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Editorial

Adipose Tissue Angiogenesis: An Emerging Therapeutic Target for Obesity and Metabolic Disease

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Obesity is now epidemic worldwide and its related metabolic disorder is one of the most important risk factors for cardiovascular disease. Adipose tissue (AT) plays a crucial role in the regulation of glucose homeostasis and energy metabolism through the secretion of adipocytokines from white adipose tissue (WAT) and by thermogenesis in brown adipose tissue (BAT) [1]. Obesity is characterized by excessive expansion of AT. Healthy WAT expansion is accompanied by adequate neovessel formation, but excessive adiposity triggers adipose tissue hypoxia due to imbalanced vascularization and results in chronic inflammation in WAT, leading to the obesity-related impairment in glucose homeostasis [2,3]. AT, especially BAT, is a well-vascularized organ, and its high degree of specification of lipolysis and fatty acid oxidation allows BAT to significantly contribute to the overall energy balance [4]. Oxygen consumption in BAT is enormously high, which is supported by a particularly high blood perfusion, thus its thermogenic activity can counteract the obese phenotype. Moreover, blood vessel density in BAT is strongly correlated with the thermogenic capacity and metabolic rate [5-7]. These results collectively indicate that AT anigiogenesis in WAT and BAT is a crucial factor in the pathogenesis of obesity and its related metabolic disorders.

Accordingly, AT angiogenesis is considered as a therapeutic target for obesity and metabolic diseases. The therapeutic intervention of obesity targeting the AT vasculature was first performed by inhibiting blood vessel formation. Angiogenic inhibitors such as small chemical compound TNP-470, angiostatin, and endostatin were tested in genetically and diet-induced obese mice with regard to their antiobesity effects [4,8,9]. Inhibition of angiogenesis remarkably reduced body weight of obese mice in association with decreased AT vascularity. However, it remains unclear whether this reduction in adiposity simply ameliorates obesity-related metabolic disorders. Treating metabolic disorders is more important for preventing cardiovascular diseases, which largely determines the prognosis of obese population than decreasing body weight. AT is not without benefit, it is necessary to maintain proper glucose homeostasis and energy metabolism. Therefore, preservation of adipocyte health might be more important than a decrease in adipocyte numbers. From this point of view, decreased AT vascularity may even worsen AT dysfunction because of exacerbated hypoxia, resulting in impaired glucose homeostasis. In addition, decreased vascularization of BAT potentially reduces the thermogenic capacity, leading to reduced energy expenditure. Therefore, long term treatment with angiogenic inhibitors may actually aggravate obesity. However, elimination of the dysfunctional proinflammatory adipocytes by inhibiting angiogenesis could be beneficial under certain conditions because it reduces AT inflammation in obese animals at least on a temporary basis [4]. More recently, enhancing AT angiogenesis has been shown to protect mice from obesity-related metabolic disorders in association with reduced AT hypoxia [10-12]. Of note, enhancing AT angiogenesis also protects mice from obesity at least partly by the increase in energy expenditure [11]. Overexpression of vascular endothelial growth factor (VEGF) in both WAT and BAT markedly decrteased weight gain during a high-fat diet (HFD), whereas mice with targeted expression of VEGF in WAT showed a modest body weight differences in comparison with wild-type mice. This is probably because enhanced angiogenesis in BAT augmented or maintained the thermogenesis during an HFD, leading to an increased energy expenditure, which counteracts the obese phenotype. Importantly, after the HFD, adipose tissue-specific deletion of VEGF caused reduced vascular density and exacerbated hypoxia in AT, consequently inducing severe insulin resistance despite the significant decrease in body weight compared with wild-type mice [11]. Moreover, angiogenesis inhibition during early stages of HFD-induced obesity aggravated systemic metabolic disorders. Therefore, inhibiting angiogenesis is a double-edged sword that shows dichotomous effects on obesity and its related metabolic disorders depending on the stage of obesity [10,11]. It is noteworthy that enhanced AT angiogenesis during an HFD increased adipose vascularization, reduced hypoxia, decreased body weight, and improved the metabolic disorders [10]. These results collectively suggest that enhancing AT angiogenesis is more preferable to treat obesity and obesity-related metabolic disorders than AT angiogenesis inhibition. Thus, the elucidation of the detailed molecular mechanisms involved in the regulation of AT angiogenesis is therefore very important. We recently identified a novel gene, termed apoptosis regulator through modulating IAP expression (ARIA) that regulates endothelial functions and angiogenesis by modulating endothelial phosphoinositide 3-kinase (PI3K) /Akt signaling [13,14]. ARIA (also known as Ecscr) is a transmembrane protein and binds to phosphatase and tensin homolog deleted from chromosome 10 (PTEN), a nonredundant plasma membrane lipid phosphatase that antagonizes PI3K, to enhance its membrane association, thus increasing its antagonism toward PI3K [14]. ARIA is highly expressed in endothelial cells, especially in AT vasculatures, and its loss enhances endothelial angiogenic capacity by enhancing PI3K/Akt signaling [14,15]. ARIA-deficient mice did not show a difference with regard to body weight and adiposity compared with wild-type mice. Nevertheless, ARIA-

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deficient mice exhibited significant resistance to obesity and obesity-related metabolic disorders when fed an HFD [15]. Mechanistically, loss of ARIA significantly enhanced angiogenesis in both WAT and BAT during an HFD, and thus ameliorated inflammation in WAT and augmented thermogenic capacity in BAT [15]. These results establish ARIA as a potential therapeutic target to treat obesity and its related metabolic disorders by targeting AT angiogenesis.

In conclusion, AT angiogenesis is an emerging therapeutic target for treating obesity and metabolic diseases. However, angiogenesis plays crucial roles in homeostasis maintenance in various tissues. Moreover, tumor angiogenesis is a significant factor in tumor growth. Therefore, systemic intervention for inducing angiogenesis may cause unexpected and/or unfavorable effects. Thus, specificity for AT is essential for considering the feasibility of therapeutic angiogenesis. Further understanding of the molecular mechanisms involved in AT angiogenesis under physiological and pathological conditions is necessary to establish novel strategies by modulating AT angiogenesis for unmet medical needs for obesity and obesity-related metabolic disorders.

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