Therapeutic value of brown adipose tissue
Correcting metabolic disease through generating healthy fat

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Brown adipose tissue (BAT), an important endocrine organ long known for thermogenesis and energy consumption, has received much attention in recent years for its potential to combat obesity. In general, BAT can enhance metabolism and improve overall health. Our recent work demonstrates the ability of embryonic BAT transplants to correct type 1 diabetes (T1D) without insulin, via mechanisms somewhat different from those involved in BAT-associated weight loss. BAT transplants seem to reverse T1D by decreasing inflammation and increasing functionality in the surrounding white adipose tissue (WAT), thereby enabling it to secrete hypoglycemic adipokines, which compensate for the function of insulin. Thus BAT can transform unhealthy WAT to a healthy status, sufficient to replace the function of endocrine pancreas and establish insulin-independent glycemic regulation. Several studies, including ours, demonstrate the remarkable ability of BAT to correct metabolic disorders and hint at its beneficial effects on inflammation. Hence, addition of more BAT to the body, through transplantation or stimulating regeneration, may well be the therapy of the future for the simple correction of numerous diseases.

Introduction

Obesity is a more serious health issue today than at any known period in history, posing an increasing threat to populations worldwide. According to current statistics, over 34% of adults and 32% children of age 2–19 in the US are obese.[1-3] The same reports show that obesity is associated with a marked excess in mortality in the US, and that obesity is an established risk factor not just for insulin resistance, type 2 diabetes (T2D) and cardiovascular disease (CVD), but for numerous other health conditions, including asthma, cancer and degenerative joint disease. Such statistics lead to the general belief that excess adipose tissue in itself is harmful. This assumption, while widespread, is not entirely correct. Emerging studies increasingly show that it is not the quantity of adipose tissue, but its quality that determines predilection to disease.[4,5] Insulin resistance is associated with inflammation, oxidative stress, and a deficient activity of adenosine monophosphate-activated protein kinase (AMPK) rather than obesity itself, while obese individuals without WAT inflammation and with adequate AMPK activity seem to be protected from insulin resistance.[4,5] In other words, adipose tissue, when maintained in a healthy status, can be a powerful ally that protects against disease. Recent reports, including ours, show that the overall health of adipose tissue can be remarkably improved by increasing the content of BAT in the body, leading to an eventual correction of various metabolic disorders. This commentary will take a critical look at the existing studies and explore the therapeutic potential of BAT.

WAT in Health and Disease

In recent years, adipose tissue has received much attention as a versatile endocrine organ with powerful effects on whole body

metabolic homeostasis. WAT, the large energy reserve distributed all over the body, is classified into subcutaneous and intra-abdominal fat depots, which are then further subdivided according to their specific location.[6,7] WAT, long believed to be merely a storage depot, is now known to secrete a variety of hormones involved in multiple functions including nutrient metabolism, satiety signaling, immune/inflammatory response and angiogenesis.[8-10] The major hypoglycemic adipokines secreted by WAT are adiponectin and leptin. Adiponectin, whose levels are inversely proportionate to insulin resistance,[11,12] is well known for its insulin-sensitizing effects on peripheral tissues including liver, skeletal muscle and adipose tissue.[13] Mainly through AMPK and the PPARα pathways, adiponectin increases fatty acid oxidation; inhibits gluconeogenesis; and exerts anti-inflammatory and anti-atherosclerotic effects,[14-16] which collectively enhance overall health. Leptin, long known for its central effects on decreasing appetite and food intake, also has direct peripheral effects.[8,17] Leptin receptors are expressed in many peripheral tissues including adipose tissue, liver and skeletal muscle, where leptin increases oxidation of lipids and fatty acids through AMPK mediated mechanisms. Obesity is associated with leptin-resistance leading to compensatory increases in leptin levels, whereas enhanced sensitivity to leptin results in leanness and protection from diet-induced obesity. Non-metabolic effects of leptin include enhancing immune response, pro and anti-inflammatory effects, and angiogenesis.[8,17] Numerous other hormones of WAT origin, such as apelin, resistin, retinol-binding protein 4 and angiopoietin-like proteins also have direct or indirect effects on glucose homeostasis through influencing functions such as insulin sensitivity, lipogenesis/lipolysis, and inflammation.[8-10] Collectively, these extra-pancreatic hormones complement endocrine pancreas in overall glucose regulation. However, WAT can exert a beneficial influence only as long as it remains healthy. Inflammation results in conversion of WAT from a beneficial to harmful organ, which then secretes increasing amounts of hyperglycemic

adipokines and pro-inflammatory cytokines, leading to a vicious cycle of insulin resistance and T2D.[7-9,18] Such inflammation is generally associated with obesity, and/or inappropriate distribution of WAT in the body. Visceral and subcutaneous fat are well known to be different in their innate characteristics, visceral fat being significantly deficient in the expression of favorable adipokines such as adiponectin, and higher in lipolytic activity as well as expression of pro-inflammatory cytokines.[7,19,20] Increase of abdominal visceral fat deposits (visceral adiposity) predisposes to insulin resistance, diabetes and cardiovascular disease, while subcutaneous fat does not pose such risks.

Recent studies increasingly show that specific characteristics of WAT, including the degree of inflammation, oxidative damage and AMPK activity, rather than the quantity of WAT, determine the predilection to disease. In other words, obesity does not necessarily lead to insulin resistance and CVD. For example, obese individuals with the same body mass index can be divided into insulin-sensitive obese (ISO) and insulin-resistant obese (IRO), with significant differences in their adipose tissue. ISO subjects have little or no inflammation in both their visceral and subcutaneous WAT, while IRO subjects have a constant low grade inflammation in their WAT as well as increased levels of pro-inflammatory cytokines in circulation.[4-7] In addition to insulin-resistant obesity, diseases characterized by loss of adipose tissue such as T1D and lipoatrophic diabetes, also exhibit inflammation.[21-23] T2D and insulin-resistant obesity are associated with inflamed and non-functional WAT generally in large quantities, whereas T1D is accompanied by loss of WAT as well as inflammation of any remaining WAT.

Thus, there is strong evidence for a link between inflammation and metabolic disease, and decreasing inflammation is a promising approach to improve and correct such disorders. A major mechanism of insulin-sensitizing agents such as thiazolidinediones is to reduce inflammation in adipose tissue.[24-26] More specific anti-inflammatory agents such as interleukin inhibitors are currently under investigation for treatment of T2D.[27] A

physiologically sound method to accomplish decrease of WAT inflammation and improve its functionality is to increase the content of BAT in the body. Our recent report on BAT transplants demonstrates reversal of T1D in a mouse model following dramatic decrease of WAT inflammation.[28]

BAT

BAT is found in large quantities in newborns, and decreases to a few local depots in adults. In adult humans, BAT is located in several small depots including cervical, supraclavicular, paravertebral, mediastinal and paraaortic, and in diffuse clusters within skeletal muscle tissue. Unlike WAT, which stores and accumulates fat, BAT metabolizes fat, generates heat and increases overall metabolism. For these purposes it contains large amounts of mitochondria and uncoupling protein 1 (UCP-1), which are considered the defining morphological markers for BAT. BAT is highly vascularized and innervated compared with WAT, and brown adipocytes contain small multilocular lipid droplets as opposed to the large unilocular droplets found in white adipocytes.[29,30] WAT and BAT appear at different times during development, and were recently shown to have distinct developmental origin.[30-32] While WAT is believed to originate from mesodermal stem cells, BAT originates from dermatomyotomal precursor cells in common with skeletal muscle and has an interchangeable developmental relationship with skeletal muscle rather than WAT.[30-32] Thus, except for containing lipid droplets there is not much similarity between brown and white adipose tissue, and WAT can be harmful under certain circumstances such as insulin resistant obesity, T2D and metabolic syndrome. However, situations where BAT and WAT functionally complement each other can produce enormous benefits including correction of metabolic disease.

Reversal of T1D with BAT

T1D is characterized by auto-immune mediated destruction of pancreatic β cells, resulting in absolute deficiency of insulin.

Through the past century, treatments for T1D focused on replacement of insulin, either directly or through transplantation of insulin secreting tissue. These therapies have numerous limitations including possible fatal hypoglycemic episodes associated with direct insulin replacement and shortage of donor tissue as well as the need for life-long immuno-suppression with islet/pancreas transplantation. Treatment of T1D without insulin is a relatively new concept, first introduced in the past decade with the use of specific hypoglycemic adipokines for amelioration of diabetes in animal models. Adiponectin acutely decreased blood glucose in diabetes both type 1 and 2,[33,34] and the dramatic effects of leptin in correcting T1D without insulin were demonstrated in 2008.[35] Leptin is now well known to correct T1D independent of insulin in rodent models, likely through suppression of the hyperglycemic effects of glucagon.[36,37] While these reports demonstrate the remarkable ability of alternate hormones to compensate for insulin, monotherapy with individual adipokines still carries the same complications associated with insulin monotherapy in addition to difficulty in administration. Although leptin therapy shows great promise as an adjunct or alternative to insulin, adverse effects associated with large supraphysiological doses of leptin should be kept in mind. The pro-inflammatory and immunogenic properties of leptin can easily pose danger at high doses, while hypertension, thrombosis, and hypoglycemic risk from excessive suppression of glucagon are also possible.

The possibility of regulating blood glucose using a physiological combination of alternate hormones was first suggested in our early studies, where subcutaneous transplants of embryonic pancreatic tissue resulted in correction of chemically induced T1D with no accompanying increase in insulin.[38,39] Diabetic mice who received embryonic pancreatic transplants made a complete and permanent recovery with no detectable increase in the insulin response, exhibiting proliferation of WAT and increased plasma levels of adipokines instead. These findings led to the hypothesis that possible factors generated from newly-formed adipose tissue

may compensate for insulin in its absence. Streptozotocin (STZ)-diabetic mice had little or no endogenous pancreatic insulin, and there was no detectable increase in plasma insulin after reversal of diabetes following transplants.[38] Thus, complete glucose regulation appeared to be achieved with no insulin response. Nevertheless, a possible contribution from insulin originating from the subcutaneous embryonic pancreatic transplants, however minute, cannot be disregarded. To determine whether adipose tissue alone can compensate for insulin, we sought to reproduce the results with no possible contribution from insulin, by replenishing adipose tissue in STZ-diabetic mice without transplanting pancreatic tissue. Adipose tissue replenishment was attempted via transplantation of WAT from healthy adult donors, and regeneration of recipients' WAT through transplantation of different embryonic tissue types. Adult WAT transplants did not survive, and no other non-pancreatic embryonic tissue could regenerate healthy WAT, except for embryonic BAT. Remarkably, embryonic BAT transplants resulted in dramatic proliferation of healthy subcutaneous WAT followed by reversal of diabetes independent of insulin.[28] Return to euglycemia was accompanied by progressive increases in plasma levels of adiponectin, leptin and insulin-like growth factor-1 (IGF-1) and suppression of glucagon. STZ-induced diabetes is associated with inflammation of subcutaneous WAT in addition to loss of WAT. BAT transplants correct both these problems, resulting in proliferation of WAT as well as marked decrease of inflammation. Thus the mere presence of BAT improves the health of WAT, which in turn can improve glucose regulation. This goes in with recent reports showing that human T1D is associated with a systemic inflammatory response particularly affecting adipose tissue and muscle,[22,23] and that BAT has numerous beneficial effects including improved metabolism and possible protection against inflammation.[40-42]

Demonstrating BAT transplants' ability to reverse T1D without insulin is a promising step toward simpler and safer therapies for this serious disease. However

it is questionable whether the current data from mouse models with chemically induced diabetes would be directly translatable to human T1D with auto-immune mediated insulitis. Considering that BAT transplants decrease inflammation, a major pathogenic component of human T1D, there is a good chance of reproducing these results. It is also noteworthy that decrease of endogenous BAT results in increased systemic inflamation.[42] The extent or mechanisms of the anti-inflammatory effect of BAT are not yet documented. Work in progress includes testing BAT transplants in non-obese diabetic (NOD) mice, a model of insulitis closely related to human T1D, and characterizing the inflammatory response in diabetic animals in the presence and absence of BAT transplants. Other limitations of this technique include the need for embryonic tissue which is currently not applicable in clinical situations, and the underlying mechanisms not being fully evident.

Therapeutic Value of BAT in Other Metabolic Diseases

Reports as early as the 80s show a positive relationship between brown fat content and nutritional homeostasis, and beneficial effects of BAT in metabolic disease are reported with increasing frequency in recent studies. For example, mice deficient in BAT become progressively obese without hyperphagia.[41] Selective stimulation of β-3 adrenergic receptors, abundantly expressed in BAT, leads to increased energy expenditure and weight loss without affecting food intake.[41] Mice with induced brown fat lipoatrophy show increased visceral adiposity associated with excessive secretion of pro-inflammatory cytokines, followed by vascular insulin resistance and vascular dysfunction.[42] Treatment with thyroxine (TH) supplements in a T2D patient was shown to result in full remission of diabetes preceded by proliferation of BAT.[43] The patient originally had severe insulin resistance leading to uncontrolled hyperglycemia and consequent complications including blindness. Remarkably, high doses of TH resulted in resolution of hyperglycemia and complete insulin independence, associated with increase of

BAT in subcutaneous depots. Withdrawal of TH therapy resulted in diminished volume of BAT depots as well as return to hyperglycemia and insulin dependence. While additional studies are needed to demonstrate statistical significance, this is an intriguing observation indicating powerful effects of BAT in glucose regulation.

The presence of active BAT in adult humans was demonstrated only recently,[44,45] and since then there has been increasing interest in the therapeutic potential of BAT in combating obesity. Several reports suggest a link between the quantity of BAT and generalized leanness or decrease in obesity.[41,46-48] This is not surprising, considering BAT's active role in fat metabolism and energy expenditure. Specific transcriptional factors arising from BAT such as PRDM16 are now known to impart BAT-like properties to WAT, i.e., cause "browning" of WAT, which results in overall increase of energy expenditure, decrease of weight gain and improvement of glucose homeostasis.[49,50] Another recently identified messenger molecule originating from skeletal muscle, irisin, also improves energy expenditure in mice with no changes in movement or food intake, leading to improvements in obesity and glucose homeostasis.[51] Induction of BAT in WAT depots can also be accomplished with other stimuli, such as cyclooxygenase 2 (COX2) or cardiac natriuretic peptides (NPs), leading to increased energy expenditure.[52,53] Thus, increasing BAT in the body is undoubtedly beneficial, and overt adverse effects are not yet reported.

Mechanisms of BAT-Mediated Reversal of Diabetes

The aforementioned studies generally point to a mechanism where BAT improves glucose homeostasis by direct increase in energy metabolism. Browning of WAT results in increased numbers of adipocytes containing UCP-1 followed by significant decrease in weight and increased energy expenditure; accompanied by improved glucose homeostasis.[49-51] Reversal of T1D following BAT transplants does not seem to follow the same mechanisms, at least according to currently available data. While BAT transplants greatly improve the overall health of WAT, so far there is little evidence of browning. UCP-1 expression at the transplant site gradually decreases with time, and the surrounding WAT does not show UCP-1 expression.[28] Furthermore, as opposed to the weight loss observed with browning of WAT, BAT transplants result in significant weight gain through replenishment of WAT. Interestingly there is consistent expression of IGF-1 both in the BAT transplant area as well as surrounding WAT, and plasma IGF-1 levels in the transplant recipients are significantly elevated compared with normal and diabetic controls. There are several mechanisms by which IGF-1 may improve glucose homeostasis in transplant recipients. Insulin receptor is involved even in the absence of detectable insulin, as pharmacological inhibition of this receptor results in acute impairment of glucose tolerance.[28] Due to structural similarity in their receptors, IGF-1 may promote glucose uptake through occupying the insulin receptor.[54,55] IGF-1 is also known to promote adipogenesis through stimulating proliferation and differentiation of preadipocytes, making more functional cells available for glucose uptake.[55] In addition, IGF-1 is among several growth factors arising from BAT known to have anti-inflammatory properties.[29,56] Although not as widely documented as its metabolic effects, the anti-inflammatory action of BAT has been suggested in several studies.[40-42] It is noteworthy that the BAT transplants used in our study were of embryonic origin, containing more growth factors and angiogenic factors than adult BAT or BAT cells induced in WAT by the aforementioned mechanisms. Such factors include fibroblast growth factor-21 (FGF21), nerve growth factor and transforming growth factor-β, all of which are generally known to have significant anti-inflammatory properties. In addition, FGF21 has numerous beneficial effects on metabolism including insulin-independent glucose uptake into adipose tissue via GLUT-1 receptors,[57-59] and may play a key role in the new equilibrium. Other possible candidates include gut-derived incretins such as glucagon-like peptide-1, which has a variety of insulin-independent glucose-lowering effects as well as an active role in adipocyte regeneration.[60,61] It appears that BAT transplants merely improve the health of surrounding WAT, enabling it to function better as an endocrine organ. Overall, our current results indicate that BAT transplants transform the scanty and inflamed WAT in STZ-diabetic mice into a healthy and voluminous endocrine organ that can maintain glucose regulation without insulin.

Antidiabetic effects of healthy WAT has been reported before. WAT transplants from healthy donors are known to correct lipodystrophic diabetes[62] and improve insulin resistance and obesity in leptin deficient ob/ob mice,[63] while the recipients' own WAT remains inflamed. Thus WAT transplants are unable to transform inflamed WAT to a healthy state, as BAT transplants can. However, correction of metabolic disease through transplanting healthy adult WAT would be a simpler and easier treatment than embryonic BAT, and should be considered. A likely reason adult WAT transplants did not survive in our T1D recipients is that they had no insulin to maintain transplanted adipose tissue. In the presence of BAT, however, new healthy WAT can regenerate and proliferate without insulin. Once the underlying mechanisms of BAT-induced insulin-independent glucose regulation are elucidated, new methods may be designed to transplant and maintain healthy subcutaneous WAT as a therapy for T1D.

Future Potential

As the aforementioned reports show, loss of BAT is harmful and increasing BAT in the body can correct many disease states. A convenient and clinically applicable method to increase BAT is yet to be discovered. While our work with embryonic BAT transplants was dramatically successful in reversing STZ-induced diabetes in mice, embryonic BAT is not a viable option for human patients. We are currently looking to reproduce the results with human BAT cell lines, which may prove to be an excellent alternative translatable to clinical settings.

Conversion of endogenous WAT to BAT, i.e., browning of WAT, is a promising alternative method of increasing BAT

content. This is part of the mechanism of certain pharmacological agents already in the market such as PPARγ activators,[24-26] while newly discovered physiological compounds such as irisin show promise in recruiting BAT cells more efficiently.[51] Other studies demonstrate the possibility of inducing the recipients' own BAT. For example, thyroid hormones, activation of β-3 adrenergic receptors, administration of NPs or stimulation of COX-2 are all known to stimulate BAT development.[41,43,52,53] Such approaches have great potential in establishing physiological regulation through increased endogenous BAT. However a lot of caution should be exercised considering many of these mechanisms are associated with pathological states, for example NPs are generated in heart failure and COX-2 is an inflammatory mediator.

Transplantation of healthy WAT is a promising approach to correct insulin-resistant diabetes and obesity.[62-64] However there are ongoing problems with possible transplant rejection and immune response, and this method is currently not usable in T1D where adequate insulin is not available to prevent lipolysis of WAT grafts. Considering BAT transplants lead to proliferation of WAT without insulin, it is possible that specific factors arising from BAT may help maintain WAT grafts. Once identified, BAT-derived messengers may prove useful in maintaining WAT transplants, which in turn would be a convenient therapy for T1D as well as other metabolic disorders.

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