxidative environment. Despite the ability of APMs to expand by *in situ* proliferation [106], pioneer studies have also revealed the requirement of inflammatory monocyte infiltration into the vessel wall for the initiation and progression of atherosclerosis [107–109]. We and others also found that atherogenic stimuli, such as hypercholesterolemia for instance, triggered bone marrow myelopoiesis supporting the hypothesis that the expansion of APMs in atherosclerosis partly originated from circulating monocytes as reviewed elsewhere [100,105] (**Figure 4**). Of note, in humans, circulating monocytes have also been positively correlated with cardiovascular events [110–113]. Thus, the APM pool may rely on both trMacs expansion and moMacs infiltration. Overall, severe deficiency of monocytes and macrophages in osteopetrotic (op/op) mice, lacking the macrophage colony stimulating factor 1 (CSF1), led to protection against hypercholesterolemia-induced atherosclerosis [114–116]. Thus, clearing macrophages from the intimal space by inducing their death could limit atherosclerotic plaque burden. However, induction of macrophage apoptosis at an early or late stage of atherosclerosis development has revealed a more complex scenario [117]. Indeed, while efficient clearance of dying macrophages through efferocytosis at the early stage of the pathology is operative and limits plaque development, macrophage death at later stages is deleterious as efferocytosis become dysfunctional as plaques progress. Consistently, an imbalance between macrophage apoptosis and efferocytosis has been observed in advanced atherosclerosis lesions leading to secondary necrosis and formation of necrotic core [118] (**Figure 4**). Overall, macrophages with different origins support the development and progression of the atherosclerotic plaque. However, in addition to their developmental diversity, the atherosclerotic plaque environment may also reprogram APMs and promote their functional diversity.

Diversity of atherosclerotic plaque macrophages in atherosclerosis.

As recently summarized, scRNAseq and Cytometry by Time of Flight (CyTOF) technologies have recently extended our ability to comprehend immune cell diversity in atherosclerotic plaques [119]. Indeed, multiple studies applied scRNAseq to CD45⁺ immune cells isolated from human plaque samples of endarterectomy patients [120] and to aortic cells extracted from control and atherosclerotic mice [121–125] in the past few years. Briefly, three APM subsets have been identified, considerably changing the paradigm in the field. Despite the common use of the mannose receptor (MRC1 or CD206) as a canonical marker of alternatively activated anti-inflammatory macrophages, a CD206⁺ APM subset unexpectedly

expressed some markers of inflammation. It is yet unknown if this subset derived from recruited monocytes, which could partly explain the inflammatory status. A resident LYVE1⁺ APM subset [126] was also identified and could reflect the population of macrophages in close contact to blood vessels found in several tissues [127], which are specialized to detect and phagocytose invading pathogens. Interestingly, similar to obese adipose tissue and fatty liver, a TREM2⁺ APM subset has been characterized as the one becoming foam cells [121,124]. Thus, one could expect the localization of this subset to be in close contact to the necrotic core, similar to their localization in the CLS of the adipose tissue, in order to clear lipids and cell debris (**Figure 4**). Further investigation is now needed to decipher the developmental connection between APM subsets, highlight their zonation and assign them with specific functions. Such work would uncover their potential roles in tissue inflammation and repair, and eventually understand how they participate to plaque remodeling.

Metabolic rewiring of efferocytes in atherosclerosis.

We and others have extensively reviewed the immunometabolic regulation of macrophages, including during atherosclerosis, over the last few years [100,128–132]. We will thus only briefly summarize the recent and emerging role metabolism plays during efferocytosis and its consequence on the disease. Impaired efferocytosis is thought to be a major mechanism driving plaque progression [133,134] and a process requiring an exquisite metabolic adaptation to face the huge amounts of excess cholesterol APM face in this context [135,136]. Recently, a novel solute carrier (SLC) program induced upon efferocytosis was shown to support early glucose uptake and subsequent lactate release, influencing surrounding cells [137] (**Figure 4**). Consequently, specific deficiency of Slc2a1 in macrophages, their main glucose transporter, increased necrotic core area [137,138]. Besides glycolysis, the requirement of mitochondrial complex III and oxidative phosphorylation (OXPHOS) to the resolution of inflammation post efferocytosis was also recently uncovered [139] (**Figure 4**). Interestingly, respiratory chain dysfunction was previously linked to enhanced mitochondrial oxidative stress, and this correlates with the progression of human and mouse atherosclerotic lesions [140]. Defective macrophage uncoupling protein 2 (UCP2)-dependent proton leaks following OXPHOS was also shown to be detrimental in atherosclerosis, in part by impairing efferocytosis [141–144]. We recently identified an upstream role of the lysosomal acid lipase (LIPA) in hydrolyzing fatty acid and cholesterol during efferocytosis [145]. This reprogrammed the mitochondria for efficient OXPHOS and in turn promoted continued clearance of apoptotic cells [145]. Consistently, TFEB, the master regulator of the autophagy-lysosomal program, protected against atherosclerosis in part by enhancing the degradative capacity of macrophages [146]. These findings highlight the importance of the two major metabolic routes (i.e., glycolysis and fatty acid oxidation) during efferocytosis and their impact on the metabolic inflammation observed in atherosclerosis. Importantly, metabolites released from apoptotic cells can also participate to the metabolic rewiring observed during efferocytosis [147]. For instance, arginine derived from apoptotic cells can be metabolized into the putrescine pathway to prepare cytoskeletal rearrangement and favor continual efferocytosis [148]. Although deficiency of myeloid Arginase 1 in mouse model of atherosclerosis was not sufficient to affect plaque development, it clearly limited plaque regression [148,149], during which efferocytosis is likely to play a leading role in clearing the intima space from cell debris. Thus, different metabolic pathways control the APM efferocytic response, highlighting their central immunometabolic role in atherosclerosis.

Adventitial macrophages as part of the atherosclerotic plaque macrophage network.

The progressive increase of macrophages, among other immune cells, in the adventitia surrounding arteries contributes to the development of organized artery tertiary lymphoid

organs (ATLOs) as reviewed elsewhere [150,151] (**Figure 4**). The role of macrophages, arising from both embryonic precursor and circulating monocytes after birth [152], in these structures remains poorly understood. Inflammation could also trigger the recruitment of myeloid cells to these structures [153,154]. To speculate about the role of ATLOs macrophages, we can make a parallel with the fat-associated lymphoid clusters (FALCs) described in the adipose tissue. In FALCs, monocyte-derived macrophages that express TNF α may participate to the communication with stromal cells [155]. Among stromal cells, the immediate connective tissue coat contains myofibroblasts, a loose network of extracellular matrix components, small blood and lymph vessels as well as adrenergic nerve axons. Thus, although ill defined, regulation of these adventitial constituents by immune cells could support arterial wall homeostasis, neuronal sensing and deliverance of nutrients and oxygen from small blood vessels to medium- and large-sized arteries [156,157]. While the topic has not been widely covered so far, it is expected to see an increase in studies aimed at identifying the role of adventitial macrophages in the future.

Concluding remarks

Over the last decades, an explosion of fate-mapping approaches and imaging modalities to assess the origin, zonation and behavior of macrophages has provided new insights into the versatility of macrophages in metabolic tissues such as the adipose tissue, liver and arterial wall at steady state or during cardiometabolic diseases. One of the common denominators in cardiometabolic diseases is the defect in the macrophage capacity to limit ectopic lipid storage in metabolic tissues during pathological states. However, challenges remain as to whether macrophage metabolic rewiring is causal to this defect. For instance, future works will be required to delineate the critical ying and yang function of the newly identified TREM2⁺ moMac subset in cardiometabolic diseases. Another important defective process in pathological metabolic tissue is the defect in efferocytosis that limit the clearance of apoptotic cells present in fatty tissues. One of the simple explanations could be that handling of lipid deposition by macrophage could compete with their efferocytic function. However, macrophages are known to eat something bigger than their head [158]. Thus, understanding which macrophage subset sense the nutritional or necrotic status of the disease tissues will greatly benefit the development of new strategies aimed at targeting specialized macrophage subset in cardiometabolic diseases.

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Figure legends

Figure 1. White adipose tissue macrophage heterogeneity in obesity. Under homeostatic condition, adipose tissue resident macrophages are derived from embryonic precursors and self-sustain by local proliferation. Monocytes that are constantly generated in the bone marrow through myelopoiesis circulate in the blood for immune surveillance. Upon high fat diet-induced obesity, the expansion of the adipose tissue is associated with a remodeling of the macrophage landscape. Adipocyte hypertrophy is associated with local insulin-resistance, uncontrolled lipolysis, local inflammation and increased cell death that send signals to recruit circulating monocytes. The recruited monocytes differentiate into macrophages (moMacs) and adapt their behavior to face the local lipid-rich environment. They are primarily found close to dead adipocytes in ‘crown-like structures’ (CLS).

Figure 2. Subcutaneous and brown adipose tissue macrophage heterogeneity in thermogenesis. Macrophages control uncoupling protein 1 (UCP1)-dependent heat production in subcutaneous and brown adipose tissue. The contribution of tissue resident macrophages (trMacs) versus monocyte derived macrophages (moMacs) remains ill defined. Nevertheless, thermogenic stimulation such as cold exposure or β 3-adrenergic activation support bone marrow myelopoiesis and subsequent monocyte recruitment into thermogenic adipose depots. At least, three functions of macrophages have been linked to nonshivering thermogenesis. First, interactions between Vcam1 on trMacs and integrin α 4 on adipocytes control UCP1-dependent thermogenesis. Second, trMacs associated to peripheral nervous nerves can control the sympathetic tone by regulating SEMA6A-PLXNA4 interactions and associated neuronal density or by uptaking and degrading norepinephrine (NE) through SLC6A2 and MAOA, respectively.

Figure 3. Liver macrophage heterogeneity in non-alcoholic steatohepatitis (NASH). Tissue resident Kupffer cells of embryonic origin (emKCs) are located in hepatic sinusoids while another population of capsular macrophages surrounds the liver. Upon hepatic injury, a large number of circulating bone marrow-derived monocytes enter the liver where they differentiate into Kupffer cells (moKCs). Their differentiation is supported in part by the Notch ligand DLL4 secreted by sinusoidal endothelial cells (LSECs). The liver X receptor ($LXR\alpha$) is critical to forge KC identity. As compared to moKCs, emKCs are less inflammatory and have a better ability to facilitate hepatic triglyceride storage as well as to limit hepatic injury. A subset of $TREM2^+$ moMacs, resembling to the lipid-associated macrophages (LAMs), also accumulates during NASH.

Figure 4. Atherosclerotic plaque macrophage heterogeneity in atherosclerosis. Hypercholesterolemia and modified low-density lipoprotein favor local and peripheral inflammation in atherosclerosis. It triggers bone marrow myelopoiesis supporting the hypothesis that the expansion of atherosclerotic plaque macrophages (APMs) partly originated from circulating monocytes. At least three APM subsets have been identified but their origin and function remain poorly understood. $CD206^+$ APMs could be tissue resident macrophages of embryonic origin, similar to the $LYVE1^+$ APMs that resemble the tissue-resident macrophages in close contact to blood vessels observed in other tissues. The $TREM2^+$ APM subset has been identified as the one becoming foam cells and is expected to localize around the necrotic core where they may primarily exert their phagocytic function. An increased number of macrophages has also been identified in artery tertiary lymphoid organs (ATLOs) but their role remains to be clarified.

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Figure. 1

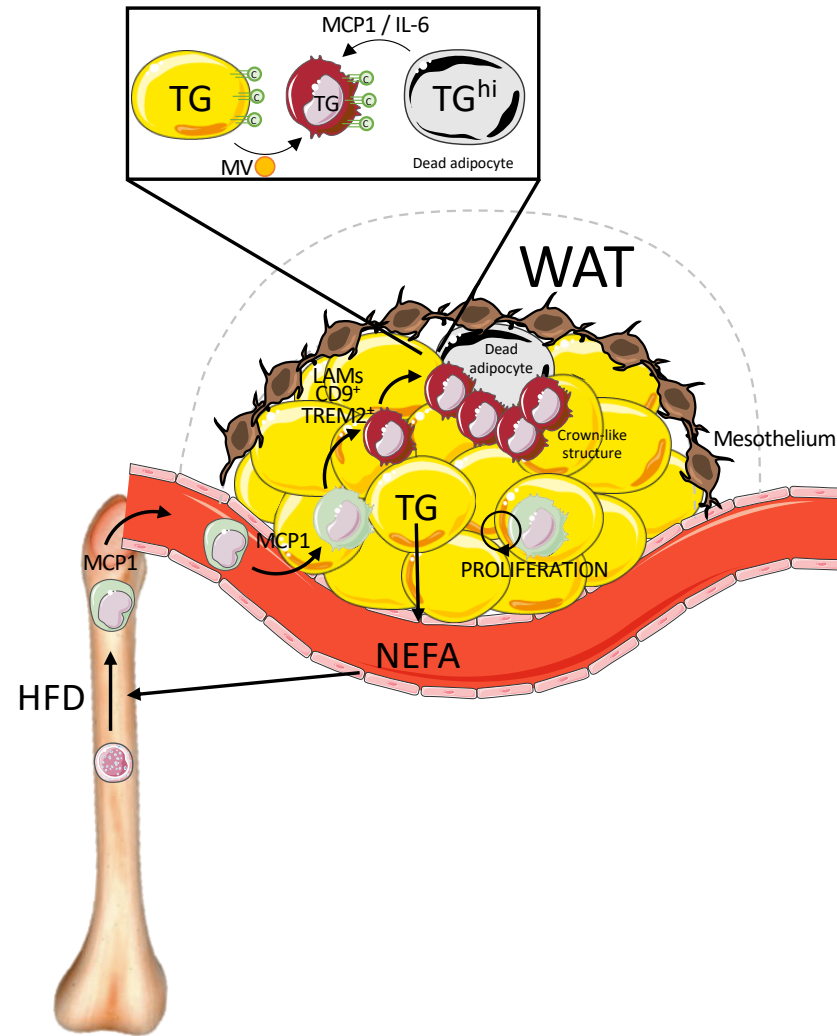


Figure. 2

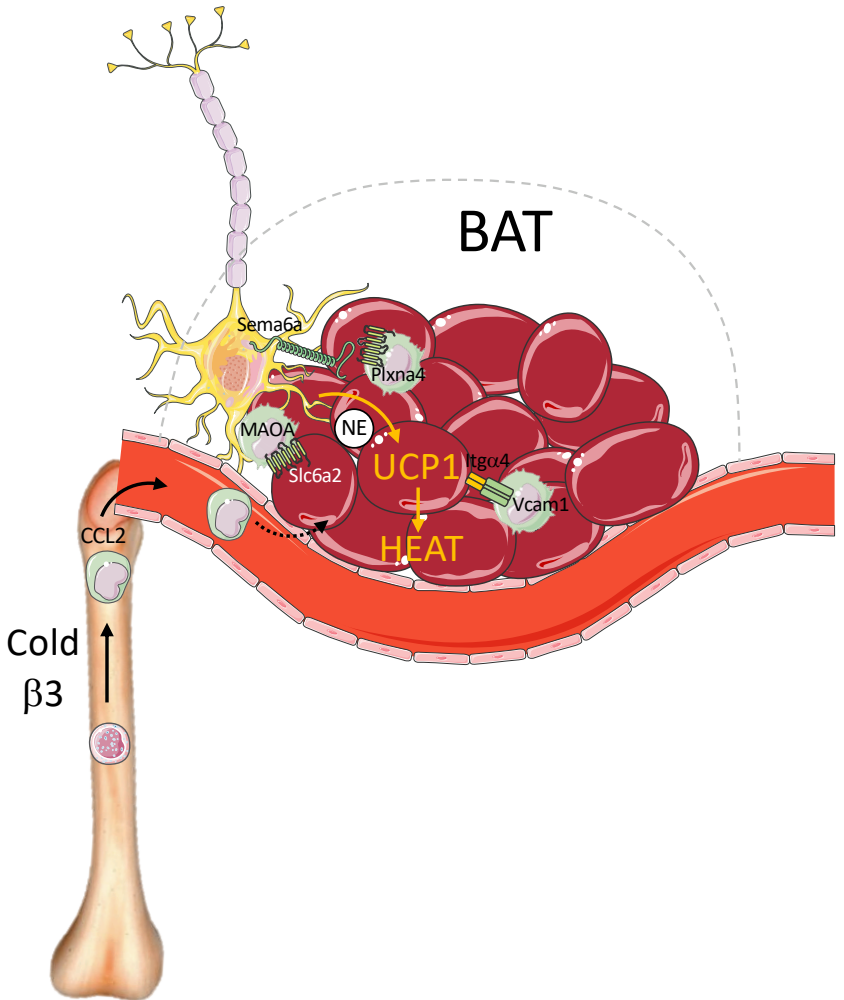


Figure. 3

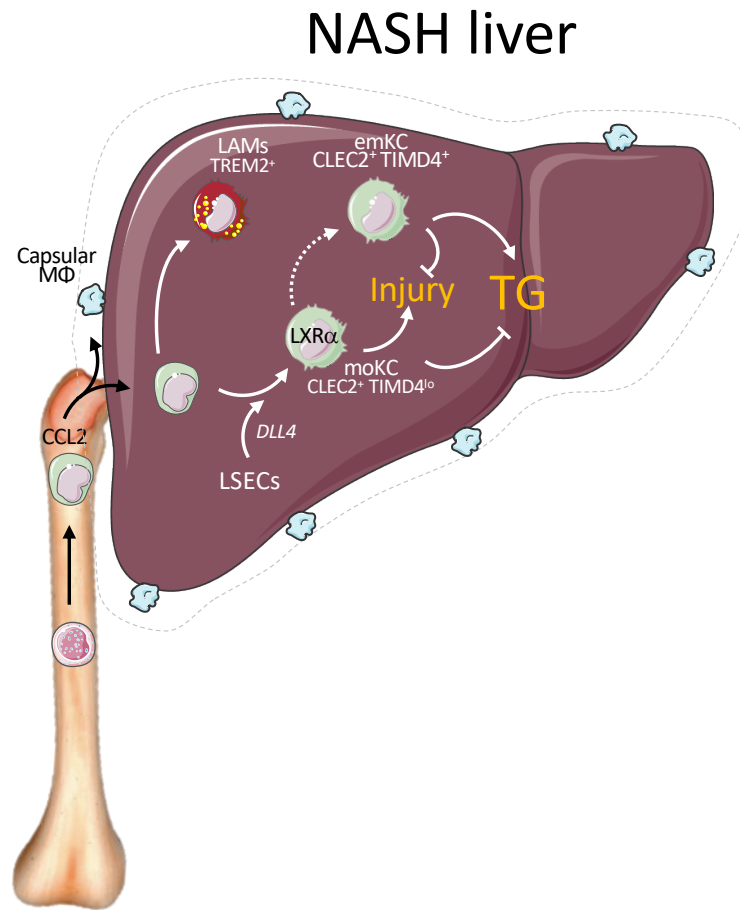


Figure. 4

