Review

Adiponectin: a versatile player of innate immunity

Yan Luo[1,2] and Meilian Liu[1,2,*]

[1] Institute of Metabolism and Endocrinology, Metabolic Syndrome Research Center, the Second Xiangya Hospital, Central South University, Changsha 410011, China
[2] Department of Biochemistry and Molecular Biology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA
* Correspondence to: Meilian Liu, E-mail: meilianliu@salud.unm.edu

Adiponectin acts as a key regulator of the innate immune system and plays a major role in the progression of inflammation and metabolic disorders. Macrophages and monocytes are representative components of the innate immune system, and their proliferation, plasticity, and polarization are a key component of metabolic adaption. Innate-like lymphocytes such as group 2 innate lymphoid cells (ILC2s), natural killer T (NKT) cells, and gamma delta T (γδ T) cells are also members of the innate immune system and play important roles in the development of obesity and its related diseases. Adiponectin senses metabolic stress and modulates metabolic adaption by targeting the innate immune system under physiological and pathological conditions. Defining the mechanisms underlying the role of adiponectin in regulating innate immunity is crucial to adiponectin-based therapeutic intervention.

Keywords: adiponectin, innate immunity, macrophage, innate-like lymphocyte

Introduction

Adiponectin is an adipokine whose expression and circulating levels are downregulated during obesity in human subjects and exerts anti-diabetic effects (Fisher et al., 2005; Kadowaki and Yamauchi, 2005; Ahima, 2006). Moreover, it is well established that adiponectin acts as an endogenous insulin sensitizer (Berg et al., 2001; Yamauchi et al., 2001; Tsao et al., 2002). In addition, adiponectin plays an important role in regulating immune responses such as inflammation, being a critical pathogenic mediator of the development of obesity-induced insulin resistance (Esmaili et al., 2014). However, whether adiponectin acts as an anti- or pro-inflammatory factor is still a matter of much debate (Maeda et al., 2002; Xu et al., 2003; Tsatsanis et al., 2005; Park et al., 2007). Some studies report that adiponectin functions as an anti-inflammatory mediator during the progression of metabolic diseases (Maeda et al., 2002; Xu et al., 2003). In contrast, other studies show that adiponectin promotes an inflammatory response by activating NF-κB and inducing inflammatory cytokines IL-1 and IL-6 under certain circumstances (Tsatsanis et al., 2005; Park et al., 2007).

Innate immunity has been defined as the non-specific first line of defense against foreign pathogens. It contains an integral facet of the immune response, which is mediated by dendritic cells (DCs), natural killer (NK) cells, macrophages, neutrophils, basophils, eosinophils, mast cells, and innate-like lymphocytes. Over the past decade, the innate immune response mediators, particularly macrophages and innate-like lymphocytes, have been identified as key modulators in the regulation of energy and glucose homeostasis (Molofsky et al., 2013; Brestoff et al., 2015). Moreover, accumulating evidence suggests that adiponectin regulates energy expenditure and insulin sensitivity via innate immune response-dependent mechanisms (Tsuchida et al., 2005; Luo et al., 2010, 2011; Awazawa et al., 2011; Hui et al., 2015). In this review, we will summarize and discuss the recent findings concerning adiponectin regulation of innate immunity.

Adiponectin regulation of macrophage proliferation, plasticity, and polarization

Macrophages are present in metabolic tissues such as fat, liver, and muscle, and their proliferation, plasticity, and polarization are driven by obesity (Weisberg et al., 2003; Chawla et al., 2011; Odegaard and Chawla, 2011; Bai and Sun, 2015). Obese adipose tissue expression of inflammatory molecules, such as CCR2, can recruit and activate monocytes and macrophages (Weisberg et al., 2003, 2006; Bai and Sun, 2015). Activated macrophages including M1 and M2 macrophages, in turn, modulate thermogenesis, inflammation, and insulin sensitivity (Bourlier and Bouloumie, 2009; Chawla et al., 2011; Nguyen et al., 2011; Odegaard and Chawla, 2011; Qiu et al., 2014; Rao et al., 2014; Hui et al., 2015; Lackey and Olefsky, 2016). M1 or classically activated macrophages trigger the production of pro-inflammatory cytokines and mediate obesity-induced insulin resistance and type 2 diabetes (Chawla et al., 2011; Bai and Sun, 2015). In contrast, M2 or alternatively activated macrophages are polarized by IL-4 and IL-13 and play an important role in the promotion of oxidative metabolism, induction of tissue repair, and blockade of inflammatory responses (Nguyen et al., 2011; Odegaard and Chawla, 2011; Mantovani et al., 2013). Therefore, understanding macrophage activation,

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which is defined across M1 and M2 polarization states (Mantovani et al., 2004; Gordon and Taylor, 2005), is critical for identification of therapeutic targets toward inflammation-associated metabolic diseases.

Adiponectin, a 30-kDa adipokine exclusively secreted from adipose tissue, exists in cells and plasma in three major forms: trimers, hexamers, and the high-molecular-weight (HMW) form (Scherer et al., 1995; Hu et al., 1996; Maeda et al., 1996; Pajvani et al., 2004). Adiponectin has a similar structure as a complement factor C1q (Scherer et al., 1995). C1q is a well-known component of innate immunity and plays a vital role in regulating macrophage polarization as well as other types of innate immune cells (Bohlson et al., 2014; Kouser et al., 2015). Both C1q and adiponectin promote clearance of apoptotic cells through Mer tyrosine kinase (Mer), a receptor that regulates efficient efferocytosis and prevention of autoimmunity (Galvan et al., 2014). As the most abundant adipokine in the body, adiponectin exerts multiple protective properties against inflammation (Yokota et al., 2000; Ouchi et al., 2001), obesity (Scherer et al., 1995; Hu et al., 1996; Maeda et al., 1996; Pajvani et al., 2004), insulin resistance (Tomas et al., 2002; Gil-Campos et al., 2004; Haluzik et al., 2004; Hoffstedt et al., 2004), and cardiovascular diseases (Goldstein and Scalia, 2004; Ouchi et al., 2004; Shibata et al., 2005). Downregulation of adiponectin has been shown to be associated with high levels of inflammatory markers and various metabolic disease states (Ouchi et al., 2003; Gil-Campos et al., 2004; Pischon et al., 2004). There is extensive evidence showing that adiponectin acts as anti-inflammatory mediator through the regulation of M1 and M2 macrophage proliferation, plasticity, and polarization (Yokota et al., 2000; Wolf et al., 2004; Wulster-Radcliffe et al., 2004; Ajuwon and Spurlock, 2005; Ohashi et al., 2010; Hui et al., 2015). However, adiponectin has also been proposed to exert pro-inflammatory effects under certain circumstances.

Adiponectin suppresses M1 macrophage activation and promotes M2 macrophage proliferation, which accounts for its anti-inflammatory properties. Adiponectin deficiency leads to a classically activated macrophage phenotype *in vivo*, and recombinant adiponectin acts to promote a switch to an anti-inflammatory phenotype in macrophages (Ohashi et al., 2010). On the one hand, adiponectin suppresses inflammatory activation through downregulation of M1 macrophage markers such as TNF-α, MCP-1, and IL-6 (Wolf et al., 2004; Wulster-Radcliffe et al., 2004; Ajuwon and Spurlock, 2005; Ohashi et al., 2010). On the other hand, adiponectin promotes an anti-inflammatory response as evident by an upregulation of the anti-inflammatory M2 markers arginase-1, Mgl-1, and IL-10 in murine and human macrophages (Wolf et al., 2004; Ajuwon and Spurlock, 2005; Ohashi et al., 2010). The suppressing effect of adiponectin on M1 macrophage markers and promoting effect of adiponectin on M2 macrophage markers have been well studied in various cell types of macrophages (Figure 1). However, the underlying mechanisms remain to be elucidated (Chinetti et al., 2004; Wolf et al., 2004; Wulster-Radcliffe et al., 2004; Ajuwon and Spurlock, 2005; Tsatsanis et al., 2005; Park et al., 2007, 2008a, b; Yamaguchi et al., 2008). Since alternative

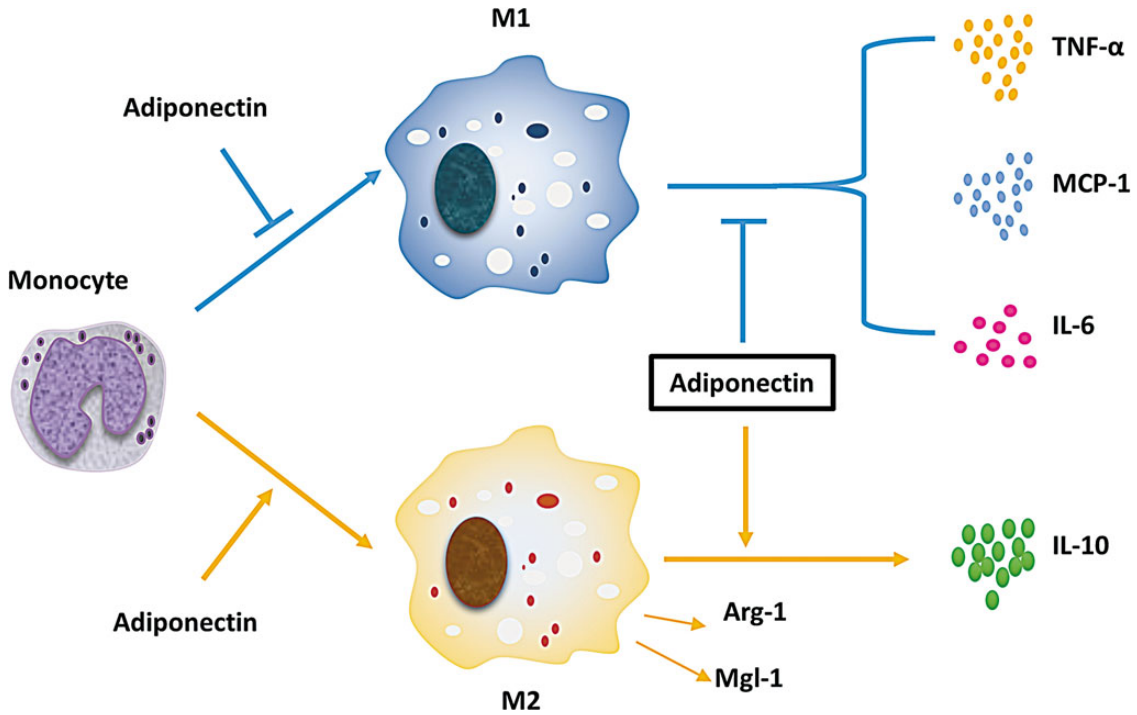

Figure 1 Adiponectin regulation of macrophage proliferation and polarization. Adiponectin acts as an anti-inflammatory factor and regulates macrophage proliferation and polarization. On the one hand, adiponectin suppresses differentiation and classical activation of M1 macrophages by downregulating pro-inflammatory cytokines, such as TNF-α, MCP-1, and IL-6 in macrophages. On the other hand, adiponectin promotes M2 macrophage proliferation and expression of anti-inflammatory M2 markers, such as Arg-1, Mgl-1, and IL-10.

macrophage polarization is prototypically driven by type 2 helper T cell (Th2) cytokines IL-4 and IL-13 *in vivo* (Odegaard and Chawla, 2011), it has drawn lots of attention as to whether adiponectin shares a similar mechanistic pathway as Th2 cytokines in regulating macrophage function. Although IL-4 was recently found to be derived from adipocytes and shown to positively regulate M2 macrophage activation and insulin sensitivity (Kang et al., 2008), it remains controversial whether adiponectin is as effective as IL-4 at conferring an anti-inflammatory phenotype to macrophages (Yokota et al., 2000; Ohashi et al., 2010). In addition, different from IL-4, adiponectin behaves as an initial pro-inflammatory factor in response to lipopolysaccharide (LPS), and helps to desensitize cells to further pro-inflammatory stimuli (Tsatsanis et al., 2005, 2006; Park et al., 2007).

Moreover, adiponectin has been shown to inhibit the inflammatory response by suppressing macrophage proliferation. Since monocytes can differentiate into M1 macrophages as well as alternative M2 macrophages, approaches that limit M1 while promoting M2 differentiation represent a unique therapeutic strategy. Yokota et al. (2000) found that adiponectin not only inhibits mature macrophage functions, such as phagocytosis and cytokine production, but also suppresses proliferation of myelomonocytic progenitors by promoting apoptosis. In addition, adiponectin has recently been shown to induce adipose M2 macrophage proliferation (Yokota et al., 2000; Hui et al., 2015). These findings suggest that adiponectin is a critical modulator of both M1 and M2 macrophage proliferation (Figure 1). Given that alternative activation of the M2 macrophage plays a critical role in regulating browning of white adipose tissue by producing and secreting norepinephrine, a hormone driving browning effect and thermogenesis in fat (Nguyen et al., 2011), induction of M2 macrophage proliferation by adiponectin provides a novel mechanism by which adiponectin promotes a cold-induced browning effect in subcutaneous adipose tissue (Hui et al., 2015). This study also demonstrates that the beneficial effect of adiponectin on metabolism is mediated by alternative activation of M2 macrophages and subsequent promotion of browning in adipose tissue. Taken together, these studies suggest that adiponectin is an important regulator of macrophage proliferation, plasticity, and function in inflammation and its related metabolic disorders (Figure 1).

Adiponectin action in monocytes/macrophages

Adiponectin exerts multiple beneficial effects by binding to its receptors, adiponectin receptor 1 and receptor 2 (AdipoR1 and AdipoR2) (Yamauchi et al., 2003, 2007; Kadowaki et al., 2006). As the predominant receptors for adiponectin, AdipoR1 and AdipoR2 play important roles in the regulation of inflammation, glucose and lipid metabolism, and oxidative stress shown both *in vivo* and *in vitro* (Yamauchi et al., 2003, 2007, 2014; Chinetti et al., 2004; Yamaguchi et al., 2005). In addition, T-cadherin, a cell surface-anchored glycoprotein, is effective in binding to adiponectin and mediates adiponectin signaling, while it falls short of being a receptor that both binds and transduces intracellular signaling pathways (Denzel et al., 2010). There is accumulating evidence showing that adiponectin exhibits insulin-sensitizing effects through multiple signaling pathways downstream of adiponectin receptors, such as AMPK, Ca^{2+}, PPARα, ceramide, and S1P (Yamauchi et al., 2007; Zhou et al., 2009; Iwabu et al., 2010; Holland et al., 2011). However, the signaling events underlying adiponectin modulation of immune cell function remain to be established.

AdipoR1, AdipoR2, and T-cadherin are present in monocytes/macrophages with high abundance of AdipoR1 (Chinetti et al., 2004; Yamaguchi et al., 2005; Hui et al., 2015); however, whether these receptors play important roles in mediating anti-inflammatory action of adiponectin in macrophages remains controversial. AdipoR1 predominantly binds to globular adiponectin (gAd) and mediates adiponectin suppression of NF-κB activation and pro-inflammatory cytokine expression in macrophages (Yamaguchi et al., 2005; Mandal et al., 2010a, b). On the other hand, AdipoR2 is required for full-length adiponectin-mediated M2 polarization (Mandal et al., 2011). In addition, T-cadherin, rather than AdipoR1 or AdipoR2, is stimulated by cold exposure and is essential for the stimulatory effects of adiponectin on M2 macrophage proliferation (Hui et al., 2015). However, suppression of AdipoR1, AdipoR2, or T-cadherin has little effect on adiponectin-stimulated uptake of apoptotic THP-1 cells (Takemura et al., 2007). These findings suggest that adiponectin may regulate macrophage proliferation and function through currently unknown receptor-mediated mechanisms.

Several intracellular signaling pathways appear to mediate adiponectin action in regulating macrophage proliferation and function (Figure 2). Firstly, Toll-like receptor (TLR)-mediated NF-κB signaling plays a critical role in adiponectin suppression of M1 macrophage proliferation and function (Ajuwon and Spurlock, 2005; Tsatsanis et al., 2005; Yamaguchi et al., 2008). Furthermore, adiponectin promotes endotoxin tolerance via activation of the Erk pathway in primary macrophages (Zacharioudaki et al., 2009). Against its anti-inflammatory action, adiponectin has been shown to initially promote a pro-inflammatory response by upregulation of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 by activating NF-κB and Erk pathways (Lappas et al., 2005; Tsatsanis et al., 2005, 2006; Park et al., 2007). However, the pro-inflammatory action of adiponectin is a transient effect, which contributes to LPS tolerance and eventually dampens LPS-mediated cytokine production in macrophages with continuous exposure to adiponectin, suggesting that chronic adiponectin induces LPS resistance (Tsatsanis et al., 2005, 2006; Park et al., 2007). Consistent with this, gAd treatment profoundly suppressed the ability of LPS to increase TNF-α transcription and reduced LPS-induced stabilization of TNF-α mRNA (Park et al., 2007, 2008b). Moreover, adiponectin promotes the expression of anti-inflammatory factor IL-10 via cAMP-dependent mechanisms in macrophages (Park et al., 2008a). In addition to NF-κB, Erk, and cAMP pathways, the Akt pathway was recently reported to mediate adiponectin-induced M2 macrophage proliferation (Hui et al., 2015). Whether adiponectin activates these signaling pathways in an adiponectin receptor-dependent manner in macrophages remains to be clarified in the future.

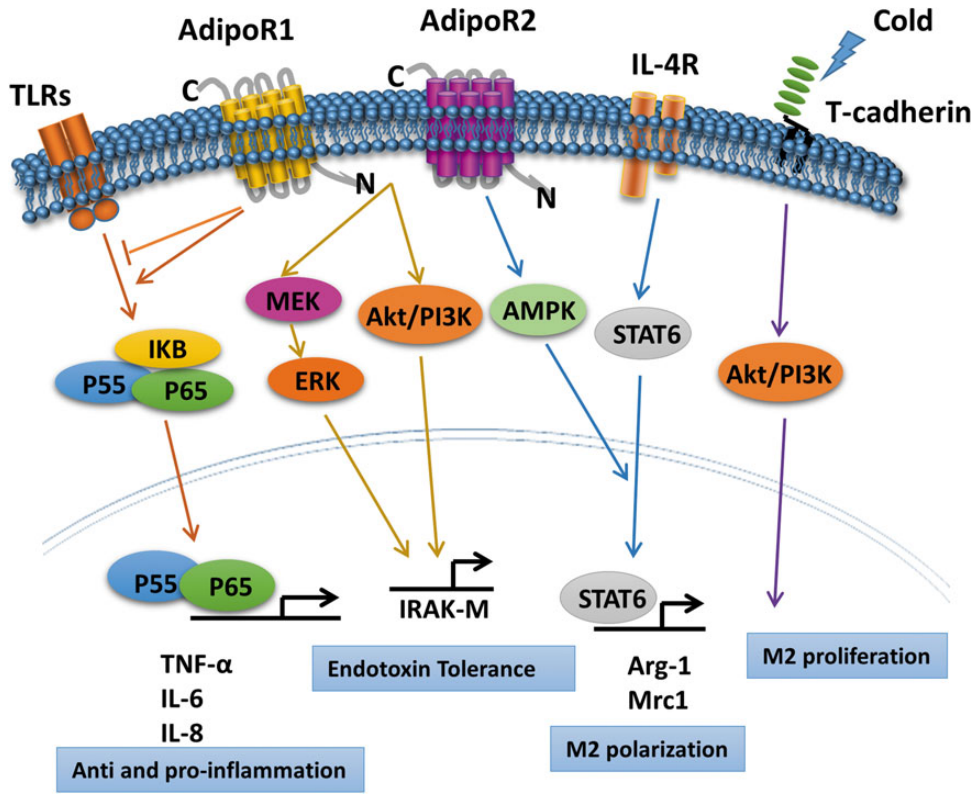

Figure 2 Adiponectin action is mainly mediated by adiponectin receptors and downstream signaling pathways in monocytes/macrophages. AdipoR1 mediates the suppressing effect of adiponectin on NF-κB activation and subsequent transcriptions of TNF-α, IL-6, and IL-8 in macrophages. AdipoRs and downstream activation of Tpl2/MEK/Erk and Akt/PI3K pathways mediate the promoting effect of adiponectin on endotoxin tolerance in macrophages. In addition, adiponectin induces M2 macrophage proliferation via T-cadherin and Akt/PI3K-dependent mechanisms and promotes M2 macrophage activation through AdipoR2 and AMPK.

Adiponectin regulation of innate-like lymphocytes

Innate-like lymphocytes, including group 2 innate lymphoid cells (ILC2), gamma delta T (γδ T) cells, natural killer T (NKT) cells, B1 cells, and marginal zone B cells, have emerged as an important cellular component of the immune system and have been suggested to regulate both innate and adaptive immunity. Interestingly, several types of innate-like lymphocytes such as ILC2, γδ T, and NKT cells are present in metabolic organs including adipose tissue and play important roles in regulating energy and glucose metabolism (Lynch et al., 2009, 2012; Brestoff et al., 2015; Lee et al., 2015). Consistently, ILC2s and NKT cell fractions are decreased, while γδ T cell density is increased in adipose tissue of obese mice or human subjects, indicating the correlation between these types of innate-like lymphocytes and obesity (Brestoff et al., 2015; Costanzo et al., 2015; Lee et al., 2015; Mehta et al., 2015). Therefore, ILC2s, NKT, and γδ T cells have offered novel therapeutic approaches for the treatment of metabolic diseases such as obesity, insulin resistance, and type 2 diabetes. Adiponectin has been proposed to regulate energy and glucose metabolism by targeting innate-like lymphocytes (Figure 3).

ILC2s were first discovered in the lung (Price et al., 2010), which are activated by epithelial cell-derived cytokines IL-33, IL-25, and thymid stromal lymphopoietin (TSLP) in response to allergens. Activated ILC2s orchestrate type 2 innate and adaptive immune responses (Koyasu and Moro, 2013; Licona-Limon et al., 2013; Cayrol and Girard, 2014). Very recently, ILC2s were identified in murine and human adipose tissue as a conserved characteristic of obesity, and have been shown to drive browning of fat and prevent the development of obesity (Brestoff et al., 2015; Lee et al., 2015). On the one hand, ILC2s produce IL-5 and IL-13, type 2 cytokines that stimulate the maturation and infiltration of eosinophils and activate M2 macrophages, respectively. Both eosinophils and M2 macrophages subsequently promote adipose tissue browning (Nguyen et al., 2011; Molofsky et al., 2013; Lee et al., 2015). On the other hand, IL-33-elicited ILC2s themselves produce methionine-enkephalin peptides that directly target adipocytes to promote browning and thermogenesis (Brestoff et al., 2015). In addition, cold stress enhances the ILC2 population through IL-33 in white adipose tissue (Brestoff et al., 2015). However, whether ILC2s are recruited into or produced in adipose tissue remains unclear. Mechanistically, the regulation of ILC2 function in adipose tissue also has yet to be defined. Hui et al. (2015) found that adiponectin promotes M2 macrophage proliferation and subsequent browning effect and energy expenditure. However, adiponectin deficiency has little effect on ILC2 population and downstream cytokines including IL-4 and IL-13 in white adipose tissue in response to chronic cold, a well-defined stimuli promoting browning of fat (Hui et al., 2015). However, two

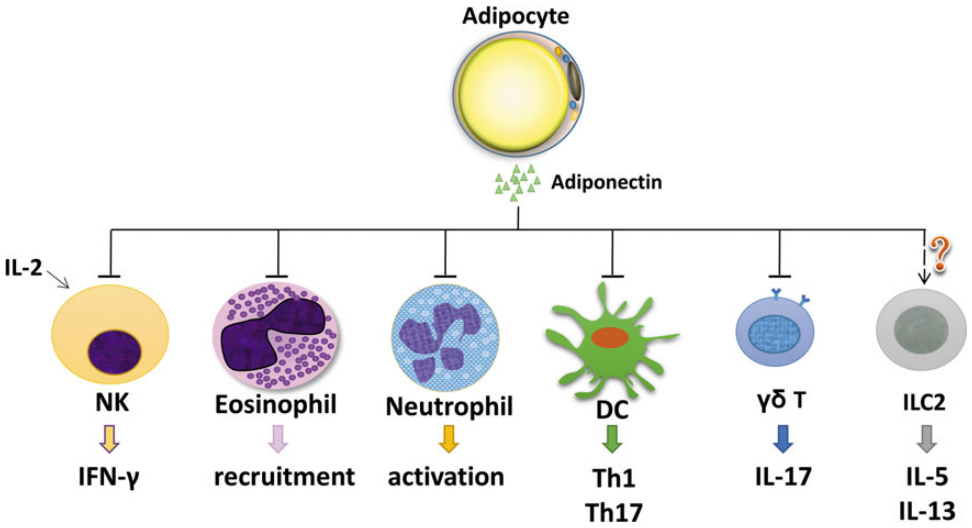

Figure 3 Adiponectin plays a critical role in the regulation of non-macrophage innate immune cells. Accumulating data suggest that adiponectin suppresses the activation of eosinophils, neutrophils, γδ T cells, NK cells, and DCs through common or different intracellular signaling pathways, whereas adiponectin appears to have little effect on recruitment and activation of ILC2 in adipose tissue under chronic cold stress.

groups have reported that adiponectin knockout (KO) mice display increased thermogenesis and energy expenditure (Kajimura et al., 2013; Qiao et al., 2014). Moreover, acute cold stress has been shown to induce the activation of ILC2s in adipose tissue (Brestoff et al., 2015). During chronic stress, ILC2 population and activity are both significantly decreased, suggesting that secondary effects of chronic stress may account for suppression of ILC2s in adipose tissue (Hui et al., 2015). These inconsistent observations highlight the need to further study what is the true physiological function of adiponectin in the regulation of innate immunity and energy expenditure.

In addition, NKT cells are present in human adipose tissue and play an important role in regulating metabolic pathways (Akbari et al., 2003; Lynch et al., 2009, 2012). Invariant NKT cells are decreased in human obesity, and confer protection against the development of metabolic syndrome and inflammation in an IL-4 and IL-10-dependent manner (Lynch et al., 2009, 2012). However, the density of total T lymphocytes is increased in adipose tissue during the development of obesity (Kintscher et al., 2008; Duffaut et al., 2009). Although there is no direct evidence showing that adiponectin regulates NKT cell function, it was reported that adiponectin activates plasma B cells and induces secretion of the B cell-derived peptide PEPITEM, which inhibits memory T cell migration (Chimen et al., 2015). Moreover, AdipoR1 and AdipoR2 are expressed in B cells and may mediate the suppressing effect of adiponectin on B cell-specific PEPITEM production and secretion.

Notably, γδ T cells, another type of adipose resident innate-like lymphocytes, are positively correlated with obesity and promote diet-induced inflammation and insulin resistance (Costanzo et al., 2015; Mehta et al., 2015). γδ T cells, which contain $\gamma\delta^+$ T cell receptor (TCR), only compose a minority of total T cells and are predominantly $CD4^-$ and $CD8^-$. Some subsets of γδ T cells show anti-tumor and immunoregulatory activities (Girardi, 2006). A very recent study shows that adiponectin deficiency results in marked upregulation of dermal γδ T cells and severe psoriasiform skin inflammation through induction of IL-17 (Shibata et al., 2015). This study also demonstrates that adiponectin negatively regulates the recruitment of inflammatory cells and IL-17 production via AdipoR1- but not AdipoR2-dependent cell autonomous mechanisms in the skin (Shibata et al., 2015). However, whether adiponectin modulates the function of adipose resident γδ T cells remains to be clarified.

Adiponectin regulation of other innate immune cells

Adiponectin and eosinophils

Eosinophil granulocytes, usually called eosinophils, appear brick-red after staining with eosin and act as one of the immune system components responsible for allergen-induced inflammation responses and parasitic infection. Recent studies demonstrate that eosinophils are recruited to adipose tissue and are responsible for the alternative activation of macrophages as well as browning of adipose tissue through IL-4 in response to cold (Qiu et al., 2014; Rao et al., 2014). Adiponectin negatively regulates the recruitment of eosinophils in the airways, suppressing allergic airway inflammation (Medoff et al., 2009). Furthermore, adiponectin suppresses eosinophil recruitment through the regulation of the macrophage-derived chemokine CCL11/eotaxin (Medoff et al., 2009). Although both AdipoR1 and AdipoR2 have been detected in human eosinophils (Yamamoto et al., 2013), whether adiponectin regulates the function of eosinophils through an adiponectin receptor-mediated signaling pathway remains to be clarified. Moreover, whether adiponectin plays a role in regulating the function of adipose resident eosinophils remains to be investigated.

Adiponectin and neutrophils

Neutrophils, the most abundant immune cell population in the blood, work as the first defense against microbial pathogens,

migrating to eliminate pathogens through phagocytosis, degranulation, neutrophil extracellular traps (NETs), and reactive oxygen species (ROS) production (Wright et al., 2010). Full-length adiponectin inhibits the phagocytic ability of neutrophils by suppressing NADPH oxidase and ROS production in an AMPK-dependent manner (Chedid et al., 2012). Consistently, adiponectin suppresses ceramide accumulation in the neutrophil membrane and subsequently inhibits neutrophil apoptosis through AMPK (Rossi and Lord, 2013b). In addition, adiponectin treatment inhibits neutrophil phagocytosis of *Escherichia coli* through inhibiting PI3K/PKB pathways and Mac-1 activation (Rossi and Lord, 2013a). These data demonstrate that adiponectin negatively regulates the function of neutrophils.

Adiponectin and NK cells

NK cells are defined as large granular lymphocytes (LGL) that play a critical role in the innate immune response. Activated NK cells trigger a pro-inflammatory response by promoting M1 macrophage activation and causing insulin resistance (Wensveen et al., 2015). Meanwhile, NK cell-activating receptor NCR1 ligands, which are expressed and localized on the surface of adipocytes, are upregulated by obesity and promote the proliferation and activation of NK cells (Wensveen et al., 2015). It has been shown that adiponectin plays an important role in regulating the function of NK cells. However, whether adiponectin suppresses or stimulates NK cells remains controversial. One *in vivo* study suggests that adiponectin downregulates the frequencies while enhancing the efficiency of NK cells in the spleen (Wilk et al., 2013). In contrast, adiponectin treatment suppresses IL-2-induced cytotoxicity and IFN-γ production in both human and murine NK cells (Kim et al., 2006). The differential effects of adiponectin *in vivo* and *in vitro* may be a result of the secondary effects of adiponectin deficiency rather than direct targeting to NK cells. Although it has been reported that adiponectin receptors are expressed in human and murine NK cells (Kim et al., 2006), there is no direct evidence showing that adiponectin receptors mediate the role of adiponectin in regulating NK cells.

Adiponectin and dendritic cells

Dendritic cells (DCs) are particularly specialized antigen-presenting cells (APCs) and are essential for the onset of immunity and its tolerance. Both density and activity of DCs are induced by obesity in mice (Stefanovic-Racic et al., 2012; Chen et al., 2014). Adiponectin appears to regulate the function of DCs, whereas it remains controversial as to whether adiponectin positively or negatively regulates DC function. Tsang et al. (2011) showed that adiponectin treatment downregulates the expression of co-stimulatory molecules and impairs activation of allogenic T cells in murine bone marrow-derived DCs, suggesting that adiponectin inactivates DCs. On the contrary, a different study found that adiponectin induces maturation and activation of DCs in both bone marrow-derived murine and monocyte-derived human DCs (Jung et al., 2012). Along this line, adiponectin stimulates DC activation via phospholipase C γ/JNK/NF-κB pathways, leading to Th1 and Th17 polarization, a mechanism that is adiponectin receptor dependent (Jung et al., 2012). The opposite conclusion may result from the differential doses and times of adiponectin treatment. Therefore, further studies are needed to understand the mechanism underlying the regulatory role of adiponectin in DCs.

Conclusion

The innate immune system senses metabolic stress, and in turn orchestrates various intermediary metabolic pathways linked with the progression of obesity and its related disorders. Adiponectin is a well-defined obesity marker and exerts multiple beneficial properties against inflammation, insulin resistance, and cardiovascular diseases. The beneficial effects of adiponectin, on the one hand, are mediated by its insulin-sensitizing action. On the other hand, adiponectin modulates metabolic adaption by targeting the innate immune system, including macrophage plasticity and polarization, innate-like lymphocyte activity, and other innate immune cell functions (Figures 1–3). However, the insulin-sensitizing effects of adiponectin do not appear under physiological conditions. The average level of plasma adiponectin in humans is 5–10 μg/ml, nearly 1000-fold higher than most other adipokines and metabolic related hormones. Therefore, the key question that remains is to decipher what the physiological role of adiponectin is. The regulatory effect of adiponectin on innate immunity under physiological conditions may emerge as an important determinant of metabolic adaption. In addition, it has been shown that adiponectin regulates bone metabolism and food intake (Kubota et al., 2007; Kajimura et al., 2013; Wu et al., 2014). A better understanding of the physiological role of adiponectin in the regulation of innate immunity may provide a basis for the development of adiponectin-based therapeutic strategies.

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