The Good Neighbor
Coping With Insulin Resistance by Modulating Adipose Tissue Endothelial Cell Function

Sumeyye Yar, Hsiang-Chun Chang, Hossein Ardehali

The prevalence of obesity is rising globally, and the United States has one of the highest obesity rates in the world: ≈17% of the young and >33% of adults are obese.1 Obesity is associated with chronic low-grade systemic inflammation, which is considered a critical underlying factor in the development of insulin resistance (IR).2 IR is a major risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease.1 In the development of obesity, white adipose tissue, particularly the abdominal adipose tissue, is the key site that mediates systemic inflammation and IR, though other organs, such as skeletal muscle and liver, have also been implicated.4 Adipose tissue is a highly vascularized organ where every adipocyte is connected to at least one capillary.5 To maintain normal adipose tissue function, the proper signaling between adipocytes and endothelial cells (ECs) from the surrounding vasculature is important.6 There is a growing body of evidence suggesting that EC dysfunction contributes to the pathogenesis of atherosclerosis, obesity, and T2DM.7 8 Therefore, it is of key interest to further study the role of the crosstalk between adipose tissue ECs and adipocytes in obesity-associated IR and to identify potential therapeutic targets for novel interventions. Recently, several reports suggested that microRNAs (miRs) are important mediators of the development of inflammation and IR in obese adipose tissue.9 Subsequently, numerous studies explored targeting specific miRs in diabetic complications to mitigate the pathological sequelae of T2DM.10 Given these points, using miRs to modulate adipocyte-EC axis in adipose tissue may offer new tools to combat the growing epidemic of obesity and its associated comorbidities.

Article, see p 810

Over the past 2 decades, several studies elucidated the underlying molecular mechanisms linking inflammation to obesity-associated IR. Hotamisligil et al10 was the first to demonstrate that tumor necrosis factor-α, a proinflammatory cytokine, mediates IR in obesity. It is now appreciated that not only tumor necrosis factor-α but also other cytokines, such as interleukin-6 and -1β, are involved in this process. In the setting of obesity, proinflammatory cytokine release from adipose tissue can (1) stimulate adipocytes or ECs to secrete monocyte chemoattractant protein-1 that attracts monocytes to adipose tissue and (2) activate several serine kinases, such as c-jun N-terminal kinase and nuclear factor κB.11 These kinases directly or indirectly inhibit insulin signaling by promoting inhibitory serine/threonine phosphorylation of insulin receptor substrate-1, which in turn decreases the activity of downstream effectors in the insulin signaling pathway, including phosphatidylinositol 3-kinases and protein kinase B (Akt).11 In the context of IR, downregulation of the phosphatidylinositol 3-kinases/Akt/nitric oxide pathway in ECs leads to vasoconstriction, as well as an increased production of proinflammatory cytokines and cell adhesion molecules, such as intercellular adhesion molecule and vascular cell adhesion molecule.12

The communication between adipose tissue ECs and adipocytes is bidirectional, and both EC and adipocyte dysfunctions have been associated with IR and T2DM.13 In clinical and basic research studies, adipocytes have been shown to alter the phenotype and function of surrounding ECs in the setting of obesity.13-15 Similarly, adipose tissue ECs can also affect adipocyte function. A study by Pellegrinelli et al16 was the first to highlight that adipose tissue ECs of obese subjects negatively impact adipocyte function through decreasing insulin sensitivity, increasing endoplasmic reticulum stress, and promoting proinflammatory cytokine release. This report underscores the involvement of ECs in pathological adipose tissue biology, and the group puts forward an interesting idea that targeting adipose tissue EC dysfunction in obesity could ameliorate adipocyte dysfunction, systemic IR, and improve the overall outcome of the disease.

Several miRs have been found to be dysregulated in obesity, T2DM, inflammation, and other closely associated comorbidities.9 For instance, the miR-181 family has been shown to play critical roles in cardiovascular inflammation and immune cell homeostasis.17 In earlier reports, the miR-181b was shown to ameliorate nuclear factor κB activation in ECs in response to atherosclerosis.18 In this issue of Circulation Research, Sun et al19 demonstrated a different role for miR-181b in adipose tissue ECs in the pathogenesis of diet-induced IR (Figure). They first showed that miR-181b is the predominant member of miR-181 family in adipose tissue ECs, and its expression is significantly reduced early after the initiation of high-fat diet (HFD). Intravenous injection of exogenous miR-181b, which preferentially accumulated in adipose tissue ECs, reduced adipose tissue inflammation and improved insulin sensitivity in HFD-fed mice. MiR-181b overexpressing ECs also showed an increase in Akt phosphorylation. Subsequent studies revealed that miR-181b directly targets PH domain and leucine rich...
HFD-fed mice with PHLPP2 siRNA improved glucose toler-
ance and insulin sensitivity while decreasing adipose tissue
inflammation. Together, these findings suggested that target-
ing PHLPP2 in adipose tissue ECs may be a viable treatment
approach in the setting of obesity-related IR.

Sun et al19 also observed a reduction in macrophage infil-
tration into adipose tissue and a preferential polarization of
adipose tissue macrophages to an M2 subtype in mice treated
with miR-181b. Although the reduced macrophage infiltration
may be directly related to lower EC activation, it was not clear
how altered EC activation could influence the polarization of
infiltrated and resident macrophages in the adipose tissue.

Also, in this study, the group demonstrated that conditioning
media from isolated ECs overexpressing miR-181b increas-
es glucose uptake in adipocytes in response to insulin. This
finding suggests that miR-181b expression in ECs influences
adipocyte biology through a paracrine mechanism, but the
paracrine factor(s) has yet to be identified. Additional studies
on identification of this paracrine factor(s) would help find-
ing new pharmacological targets in the adipose tissue because
direct administration of miRs as a therapy would be costly
and technically difficult. It is also worth investigating whether
the paracrine factor(s) is being secreted from ECs within
other organs, given that modulation of miR-181b in human
umbilical ECs recapitulates the altered Akt phosphorylation
seen in adipose tissue ECs. Moreover, although the regula-
tion of PHLPP2 by miR-181b may be a major mechanism for
the improvement of insulin sensitivity, it is worth investigating
whether any other potential targets of the miR-181b also play
a role in the altered adipose tissue biology and insulin sensitiv-
ity. Furthermore, because the time course for the experiments
conducted were relatively short after the induction of IR and
miR delivery, it will also be important to evaluate the longer-
term safety and efficacy of these studies.

It was clear from the study by Sun et al19 that EC activation
is closely linked to increased macrophage infiltration and
adipose tissue inflammation. However, the extent to which EC
dysfunction and altered insulin sensitivity of adipocytes, in-
dependent of inflammation, contributes to the development of
systemic IR remains unknown. Therefore, a logical next step
would be to test the effect of miR-181b in the context of anoth-
er EC dysfunction model that lacks inflammation, such as in
mice treated with nitric oxide synthase inhibitor. Additionally,
analysis of data from patients treated with nitrates or other ni-
tric oxide–potentiating agents, such as sildenafil, may provide
stronger support for developing novel therapies targeting EC
dysfunction in IR state.

The findings in this article also raise an interesting ques-
tion pertaining to the tissue-specific regulation of miR-181b.
The article demonstrated that HFD results in downregulation
of miR-181b only in adipose tissue ECs but not in skeletal
muscle or liver ECs. Tissue-specific epigenetic changes might
explain the differential response to HFD in these tissues.
Global assessment of gene expression profiles, epigenetic
markers, and transcriptional factors may reveal specific fac-
tors that respond to pathophysiological stimuli and, hence,
decrease miR-181b expression in adipose tissue ECs. These
studies would provide a better picture of the interplay between
adipose tissue ECs and adipocytes and the role of this interac-
tion in the development of obesity-associated IR.

In summary, the study by Sun et al19 demonstrated that
miR-181b expression decreases early in a diet-induced obe-

ty animal model. This reduction results in increased PHLPP2
expression, EC activation, and immune cell infiltration, as
well as decreased Akt phosphorylation. Administration of ex-
ogenous miR-181b, which preferentially accumulated in adi-
pose tissue ECs, was sufficient to improve systemic glucose
homeostasis and insulin sensitivity. These findings highlight the role of adipose tissue ECs in the pathogenesis of obesity-induced IR and the potential of using miRs as a tool to modulate EC function. Although the underlying mechanism for how ECs affect the adipocyte function and promote glucose uptake and insulin sensitivity is not clear, it is logical to hypothesize that the crosstalk between ECs and adipocytes plays an important role in the pathogenesis of IR. Further investigations into this exciting field will not only improve our understanding of the underlying molecular mechanisms of the crosstalk between ECs and adipocytes, but also provide knowledge for designing new therapies for obesity-induced IR and its comorbidities.

**Sources of Funding**

S. Yar is supported by American Heart Association Post-doctoral Fellowship 16POST26420131. H.-C. Chang is supported by American Heart Association Pre-doctoral Fellowship 12PRE11883-014-z and National Institutes of Health (NIH) T32 Training Grant (T32GM008152) given to Northwestern University. H. Ardehali is supported by the NIH grants (K02 HL107448, R01 HL127646, and 1PO1 HL108795).

**Disclosures**

Dr Ardehali receives speaking honoraria from Merck. The other authors report no conflicts.

**References**


The Good Neighbor: Coping With Insulin Resistance by Modulating Adipose Tissue Endothelial Cell Function
Sumeyye Yar, Hsiang-Chun Chang and Hossein Ardehali

Circ Res. 2016;118:776-778
doi: 10.1161/CIRCRESAHA.116.308338

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/118/5/776

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/