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. 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.

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 apparent 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 dysfunction has 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...
Adipose Tissue

- endothelial cell
- blood vessel
- adipocyte
- macrophage
- VCAM (vascular cell adhesion molecule)
- ICAM (intercellular adhesion molecule)
- insulin receptor
- Akt
- eNOS
- NOS
- Glucose uptake

Figure. Proposed mechanism and function of miR-181b in adipose tissue endothelial cells (ECs). High-fat diet (HFD) lowers miR-181b expression in adipose tissue ECs and induces insulin resistance (IR) and low-grade inflammation in adipose tissue. Delivery of miR-181b improves systemic insulin sensitivity and decreases inflammatory phenotype in adipose tissue. MiR-181b targets PH domain and leucine rich repeat protein phosphatase-2 (PHLPP2) in ECs and thus improves endothelial nitric oxide synthase-nitric oxide signaling. Adipose tissue ECs promote glucose uptake in adipocytes in a paracrine manner. MiR-181b also downregulates the expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). Akt indicates protein kinase B; eNOS, endothelial nitric oxide synthase; miR, microRNA; and NO, nitric oxide.

Repeat protein phosphatase-2 (PHLPP2), a phosphatase that dephosphorylates Akt and is expressed only in adipose tissue but not in the liver. The challenge was, then, to test whether in vivo downregulation of PHLPP2 recapitulates the phenotype of miR-181b overexpression. Expectedly, treatment of HFD-fed mice with PHLPP2 siRNA improved glucose tolerance and type 2 diabetes (T2D) comparable to 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 sensitivity. 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 al 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, independent 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 another 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 nitric oxide–potentiating agents, such as sildenafl, may provide stronger support for developing novel therapies targeting EC dysfunction in IR state.

The findings in this article also raise an interesting question 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 factors 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 interaction in the development of obesity-associated IR.

In summary, the study by Sun et al demonstrated that miR-181b expression decreases early in a diet-induced obesity animal model. This reduction results in increased PHLPP2 expression, EC activation, and immune cell infiltration, as well as decreased Akt phosphorylation. Administration of exogenous miR-181b, which preferentially accumulated in adipose 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.

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References

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