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. Obesity is associated with chronic low-grade systemic inflammation, which is considered a critical underlying factor in the development of insulin resistance (IR). IR is a major risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease. 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. Adipose tissue is a highly vascularized organ where every adipocyte is connected to at least one capillary. To maintain normal adipose tissue function, the proper signaling between adipocytes and endothelial cells (ECs) from the surrounding vasculature is important. There is a growing body of evidence suggesting that EC dysfunction contributes to the pathogenesis of atherosclerosis, obesity, and T2DM. 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. 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.

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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 any other potential targets of the miR-181b also play a role in the altered adipose tissue inflammation. Together, these findings suggested that targeting PHLPP2 in adipose tissue ECs may be a viable treatment approach in the setting of obesity-related IR.

Sun et al also observed a reduction in macrophage infiltration 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 increases 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 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 regulation 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 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 sildenafil, 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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