Adipose Extracellular Vesicles: Messengers From and to Macrophages in Regulating Immunometabolic Homeostasis or Disorders

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Adipose tissue is comprised of heterogenous cell populations that regulate both energy metabolism and immune reactions. Macrophages play critical roles in regulating immunometabolic homeostasis or disorders through cooperation with adipocytes, adipose tissue-derived stem cells (ADSCs) or other cells in adipose tissue. Extracellular vesicles (EVs) are recently recognized as efficient messengers for intercellular communication. Emerging evidences have demonstrated that adipose EVs are actively involved in the mutual interactions of macrophages, adipocytes and ADSCs, which produce considerable influences on immunometabolism under healthy or obese conditions. Here, we will elaborate the production and the characteristics of adipose EVs that are related to macrophages under different metabolic demands or stresses, whilst discuss the roles of these EVs in regulating local or systemic immunometabolic homeostasis or disorders in the context of adipocyte-macrophage dialogue and ADSC-macrophage interaction. Particularly, we provide a profile of dynamic adipose microenvironments based on macrophages. Adipose EVs act as the messengers between ADSCs and macrophages to maintain the balance of metabolism and immunity, while drive a vicious cycle between hypertrophic adipocytes and inflammatory macrophages to cause immunometabolic imbalance. This review may provide valuable information about the physio- or pathological roles of adipose EVs and the application of adipose EVs in the diagnosis and treatment of metabolic diseases.

Keywords: extracellular vesicle, macrophage, exosome, immunometabolism, adipose-derived stem cell, obesity, adipocyte, adipose tissue

INTRODUCTION

Adipose tissue is the major metabolic organ that regulates glycolipid metabolism and energy balance. There are two types of adipose tissues, which perform distinct functions in energy regulation. White adipose tissue (WAT) stores surplus energy in the form of triglycerides, whereas brown adipose tissue (BAT) dissipates energy through thermogenesis to maintain body temperature. The Imbalance between energy intake and consumption may lead to obesity manifested by excessive fat accumulation and pathological expansion of WAT (1–3). This disturbance is often accompanied by WAT inflammation, characterized by infiltration and activation of proinflammatory immune cells such as macrophages and T cells, as well as high levels of proinflammatory cytokines. The chronic inflammation caused by WAT dysfunction leads to insulin resistance in liver, muscle, adipose tissue, and result in metabolic abnormalities such as hyperglycemia, hypertension and dyslipidemia, thereby linking obesity with type 2 diabetes and cardiovascular diseases (4–7). So, WAT is the main site for local or systemic immunometabolic regulation under both healthy and pathological conditions.

Tissue immunometabolism refers to the connection of immunity and metabolism in metabolic tissues including liver, muscle, pancreas, and adipose tissue. The regulation of immunometabolism in these tissues relies on the mutual interactions among tissue parenchymal cells, stromal cells, and immune cells. These cellular interactions develop adaptation to each other to maintain immunometabolic homeostasis and normal physiological functions of metabolic organs under healthy condition or in response to acute metabolic demands. In case of obesity or chronic metabolic stresses, the infiltration and activation of immune cells may impinge the actions of metabolic hormones like insulin on parenchymal cells, and further impair the glycolipid metabolism in metabolic organs, eventually resulting in tissue maladaptation and metabolic disorder clusters. For example, lean WAT contains large amounts of immunomodulatory cells such as alternatively activated macrophages, regulatory T cells, type 2 innate lymphoid cells, which cooperate with stromal cells to maintain tissue homeostasis and support physiological functions of adipocytes. In contrast, obese WAT is characterized by accumulation and activation of immune cells including inflammatory macrophages, effector CD4$^+$ and CD8$^+$ T cells (mainly Th1 and CTL), which induce tissue inflammation and cause insulin resistance in adipocytes, hepatocytes and myocytes, thereby contributing to tissue dysfunction and associated metabolic complications (1, 8–10). In adipose tissue, adipocytes, adipose-derived stem cells (ADSCs) and macrophages act as the main players of parenchymal cells, stromal cells, and immune cells, respectively, which actively participate in immunometabolic regulation. Kinds of soluble factors, comprising adipokines, cytokines, growth factors and fatty acids, are involved in the intercellular communication to regulate immunity and metabolism, which have been well reviewed elsewhere and will not be detailed here (1, 5, 8, 11, 12). Extracellular vesicles (EVs),

as another form of soluble factors, are recently recognized as the important modulators affecting neighboring or distant cells. As membrane-coated vesicles, EVs carry and transport various of bioactive proteins, lipids, or nucleic acids from donor cells into recipient cells, thereby affecting their biological characteristics and functions (13–17). Emerging data have shown the critical roles of EVs in regulating immunometabolism in metabolic tissues, particularly in adipose tissue. Herein, we will summarize the production and characteristics of EVs from WAT and their roles in maintaining or disrupting immunometabolic homeostasis in the context of adipocyte-macrophage dialogue and ADSC-macrophage interaction.

CELLS IN ADIPOSE TISSUE RELATED TO IMMUNOMETABOLISM

In the 1960s, Rodbell pioneered the study on individual cell components of adipose tissue, and showed that hormones produced similar metabolic effects on isolated fat cells and fat tissue (18). Thus, to some extent, fat cells could be used as substitute for adipose tissue in particular studies. In fact, fat cells only account for part of the total cells in adipose tissue. Aside from adipocytes, a cluster of stromal vascular fractions, comprised of ADSCs, immune cells, endothelial cells, and other cell components, are found in WAT (19–22). Among them, both innate and adaptive immune cells such as macrophages, natural killer cells, T cells and B cells contribute to the formation of dynamic immune microenvironments with the changing metabolic status, wherein various immune cells communicate with adipocytes, ADSCs or other cells (23–26). Here, we will discuss the adipocytes, ADSCs and macrophages in detail.

Adipocytes

As the parenchymal cells of adipose tissue, adipocytes not only function as critical regulators for energy metabolism, but also serve as endocrine modulators involved in various physio- or pathological processes like appetite control and immune response (5, 11, 27–30). White adipocytes, mainly present in WAT throughout the body, contain large and unilocular lipid droplets to store energy in the form of triglycerides. In contrast, brown adipocytes, mainly distributed in BAT in the scapular area and neck, contain small and multilocular lipid droplets together with abundant mitochondria that contribute to energy dissipation in the form of heat (3, 31–33). In addition, beige adipocytes, as brown-like adipocytes induced by cold stimuli or high-fat diet (HFD) challenge, also contribute to energy consumption *via* heat production (34, 35). The three types of adipocytes function differently and cooperate with each other in response to various metabolic demands or stresses. For instance, white adipocytes contribute to WAT expansion *via* hyperplasia and hypertropia during obesity, whereas the activation of brown adipocytes and the induction of beige adipocytes reduce obesity and improve insulin sensitivity. White adipocytes play important

roles in regulating glycolipid metabolism and energy balance through storing excess energy and supplying it when needed. Large amounts of secretary factors from adipocytes, such as leptin, adiponectin, cytokines, fatty acids and EVs, are involved in these processes, which mediate the communication of adipocytes with other cells inside or outside adipose tissue (5, 11). Besides their functions in energy storage and endocrine, white adipocytes have recently been recognized to regulate both innate and adaptive immunity in adipose tissue, such as recruiting and activating macrophages, presenting antigens to invariant natural killer T cells or CD4^{+} T cells (25, 36–40). Thus, adipocytes may be the major cell components in regulating WAT immunometabolism. In this review, we mainly focus on the EVs related to white adipocytes in WAT.

ADSCs

ADSCs are the dominant stromal cells in adipose tissue that serve as progenitors responsible for the regeneration and replenish of adipocytes. ADSCs have great potentials for homing and self-renewal, as well as strong capacity for multiple differentiation toward adipocytes, chondrocytes, and muscle cells. Therefore, ADSCs are currently recognized as promising therapeutic candidates for tissue repair and regeneration (7, 8). The proliferation and adipogenesis of ADSCs are essential for the maintenance of metabolic homeostasis particularly in adipose tissue, as supported by our previous study showing distinct metabolic influences on WAT homeostasis by ADSCs from different anatomic locations (41, 42). Notably, human or mouse ADSCs showed strong capacity for immunomodulation through actively participating in both innate and adaptive immunity, such as promoting macrophage polarization toward anti-inflammatory phenotypes or inducing regulatory T cell differentiation. These immunomodulatory effects of ADSCs were perfectly reflected in the treatment of several inflammatory diseases like colitis and sepsis in animal models (43–46). While for metabolic inflammation, ADSCs also brought desirable effects on the improvements of immune microenvironments in adipose tissues or the attenuation of inflammation and tissue damages in animal models with obesity or type 2 diabetes (47–50).

Macrophages

The great interest on adipose tissue-resident macrophages (ATMs) is largely ignited by the discovery that obesity induced the infiltration and activation of macrophages in WAT to elicit inflammation and insulin resistance (51, 52). Monocyte chemoattractant protein-1 (MCP-1) is recognized as the main contributor to the increase of ATMs in obese mice. Besides, fatty acids released by necrotic fat cells are also phagocytic stimuli for ATMs, which promote their infiltration around necrotic cells to form crown like structures (12, 53, 54). In fact, macrophages are critical resident cells in WAT, which not only mediate WAT inflammation and metabolic disorders under obese condition, but also participate in the maintenance of WAT immunometabolic homeostasis under lean condition.

Macrophages mediate divergent effects on immunometabolism depending on their different phenotypes. Based on different stimuli, macrophages can be classified into classically activated M1 and alternatively activated M2 subsets. M1 macrophages activated by lipopolysaccharide (LPS) plus interferon (IFN)-γ release proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and so on; while M2 macrophages activated by IL-4 and IL-13 release IL-10 and arginase-1 to play an anti-inflammatory effect. Different from the response of macrophages to *in vitro* stimulation, ATMs *in vivo* display more complexity and flexibility in gene profiles, phenotypes, and functions. Though many researchers tend to classify ATMs into M1-like and M2-like macrophages, we will specify their characteristic phenotypes in this review unless these characters are not indicated in these studies. As evidenced by the findings from Lumeng and Fujisaka et al., two types of ATMs dominate the regulation of WAT immunometabolism in different metabolic status. Under lean condition, CD206^{+} ATMs are dominant in epididymal WAT characterized by M2 phenotypes (high expression of Ym1, arginase 1 and IL-10), which facilitate immunometabolic homeostasis in WAT. While diet-induced obesity induces a population of CD11c^{+} ATMs characterized by M1 phenotypes (high expression of iNOS and TNF-α) that drive immunometabolic disorders in WAT (55–57). Once obesity induces the phenotype switch of ATMs, proinflammatory cytokines secreted by M1 ATMs, particularly TNF-α, IL-1 and IL-6, play a direct role in promoting insulin resistance and exacerbating local or systemic metabolic dysfunction. On the contrary, IL-10 produced by M2 ATMs can relieve TNF-α-induced insulin resistance (27, 55, 58, 59). Besides aforementioned ATMs, other distinct populations of ATMs have recently been identified to exert both immune and metabolic functions and will not be detailed here (60).

ADIPOSE EVS IN REGULATING IMMUNOMETABOLISM

EVs surrounded by bilayer membranes are produced by the cells and released into extracellular space. Because of their capacity for carrying and delivering various cargos to neighboring or distant recipient cells in an easy and safe way, EVs are recently recognized as the efficient messengers between cells even organs. EVs can be divided into microvesicles and exosomes according to sizes and biogenesis. Microvesicles, sometimes referred to as microparticles or ectosomes in earlier studies, have a larger size of about 100-1000 nm in diameter, which are usually released from plasma membrane into extracellular space through outward budding. So, the molecule compositions of microvesicles are largely dependent on their cell sources and may vary a lot with cell types. In contrast, exosomes are around 30-150 nm in diameter, which are generated from the endosome membrane by inward budding to form intraluminal vesicles inside multivesicular bodies (MVBs). Exosomes are released by

the fusion of MVBs with plasma membrane and exocytosis (13, 61, 62). Thus, exosomes from different cell types usually possess some common proteins involved in exosome biogenesis and release, such as Alix, TSG101 and several tetraspanins. These molecules have been well recognized as exosome markers, among them CD9, CD63 and CD81 are commonly used as surface markers. Of note, various bioactive proteins, lipids, and nuclear acids carried by EVs contribute to their heterogeneity and complexity in molecule compositions and functional diversity. Kinds of proteins including membrane proteins, cytosolic and nuclear proteins can be found in EVs. Due to phospholipid bilayer and lipid rafts embedded within the membranes, EVs contain plentiful lipids such as sphingomyelin, cholesterol and ceramide. In addition, different kinds of DNA and RNA including mRNA and noncoding RNA are also enclosed in EVs. As for the uptake of EVs by recipient cells, several different pathways have been proposed, which include phagocytosis or micropinocytosis, direct membrane fusion, clathrin or caveolin-mediated endocytosis, as well as lipid raft-mediated endocytosis. While other particular docking receptors for EV binding remain to be uncovered. These uptake modes of

EVs may depend on the types and physiological states of recipient cells (63–67) (**Figure 1**).

Adipose EVs

In WAT, many kinds of cells including aforementioned adipocytes, ADSCs and macrophages have been found to produce EVs to regulate local or systemic immunity and metabolism. As such, EVs act as the pivotal messengers for intercellular communication inside or outside adipose tissue. To date, various profiles and functions of adipose EVs have been revealed by different groups. Based on these findings, some characteristic markers have been found in adipose EVs, which are helpful for us to understand their exact cell sources and functions in circulation or tissues. In recent studies, adiponectin and fatty acid binding protein 4 (FABP4) were usually considered as the specific markers of EVs from adipocytes (68–70), while perilipin A was identified as a biomarker of stressed adipocytes in case of obesity in both human and mice (71). In addition, it has recently been found that CD31 specific for endothelial cells was highly enriched in EVs from primary endothelial cells of the mice, which may be added to the list of
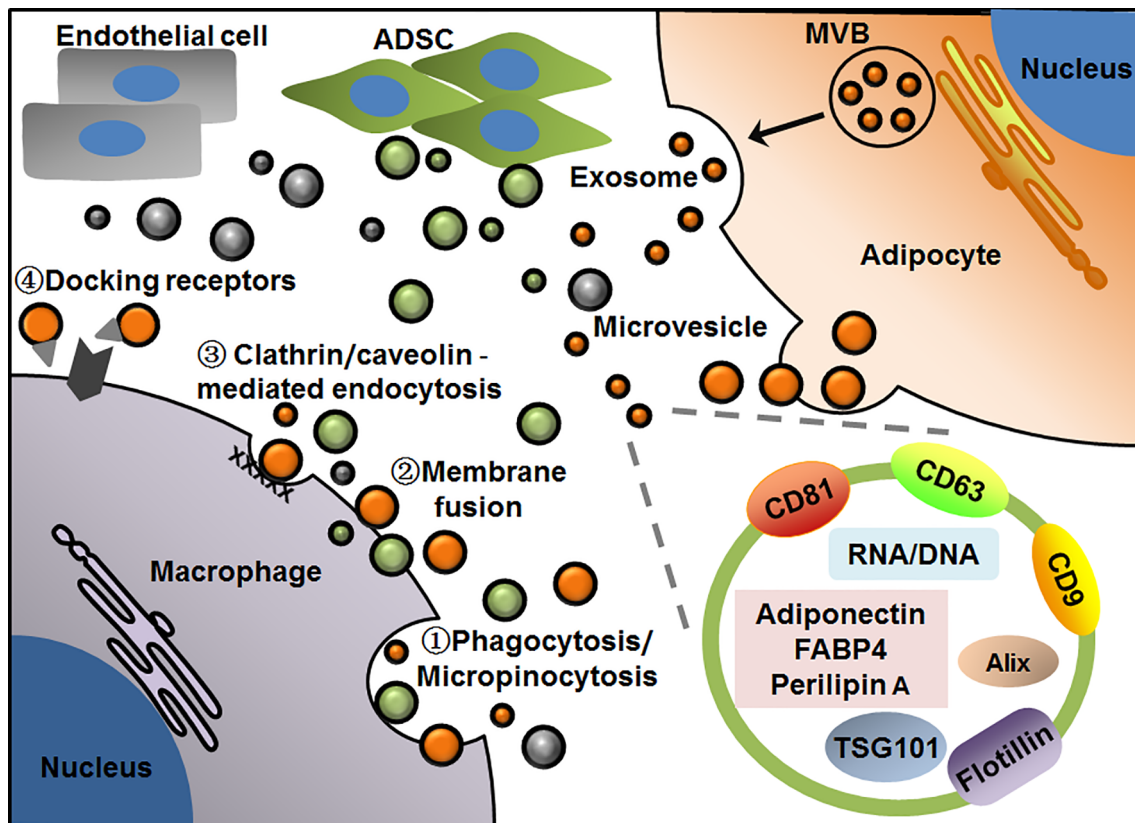

FIGURE 1 | Patterns of EV-mediated communication of adipocytes with macrophages in adipose tissue. Adipocytes release microvesicles and exosomes through outward budding of plasma membrane or exocytosis *via* MVB pathway, respectively. Macrophages take up EVs by phagocytosis/micropinocytosis①, direct membrane fusion②, clathrin/caveolin -mediated endocytosis③ or binding with particular docking receptors④. Adipocyte-derived exosomes display general markers such as CD81, CD63, CD9, Alix, TSG101 and flotillin, as well as several cell-specific molecules such as adiponectin, FABP4 and perilipin A. EVs from adipocyte, ADSC or endothelial cell are presented in orange, green and gray, respectively.

cell-specific markers of adipose EVs (72). As for EVs from other cell components, most of the studies used common exosome markers, whereas few studies reported their specific markers related to cell types. For instance, CD9, CD63, TSG101 were usually used to identify exosomes isolated from both primary ADSCs and macrophages regardless of cell sources (73) (**Figure 1**).

In terms of adipose-related EVs, several earlier studies put more attention on the alteration and overall effects of these EVs upon obesity rather than their specific sources and functions. In these studies, EVs were isolated from adipose tissue explants or plasma regardless of their cell sources (74–76), so it is relatively difficult to determine their exact cell-to-cell pathways and related regulatory mechanisms. Besides the direct influences on WAT functions (discussed later), adipose EVs also influence remote metabolic tissues such as liver and muscle by regulating local or systemic immune microenvironments. Two studies from adolescents demonstrated that exosomes with specific miRNA profile from obese visceral fat targeted TGF-β signaling pathways, which were possibly associated with inflammation and fibrosis in end-organ caused by obesity (75, 77). While another human study revealed that EVs from obese visceral fat impaired the insulin action in HepG2 hepatocytes, possibly related to their high loading of MCP-1, IL-6 and macrophage migration inhibitory factor (MIF) (74). However, there was no evidence for the direct effects of these EV miRNA or cytokines on related signaling pathways in target tissues or cells. Although accumulating data have demonstrated the package of various cytokines in EVs, the precise functions of these EV-associated cytokines remain largely unknown, possibly due to their different action modes from free soluble cytokines. Free soluble cytokines act on recipient cells through binding their specific receptors on plasma membranes to mediate relevant signaling pathways. While EV-packaged cytokines may cause more complicated effects in recipient cells, as they can be taken up through different pathways including phagocytosis, pinocytosis, or receptor-mediated endocytosis (64, 78–80). An earlier study showed that the membrane form of TNF-α carried by exosomes could activate its classical NF-κB signaling pathway. Later, Fitzgerald and colleagues revealed that cytokines could be bounded to EV surface or encapsulated inside EVs (78, 79). Thus, there is still the possibility that adipose EV-associated cytokines activate conventional signaling pathways in recipient cells. As the production of cytokines from the cells in soluble or EV-associated forms may depend on different cell types, stimulus factors and activation status (79–81), it will be more complicated to clarify the fine-tune regulation of adipose EVs on remote metabolic organs. With respect to the regulation of adipose EVs in WAT, emerging studies have demonstrated the precise cell-to-cell crosstalk, which cover the various interactions between adipocytes, stromal cells, endothelial cells, and immune cells. For example, Scherer's group recently revealed that epithelial cells communicated with adipocytes through small EVs (sEVs) in WAT. Using adipocyte-specific caveolin 1 (cav1) knockout mice and a series of *in vivo* and *in vitro* tracking techniques, they demonstrated that sEVs mediated the trafficking of cav1, a membrane-bound protein abundant in adipocytes and

endothelial cells, from neighboring endothelial cells to adipocytes. More interesting, this EV transfer was regulated by different metabolic state *in vivo*, which was increased by fasting but returned to basal levels when feeding. Particularly, the production of EVs from the endothelial cells of obese WAT was almost absent, indicating the importance of these EVs in metabolic homeostasis (72).

Adipose EVs in Adipocyte-Macrophage Dialogue

As critical parenchymal cells and immune cells of WAT, adipocytes and macrophages cooperate with each other to regulate local or systemic immunometabolic homeostasis or disorders (37, 38, 59, 82). As mentioned earlier, ATMs characterized by CD206^{+} M2 phenotypes are abundant in lean adipose tissue, while obesity induces the infiltration and activation of macrophages with CD11c^{+} M1 phenotypes. This phenotype switch of macrophages is currently believed to be caused by hypertrophic or apoptotic adipocytes in obese adipose tissue, which in turn impairs the insulin action in adipocytes (55, 59). The interaction between adipocytes and macrophages can be mediated by multiple ways such as adipocyte-derived free fatty acids and macrophage-derived cytokines, whilst EVs are emerging as the important intercellular messengers to exert functions during this process.

Actions of Adipocyte-Derived EVs on Macrophages

It has been demonstrated that both human and mice adipocytes could release EVs that were detectable in circulation. So, adipocytes are the important sources of EVs that influence the microenvironments inside even outside adipose tissue. Upon metabolic stresses like obesity, the production of adipocyte-derived EVs was increased whilst their cargos were changed (71, 83–86). To some extent, these alterations in adipocyte EVs may serve as the indicators of adipose tissue health even biomarkers of metabolic disorders. More importantly, these EVs are actively involved in regulating immunometabolic homeostasis or disorders through acting on nearby or distant target cells including adipocytes, endothelial cells, immune cells even neuron (87–89). Regarding the regulation of adipocyte-derived EVs on immune cells, most of the studies focus on macrophages rather than other cell types. Adipocytes release EVs to act on either monocytes or macrophages, thus producing regulatory effects on both immunity and metabolism. Initially, Deng et al. showed that exosome-like vesicles from visceral fat of obese mice could be taken up by blood monocytes, and then promoted their differentiation into macrophages and activation characterized by TNF-α and IL-6 secretion. Transfusion of these exosome-like vesicles from obese fat significantly impaired the insulin sensitivity of lean mice, which was dependent on toll-like receptor (TLR) 4 pathway. Through *in vitro* experiments, exosomal retinol binding protein 4 (RBP4) was verified to be responsible for the inflammatory activation of macrophages (90). This study raised the possibility that EVs from hypertrophic

adipocytes might promote ATM activation and cause obesity-associated inflammation and insulin resistance. Additionally, Renovato-Martins et al. demonstrated that microparticles (with similar sizes to microvesicles) from human obese omental fat could upregulate the expression of CD16 and CCR5 on human monocytes and increased their migration capacity. In particular, they found that these microparticles from obese fat carried abundant TLR8 compared to those from lean fat, which could be transferred into monocytes and induced the expression of CD16 (91). These observations provided evidences for macrophage migration and activation mediated by EVs from obese fat, which may explain at least in part the contribution of these EVs to ATM infiltration and activation in obese WAT. Considering these EVs were isolated from WAT explants, their exact cell sources remained to be confirmed though the circulating EVs from adipocytes were increased in response to obesity. In recent years, accumulating evidences have demonstrated the direct regulation of adipocyte-derived EVs on macrophage functions including differentiation, migration and polarization. Several studies showed that EVs from mouse or human adipocytes not only induced the migration of primary monocytes and macrophages, but also promoted their differentiation into ATM phenotypes, though EVs with different sizes might target to different pathways in recipient cells (70, 92). Several proteins like MIF, macrophage-colony stimulating factor (M-CSF) and TNF-α have been identified in EVs from in vitro-differentiated human adipocytes, which might contribute to the proinflammatory phenotypes of macrophages, and these macrophages in turn impaired the insulin action on adipocytes (70), suggesting that EVs could drive a reciprocal interaction between adipocytes and macrophages. Using primary adipocytes from obese mice, Tamara et al. demonstrated that EVs from pathologically hypertrophic adipocytes with distinct protein profile not only promoted macrophage inflammation by elevating TNF-α and IL-6, but also induced adipocyte differentiation and impaired insulin action of heathy adipocytes (93). Since these observations were obtained from in vitro culture system, the influences of in vivo micro environments and EV-associated cytokines need to be considered and determined. Notably, a recent study provided an insight into the regulation of adipocytes on ATM polarization via exosomes, in which mature adipocytes secreted exosomal miRNA (miR)-34a into macrophages and inhibited CD206+ M2 polarization by downregulating Krüppel-like factor 4. In line with the detrimental roles of miR-34a in obesity-associated metabolic dysregulation, these observations may provide an explanation for adipose tissue inflammation mediated by adipocyte-ATM crosstalk via exosomal miR-34a in obese mice (94). In a slightly different way, the upregulation of miR-155 in adipocyte-derived microvesicles from obese mice, as shown in another study, contributed to M1 polarization depending on the activation of signal transducer and activator of transcription (Stat) 1, whilst these microvesicles also elicited a significant decline of CD206+ M2 percentages in bone marrow-derived macrophages (95). These observations defined EVs as the transporters of specific miRNA from adipocytes to macrophages under obese condition, which mediated macrophage polarization through different ways, probably due to their different types and contents (**Table 1**). Considering the high heterogeneity of EV contents, the combined effects of these EV miRNA cannot be excluded.

Aside from immune regulation, some recent works also demonstrated the influences of adipocyte-derived EVs on metabolic functions of macrophages. Flaherty III et al. provided evidences for the release of lipid-filled exosomes from mice adipocytes. These exosomes were taken up by bone marrow precursors in vitro and promoted their differentiation into ATM-like cells. This study revealed an alternative pathway for lipid metabolism, by which adipocyte-derived exosomes mediated the transportation of triglyceride into macrophages and subsequent hydrolysis, thus establishing a local lipid cycle to maintain homeostasis in perigonadal WAT (83) (**Table 1**). Indeed, besides triglyceride, fatty acids were also present in specific fraction of EVs from both human and mouse adipocytes, some of them were increased by obesity and influenced the functions of target cells through regulating metabolism (96, 97). With respect to the functions of these fatty acid-loaded EVs on macrophages, it remains an open but interesting area for future study. In addition, adipocyte-derived EVs also produce influence on the cholesterol metabolism of macrophages. Visceral fat from HFD-fed mice could release exosomes to induce the formation of macrophage foam cells by impairing their cholesterol efflux, thereby exacerbating atherosclerosis in hyperlipidemic apolipoprotein E-deficient mice (98). The similar effects on cholesterol efflux were also observed in EVs shed by human visceral fat, and the majority of these EVs were verified to be adipocyte origin (99). However, if the effects of EV miRNA specified in this study could be further verified, particularly for EVs from primary adipocytes, the above conclusion would be more convincing. Based on the roles of EVs, some treatments targeting the crosstalk between adipocytes and macrophages may provide protection against obesity-associated metabolic disorders by altering the release and regulatory effects of EVs from adipocytes. For instance, exosomes from melatonin-treated adipocytes inactivated Stat3/NF-κB signaling and alleviated HFD-induced adipose inflammation, hepatic ER stress and steatosis in vivo (100, 101).

Action of Macrophage-Derived EVs on Adipocytes

In addition to taking up EVs as recipient cells, macrophages also release EVs to influence other cells. Earlier studies demonstrated that human THP-1 monocytes or differentiated macrophages produced EVs with specific miRNA, which could act on target cells to influence their functions, such as inducing monocyte differentiation into macrophages (102–106). Recently, several in vitro studies provided evidences for EV-mediated action on adipocytes by macrophages. Microvesicles from THP-1-differentiated M1 macrophages, which were induced by LPS plus IFN-γ, significantly induced insulin resistance in human adipocytes (107). While exosomes from THP-1-differentiated macrophages, which were induced by LPS, had no influences on

TABLE 1 | EVs involved in adipocyte-macrophage dialogue and ADSC-macrophage interaction.

Source	EVs	Contents	Target	Function	Reference
VAT from obese mice (adipocytes)?	Exosome-like vesicles	RBP4	Monocytes Macrophages	Promote differentiation of monocytes into macrophages Promote inflammatory activation of macrophages Induce insulin resistance in mice	Deng et al. Diabetes
Stressed 3T3-L1 adipocytes	Microparticles	–	Macrophages	Mediate attraction of macrophages *in vitro* and *in vivo*	Eguchi, A., et al. PLoS One
Human *in vitro* differentiated adipocytes	EVs	RBP4, TNF-α, MIF	Monocytes	Differentiate monocytes into macrophages with ATM characteristics (pro- and anti-inflammatory phenotypes)	Kranendonk, et al. Obesity
Mouse hypertrophied adipocytes	EVs	–	RAW264.7 macrophages	Promote inflammation of macrophages	Tamara, C. et al. Int J Mol
Mature adipocytes from VAT of obese mice	Exosomes	MiR-34a	ATMs, BMDMs	Suppress the macrophages polarization toward M2 *in vitro*	Pan, Y. et al. J Clin Invest
Primary adipocytes from VAT of obese mice	Microvesicle	MiR-155	BMDMs	Promote M1 macrophage activation	Zhang, et al. J Mol Cell Biol,
Mouse adipocyte from VAT	Exosomes	Triglyceride	Bone marrow precursors, ATMs	Induce differentiation of bone marrow progenitors into ATM-like cells	Flaherty, et al. Science
VAT of obese mouse (adipocytes)?	Exosomes	–	RAW264.7	Promote formation of macrophage foam cell formation Promote macrophage polarization into M1 phenotypes Exacerbate atherosclerosis in apolipoprotein E–deficient mice	Xie, Z. et al. J Am Heart Assoc
THP-1 differentiated- M1 macrophages (induced by LPS plus IFN-γ)	Macrovesicles	–	Human adipocytes	Induce insulin resistance in human adipocytes	Zhang, Y., et al. Nutr Metab
THP-1-differentiated macrophages (induced by LPS)	Exosomes	Specific miRNA	Human adipocytes	Change the expression of genes related to inflammation in adipocytes	De Silva, et al. J Physiol Biochem
High glucose-induced RAW264.7 macrophage	Exosomes	MiR-210	3T3-L1 adipocytes	Impair glucose uptake and mitochondrial activity in adipocytes	Tian, F., et al. Journal of Diabetes Research
ATMs from Obese mice	Exosomes	MiR-155	Mouse adipocytes	Impair insulin action and glucose uptake in adipocytes Cause insulin resistance in lean mice	Ying, W. et al. Cell
ATMs from lean mice	Exosomes	–	Mouse adipocytes	Increase insulin action and glucose uptake in adipocytes Improve insulin sensitivity in obese mice	Ying, W., et al. Cell
Obese ATMs	Exosomes	MiR-29a	Adipocytes	Impair insulin action in adipocytes Impair insulin sensitivity in lean mice	Liu, T, et al. Biochem Biophys Res Commun
Lean ADSCs	Exosomes	Stat3	Macrophages ATMs	Promote macrophage polarization into M2 phenotypes Induce WAT beiging and improve insulin sensitivity in HFD-fed mice	Zhao, H., et al. Diabetes

VAT, Visceral adipose tissue; BMDM, Bone marrow derived macrophage.

insulin-mediated glucose uptake in human adipocytes, but changed their gene expression related to inflammation pathways (108). Moreover, high glucose promoted the package of miR-210 into exosomes from macrophages, which impaired glucose uptake and mitochondrial activity in 3T3-L1 adipocytes (109). These studies showed a slight difference in the effects of macrophage-derived EVs, possibly resulting from different stimuli on the macrophages, or different EV types carrying distinct components from the macrophages. Of note, these findings reflect the fact that both inflammatory and metabolic stresses could be passed from macrophages into adipocytes through EVs (**Table 1**).

Direct evidences for the regulation of ATMs on adipocyte functions come from the animal studies. Ying and colleagues isolated exosomes from mouse ATMs and observed their transportation into 3T3-L1 adipocytes through *in vitro* experiments. Interestingly, exosomes from either obese or lean ATMs produced different effects on insulin action in both insulin-target cells and animal models. Lean mice treated with obese ATM exosomes showed obvious insulin resistance, whereas obese mice treated with lean ATM exosomes showed improvement of insulin sensitivity. Consistently, exosomes from obese ATMs impaired insulin-induced AKT activation and glucose uptake in 3T3-L1 adipocytes, whereas exosomes from lean ATMs improved this process. Compared with lean ATM exosomes, obese ATM exosomes contained abundant miR-155, which might contribute to these undesired effects probably through targeting peroxisome proliferator-activated receptor (PPAR) -γ (110). In support of this study, another report also showed the impairment of insulin action in both 3T3-L1 adipocytes and lean mice by obese ATM exosomes, in which miR-29a was identified to be increased and exerted deleterious effects dependent on PPAR-δ (111). Meanwhile, both of the studies provided evidences for the effects of ATM exosomes on insulin sensitivity in hepatocytes and myocytes besides adipocytes (110, 111). The differences in exosomal miRNA profiles and their target pathways between these two studies remain to be clarified. Possible explanation might be the influence of differences in animal models, cell or exosome isolation methods and so on. Furthermore, another interesting study found a distinct population of lipid-laden ATMs with the capacity for exosome production, which could induce proinflammatory gene signature in adipose tissue similar to obese WAT, suggesting that ATMs could perform functions in both metabolism and immunity through EVs (60). Altogether, these findings have demonstrated the considerable impacts of ATM-derived EVs on local or systemic immunometabolism by targeting adipocytes as well as other cell types *via* paracrine and endocrine (**Table 1**).

Adipose EVs in ADSC-Macrophage Interaction

In response to metabolic demands or stresses, ADSCs serve as the source of adipocytes that regulate glycolipid metabolism in adipose tissue. Meanwhile, as the main stromal cells, ADSCs also act as indispensable immune regulators inside or outside

adipose tissue. During these processes, ADSCs and macrophages cooperate to form dynamic microenvironments to regulate immunometabolic homeostasis or disorders. Accumulating data have shown that either human or mouse ADSCs have an ability to promote the alternative activation of macrophages and inhibit the inflammation of monocytes/macrophages. These effects elicited by ADSCs provided protection against several inflammatory diseases in animal models such as experimental colitis, sepsis, hepatitis and neuroinflammation (43–46, 112–114). The early evidence for the regulation of ADSCs on monocytes or macrophages came from Gonzalez-Rey's study, in which human ADSCs inhibited the production of TNF-α and IL-12 from activated macrophages of septic mice. More excitingly, systemic infusion of ADSCs protected against severe colitis and sepsis in animal models, suggesting the anti-inflammatory effects of ADSCs (44). Later, we demonstrated the strong ability of mouse ADSCs to promote the expression of IL-10 and arginase 1 in macrophages and their potential to inhibit obesity-induced WAT inflammation, further confirming the regulation of ADSCs on macrophages as well as inflammatory diseases (47). In a similar manner, ADSCs induced the alternative activation of macrophages and ameliorated colitis or neuroinflammation in animal models through several different pathways or inhibitory molecules like TSG-6 (43, 46, 112–114). Consistent with the roles of mouse ADSCs in obesity-induced WAT inflammation, human or rat ADSCs also displayed beneficial effects on relieving obesity-induced metabolic disorders, type 2 diabetes mellitus related complications in lung, liver, kidney, as well as cardiovascular diseases such as cardiac hypertrophy and aortic inflammation. And importantly, ADSC-induced macrophage polarization was actively involved in the above processes (47–50, 115–117). Conversely, macrophages with distinct phenotypes could also produce different effects on proliferation, differentiation and adipogenesis of ADSCs, either maintaining or disrupting local or systemic metabolic homeostasis (118–121). As both ADSCs and macrophages change their characteristics and functions with the alteration of metabolic status, instant information exchanges are necessary for the interaction between ADSCs and macrophages, in which soluble factors including EVs and cytokines are actively involved.

Regarding the communication of ADSCs with macrophages, several studies have provided evidences for the pivotal roles of soluble factors during these processes (122–124). Our previous study showed that ADSCs from lean mice attenuated obesity-induced WAT inflammation and metabolic disorders, in which soluble factors from ADSCs played critical roles in remodeling IL-10^{high} and arginase 1[high] M2-like macrophages (47). Considering that ADSCs produce abundant EVs, it is inevitable to add EVs to the list of ADSC-macrophage dialogue. As expected, the delivery of exosomes from lean ADSCs into obese mice produced desirable effects on relieving obesity and improving insulin sensitivity in these mice. Exosomes from lean ADSCs promoted macrophage polarization toward arginase-1[high] M2 phenotypes in visceral adipose tissue, which facilitated WAT beiging and homeostasis

in HFD-fed mice. Using primary macrophages, we demonstrated that these exosomes could carry active Stat3 to promote M2 polarization and inhibit macrophage inflammation (125) (**Table 1**). Subsequently, several other studies confirmed that exosomes from either human or mouse ADSCs showed similar effects on macrophages, and more importantly, these exosomes were applied into the treatment of different disease models related inflammation or injury in animals (73, 126–130). Notably, the therapeutic potentials of ADSC-derived EVs have also been reported in metabolism-related disease models such as type 1, type 2 diabetes or diabetic nephropathy, and more target cells like T cells, hepatocytes or podocytes have been revealed (131–135). All these observations suggest that ADSC-derived EVs may regulate immunometabolic homeostasis in multiple ways. With respect to different types, contents of EVs from ADSCs as well as their detailed regulatory mechanisms, further investigation is still required. On the other hand, there are few reports regarding the action of ATM EVs on ADSCs, though some data showed that EVs from human monocytes influenced

the expression of genes associated with cytokines or chemokines in human ADSCs (136).

CONCLUSIONS AND PERSPECTIVES

Recent studies provide evidences for the pivotal roles of adipose EVs that are produced by or act on macrophages in mediating adipocyte-macrophage dialogue and ADSC-macrophage interaction, as well as their roles in regulating local or systemic immunometabolism. Under physiological conditions, EVs released from ADSCs may dominate their interaction with macrophages to induce M2 phenotypes (IL-10^{high}, arginase 1^{high}), which facilitate the maintenance of immunometabolic homeostasis in WAT. While under pathological conditions such as obesity, EVs released from adipocytes, particularly hypertrophic adipocytes, may dominate their dialogue with macrophages to induce the infiltration and M1 polarization (TNF-α^{high}, iNOS^{high}) of macrophages. Macrophages switch
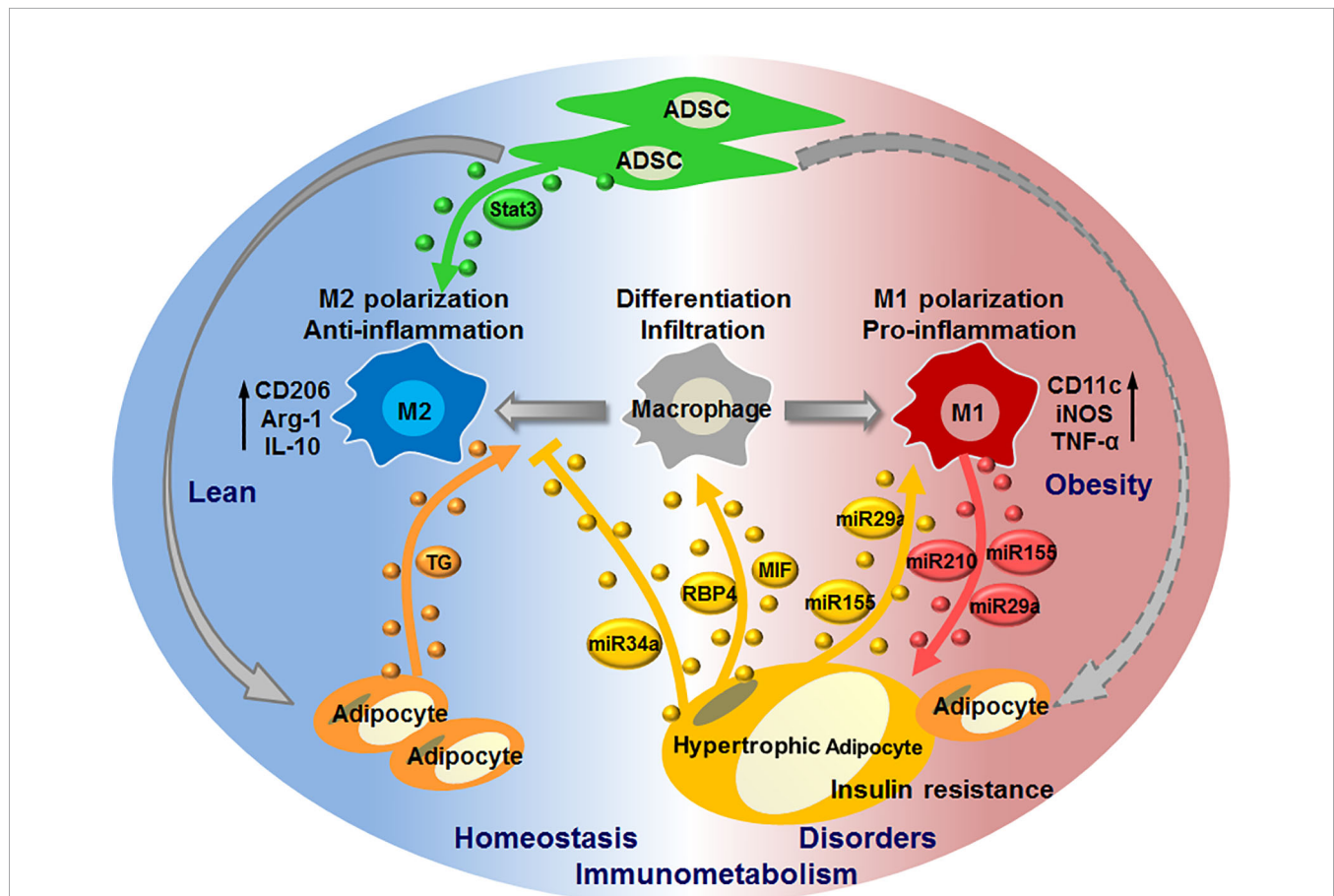

FIGURE 2 | EV-mediated interaction of macrophages with adipocytes or ADSCs in regulating immunometabolic homeostasis or disorders. Under healthy condition, ADSCs release EVs carrying active Stat3 to induce macrophage polarization toward M2 phenotypes; adipocytes release EVs to transfer lipid (triglyceride, TG) into macrophages, thereby maintaining immunometabolic homeostasis in WAT. In case of metabolic stress like obesity, hypertrophic adipocytes secret EVs with MIF, RBP4, miR-155, miR-34a, miR-29a to promote macrophage infiltration and M1 polarization, whilst suppress M2 polarization; M1 macrophages in turn cause insulin resistance of adipocytes through delivering miR-155, miR-29a, miR-210 *via* EVs, thus forming a vicious cycle to promote immunometabolic disorders in WAT.

their phenotypes to promote metabolic inflammation in WAT, and in turn release EVs to impair adipocyte functions, eventually forming a vicious cycle to aggravate immunometabolic disorders in WAT. Furthermore, adipocytes can also transfer lipid into ATMs by releasing EVs, which may mediate a lipid cycle to participate in immunometabolism (**Figure 2**).

Considering the complexity and diversity of adipose EVs, EVs from and to macrophages in immunometabolism remain to be further elucidated. For future studies in this field, several directions may be helpful. From the spatial dimension, various of EVs with distinct cell sources and targets need to be determined for their special contents and functions in specific microenvironments. From the time dimension, instant alterations of EV types, numbers and contents are required to be monitored with the change of immune or metabolic microenvironments. From the perspective of application, more promising EV-based biomarkers and therapeutic approaches are still awaiting to be identified and constructed.

AUTHOR CONTRIBUTIONS

ZZ and YT drafted the manuscript. HZ revised and edited the manuscript. ZZ designed and created the figures and tables. QW wrote and revised the manuscript, designed the figures and tables. All authors contributed to the article and approved the submitted version.

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