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REVIEW ARTICLE

Adipose-derived stem cells and obesity: The spear and shield relationship

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Abstract With the transformation of modern lifestyles and population ageing, obesity has become a global epidemic, as one of the important threat to human health of chronic non-communicable diseases (NCD). Stem cell therapy seems promising as an alternative strategy for managing obesity and related metabolic problems. Adipose tissue-derived stem cells (ADSCs) have received widespread attention, which provides new ideas for the treatment of obesity and various metabolic-related diseases, due to their abundant reserves, easy acquisition, rapid expansion, and multi-directional differentiation potential, low immunogenicity and many other advantages. Accordingly, there seems to be a "shield and spear paradox" in the relationship between ADSCs and obesity. In this review, we emphatically summarized the role of ADSCs in the occurrence and development of obesity and related metabolic disease processes, in order to pave the way for clinical practice.

Introduction

Like the rapid development of the global economy, obesity is rapidly spreading and has become an epidemic that seriously threatens human health.[1] Obesity is defined as a chronic metabolic disease, which usually refers to excessive accumulation and/or abnormal distribution of fat in the body accompanied by weight gain. Because it is closely related to inflammation, it is also considered to be a chronic, subclinical inflammation.[2,3] Obesity is also closely related to human diseases such as type 2 diabetes (T2D), hypertension and cardiovascular disease (CVD).[4–6] Insulin resistance caused by obesity is the basis for T2D in individuals with obesity,[7] and obesity is also an independent risk factor for T2D, coronary heart disease and stroke.[8,9]

In the past half century, scientific research has attempted to adopt a variety of measures to control obesity and its related metabolic diseases.[10–14] However, all these

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treatment measures have certain limitations, so there is an urgent need to introduce new intervention programs to implement them.[15] In this context, stem cell therapy sprouted in response to the needs of the times.[16–18]

Stem cell therapy is a new therapy developed with molecular biology, molecular immunology and cell biology.[19] Among all stem cells, mesenchymal stem cells (MSCs) are attractive candidate due to their vital role in adipogenesis and are proposed as new type of treatment option.[20–22] MSCs are the most studied and defined stem cells, and the cells originating from the mesoderm are called progenitor cells in the traditional sense, and have the potential for self-renewal and multi-directional differentiation, such as differentiation into bone, fat, and chondrocytes.[23] Adipose tissue-derived stem cells (ADSCs) possess the characteristics of easy access, rapid proliferation *in vitro* and autologous transplantation.[24] In the past nearly two decades, the use of adipose tissue progenitor cells as therapeutic agents has greatly increased, becoming the first choice for clinical regenerative medicine and even aesthetic medicine, and stimulating the development of new research fields and industries around the world.[25–27]

The epidemiology of obesity: status quo and dilemmas

In recent years, with the improvement of people's living standards and changes in dietary structure, obesity has become a global epidemic.[28] The data of World Health Organization (WHO) shows that nearly 2 billion adults worldwide are overweight or obese.[29] With the rise of China's economy and the consequent improvement in living standards, the number of people with obesity is also increasing rapidly. According to the "Report on Nutrition and Chronic Disease Status of Chinese Residents" issued by the State Council in 2020, the prevalence of overweight or obesity among Chinese adult residents has exceeded 50%, and more than 16% are obese. The prevalence of overweight or obesity among children and adolescents between ages of 6 and 17 is close to 20%, and that of children under the age of 6 reaches 10%. So far, China has become the country with the largest number of individuals with obesity and overweight in the world.[30] This also means that it is almost impossible to achieve the global goal set by the WHO that obesity levels in 2025 will not exceed the obesity levels in 2010.[31] Because obesity is closely related to a variety of metabolic diseases, it is urgent to control obesity, including research on effective medical methods for treating obesity.

Evaluation methods and classification of obesity

Obesity is considered to be an unhealthy state. It participates in the occurrence and development of various metabolic diseases such as insulin resistance, diabetes, and cardiovascular disease (CVD) by secreting a variety of inflammatory factors. The degree of obesity in patients can greatly affect the incidence and even mortality of diabetes, CVD, and certain tumors.[32,33] At present, according to the specificity of obesity classification, the diagnostic criteria are also different. Studies have shown that the cause of abnormal metabolism in individuals with obesity is much more associated with abnormal fat metabolism and distribution than the correlation with body weight.[34,35] Due to differences in eating habits and ethnicity, there are certain differences in the application of body mass index (BMI) in different regions of the world.[36] For example, the WHO stipulates that adults with BMI of 25–29.9 kg/m^2 are considered to be overweight, and $\geq$30 kg/m^2 is diagnosed as obesity.[37] Unlike the above, China diagnoses an adult with a BMI in 24–27.9 kg/m^2 as overweight, and $\geq$28 kg/m^2 as obesity.[38] Therefore, it is necessary to consider the differential impact of different BMI parameters in clinical applications. In addition, in addition to the common BMI as the diagnostic criteria for the assessment of systemic obesity, body fat percentage (BF%), which can objectively reflect the fat content, is also used in clinical diagnosis and treatment evaluation.[39]

According to different references, obesity has multiple classification methods. First of all, obesity can be divided into simple obesity, secondary obesity and drug-induced obesity according to different causes. Simple obesity is the most common type, accounting for about 95% of people with obesity. Its main feature is metabolic regulation disorder, which is not accompanied by obvious changes in nerve and endocrine system functions.[40] Secondary obesity accounts for about 2%–5%. It is secondary to diseases such as pituitary gland disease, meningitis, encephalitis, and hyperinsulinemia, so it is often referred to as pathological obesity. Drug-induced obesity is only seen in a small number of people who take obese drugs for a long time, accounting for about 2%.[41] For example, patients with allergic asthma, rheumatism, and rheumatoid diseases who use glucocorticoid drugs for a long time would have such obesity.[42] And it can also be seen in women who need to take estrogen drugs.[43,44] Secondly, according to the distribution of fat in different parts of the body, obesity is divided into central obesity and systemic obesity.[45] Central obesity is also called abdominal obesity, or visceral obesity. The fat of these patients is mainly deposited under the skin and in the abdominal cavity.[46] Furthermore, obesity is the result of the mutual participation and interaction of genetic and environmental factors, and genetic factors affect the body's fat mass and fat distribution, energy intake responsiveness, basal metabolic rate, nutrient absorption and utilization, and physical activity habits and so on, so it can also be classified from the perspective of genetics.[47] Based on this, it can be divided into two types: single-gene obesity and polygenic obesity.[48] The so-called single-gene obesity refers to the appearance of food addiction and significant weight gain at 2–3 weeks after birth, and it is characterized by early onset of extreme obesity and conforms to Mendelian Inheritance. The BMI of the patients generally exceeds 40 kg/m^2. Polygenic obesity, as the name suggests, is due to the participation and interaction of multiple genes, and it is also a late-onset obesity closely related to environmental factors, with a BMI level of 30–40 kg/m^2. Finally, obesity is divided into multicellular obesity and macrocellular obesity according to the anatomical characteristics of adipose tissue. Multicellular obesity is also known as adipocyte proliferative obesity. This type of obesity mainly occurs in early childhood (1–4 years old) and adolescents (7–11 years old). The number of fat cells in patients increases and is evenly distributed in

the limbs and the trunk, 70% of which may develop into adult obesity. Macrocellular obesity only has an increase in the volume of adipocytes without a change in the number. It mainly occurs in women and adults during pregnancy, and the fat is mainly accumulated in specific parts, such as buttocks, abdomen, arms, thighs and upper neck (Fig. 1).

According to the individual's phenotype, obesity is divided into: (1) normal weight obese (NWO); (2) metabolically obese normal weight (MONW); (3) metabolically healthy obese (MHO); and (4) "at risk" obese.[49] Normal weight obese individual may or may not have metabolic syndrome and that body fat mass percentage is required to define the term. The state of normal BMI (18.5—24.9 kg/m^2) and increased BF% is defined as NWO.[50] Since individuals with NWO have no significant body shape changes, they usually do not attract the attention of physicians. A current challenge when evaluating BF is that there is no consensus about the best cutoff for percent of BF to define excess fatness. The different proposed cutoff points of BF vary between 20—25% for men and 30—37% for women.[51—53]

Potential hazard and mechanism of obesity

Obesity, especially central obesity, can cause hypertension, dyslipidemia, diabetes, hyperuricemia, microthrombosis and other reactions, which is an important feature of metabolic syndrome and the initiating factor of its pathogenesis (Fig. 2).[54,55] The so-called metabolic syndrome is the general term for a group of metabolic diseases caused by insulin resistance and hyperinsulinemia, including obesity, hyperglycemia, hypertension, dyslipidemia.[56—58]

Abdominal fat accumulation will produce too much free fatty acid (FFA), which is the basis of metabolic syndrome.[59] The main mechanism is as follows: First, FFA entering the liver increases greatly, and then the oxidation of FFA increases, which inhibits the binding of hepatic insulin receptors to insulin, thereby forming hepatic insulin resistance; the concentration of FFA in the blood circulation increases, which increases the oxidation of FFA in the muscles and reduces glucose oxidative utilization, leading to peripheral insulin resistance. Secondly, excess FFA is further incorporated into triacylglycerols and deposited ectopicly in insulin-sensitive parts. Such a condition causes the lipotoxicity to pancreatic β cells, and the fat deposited in the viscera secretes a large amount of active signal molecules such as leptin, adiponectin and resistin, which are closely related to the formation of insulin resistance, hypertension, dyslipidemia and abnormalities in blood coagulation and fibrinolysis.[60—63] Central obesity is also closely related to the occurrence of hyperuricemia. Blood uric acid is mainly excreted by the kidneys, but its content is also affected by the endocrine effect of adipokines (such as visfatin, resistin, leptin, adiponectin).[64,65] Leptin has been reported to be associated with uric acid levels in type 2 diabetic patients.[66] And an independent association between leptin and uric acid was found in overweight/obese subjects.[67] A significant inverse association between serum uric acid and adiponectin levels was evident.[65] It is intriguing that this association was independent of insulin resistance and other possible confounders.[68] Individuals with lower levels may have reduced plasma antioxidant activity. On the other hand, individuals with elevated levels of uric acid

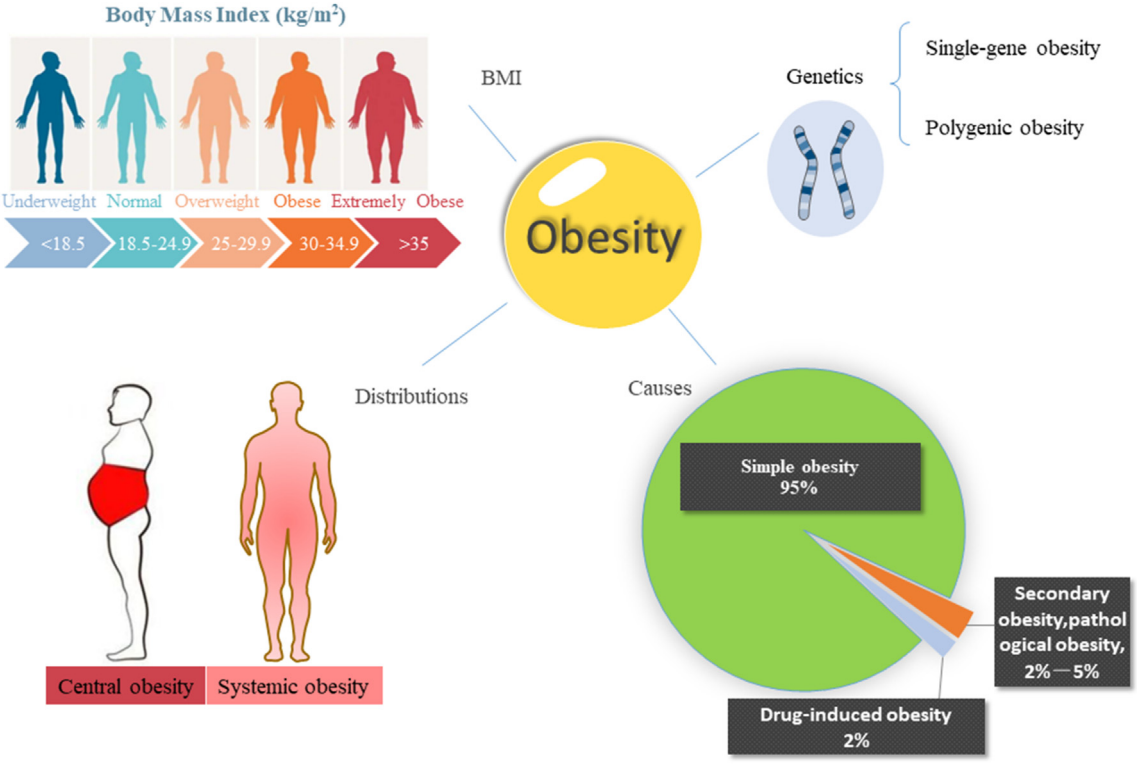

Figure 1 Various classification methods for obesity to 2021.

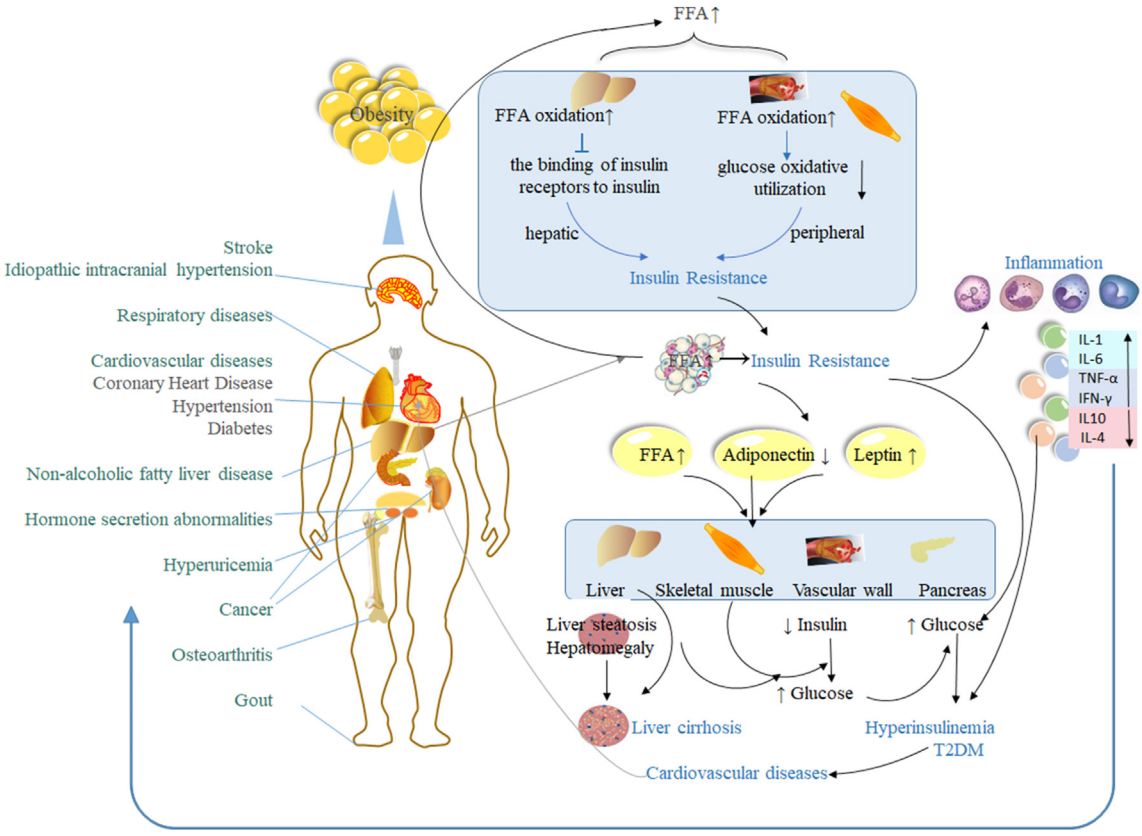

Figure 2 The mechanism of metabolic syndrome caused by obesity.

show lower levels of adiponectin, which increases the risk of metabolic disorders.[65]

Obesity can also cause insulin resistance, which is the core link in the occurrence of metabolic syndrome.[60] Insulin resistance causes a large amount of sugar accumulation in pancreatic β cells, thereby increasing insulin secretion. The resulting hyperinsulinemia leads to the weakening of the body's antioxidant capacity, causing direct damage to endothelial cells and destroying the arterial wall. The interaction between insulin resistance and FFA accumulation increases the FFA in the blood circulation, interferes with the normal metabolism of fat, produces lipid metabolism disorders, and affects sugar metabolism through multiple links, which ultimately leads to the occurrence of hyperglycemia.[69] And the state of hyperglycemia further causes endothelial damage, accumulation of blood lactic acid, and destruction of the blood—brain barrier. The changes in endothelial cell function lead to microvascular and large vessel atherosclerosis, which will aggravate the development of cardiovascular and cerebrovascular diseases.[70] High levels of FAA and insulin content stimulate sympathetic nerves to constrict blood vessels, increase cardiac output and kidney absorption of sodium, and ultimately increase blood pressure. It also stimulates the synthesis of lipoproteins and the proliferation of smooth muscle cells under the arterial intima, which causes lipid deposition in cells, thereby promoting the occurrence of atherosclerosis.[71] In addition, some cytokines, inflammatory factors, oxidative stress, hyperuricemia, microalbuminuria, non-alcoholic fatty liver and other clinical abnormalities, as well as bad living habits are also involved in the occurrence and development of metabolic syndrome.[72,73]

The origin of ADSCs and obesity

Obesity is closely related to various metabolic syndromes such as hypertension, dyslipidemia, and diabetes.[55] When obesity occurs, fat cells change significantly in terms of number, volume, fat storage, and types of adipokines secreted.[35] So, what are the origins and obstacles between ADSCs that play an important role in maintaining the normal morphology and physiological function of fat cells and the occurrence and development of obesity? Here, we have made a brief summary (Fig. 3).

Obesity is the fountain of ADSCs

The obesity epidemic has led to changes in global medical trends, one of which is the popularity of surgical abdominal plastic surgery. Although most of the postoperative liposaspirates are routinely discarded as medical waste, adipose tissues are referred to as an abundant and pluripotent resource by surgeons and many other researchers, which can be used to separate ADSCs for regenerative medicine.[74,75]

Biological characteristics of ADSCs

In 2006, the International Society for Cellular Therapy stipulated that MSCs must (1) have the capacity to

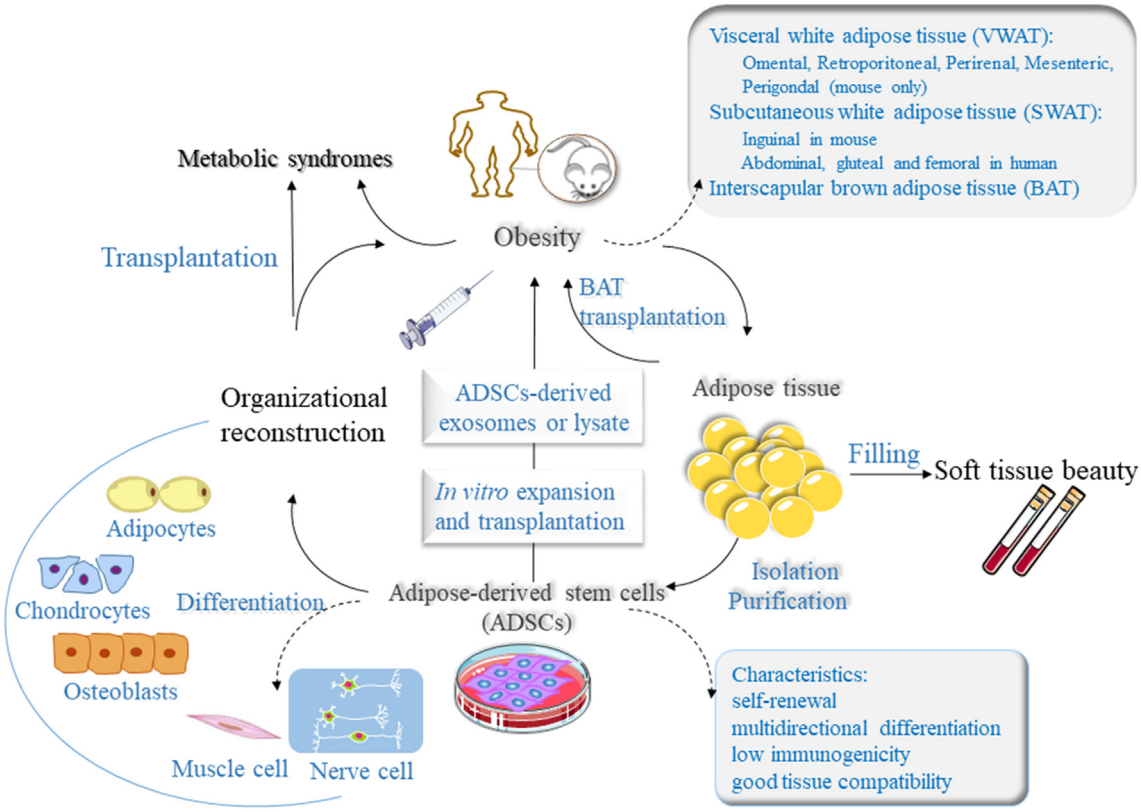

Figure 3 The origins and obstacles between ADSCs and the occurrence and development of obesity.

differentiate to osteoblasts, adipocytes, and chondroblasts under specific *in vitro* induction conditions, (2) have the ability to adhere to the bottom of standard culture conditions, (3) express CD73, CD90, CD105, and (4) not express c-kit, CD14, CD11b, CD34, CD19, CD79α, HLA-DR and other hematopoietic cell line surface markers.[76,77] In addition to the basic characteristics of MSCs, ADSCs also possess biological characteristics such as immune exemption, immune regulation, nutritional support, and secretion of adipokines.[78–82]

Localization of ADSCs in adipose tissue

There is a lot of controversy over the exact location of ADSCs in adipose tissue. A number of studies have found that ADSCs reside in the blood vessel wall and exhibit certain characteristics of perivascular cells.[83,84] There are three subpopulations of mesenchymal stem cells in the vasculature of adipose tissue: subendothelial pericytes/mural cells (SP), SP-transitional population (SPTP) and supra-adventitial adipose stromal cells (SA-ASC).[83] Other researchers have reached different conclusions: the analysis using immunohistochemical methods found that the ADSCs in the tissues *in situ* are not arranged strictly according to the distribution of blood vessels, but are scattered in the adipose tissue matrix. The cells do not express NG2, CD140b, α-smooth muscle actin and other molecular markers related to perivascular cells *in vivo*.[85] The above-mentioned different opinions may be due to: (1) Accompanying the development and growth of adipose tissue, primitive ADSCs derived from perivascular precursor cells continue to proliferate, differentiate, and migrate, gradually moving away from the vascular distribution area and losing perivascular cell-related molecular markers; (2) A part of adipose progenitor cells or precursor cells with strong proliferation ability existed in the adipose tissue matrix before birth or early after birth, and these cells are pre-coded to differentiate into adipocytes and support the growth and renewal of adipose tissue; (3) Perivascular cells and adipocyte progenitor cells exist simultaneously to support the normal renewal of adipocytes.[86] In addition, exosomes prepared by ADSCs have been used in the development of drugs for the treatment of adipose tissue inflammation.[82] Studies have shown that ADSC exosomes inhibit the infiltration and activation of intra-abdominal adipose tissue macrophages, and inhibit the production and release of pro-inflammatory cytokines, which implied that ADSC exosomes have a good inhibitory effect on adipose tissue inflammation.[87,88]

ADSCs impacts of obesity

The effect of obesogen on ADSCs

In 2006, the "obesogen" hypothesis was proposed and defined as a natural, drug-like or heterogeneous substance that could increase the number of fat cells or increase the fat storage of existing fat cells, and ultimately promote the occurrence of obesity (Fig. 4).[89,90]

Studies have confirmed that organic matter of estrogen-like substances acts as an obesity factor in animals.[91,92] Anti-diabetic thiazolidinediones (TZDs), tricyclic antidepressants, selective serotonin reuptake inhibitors, and

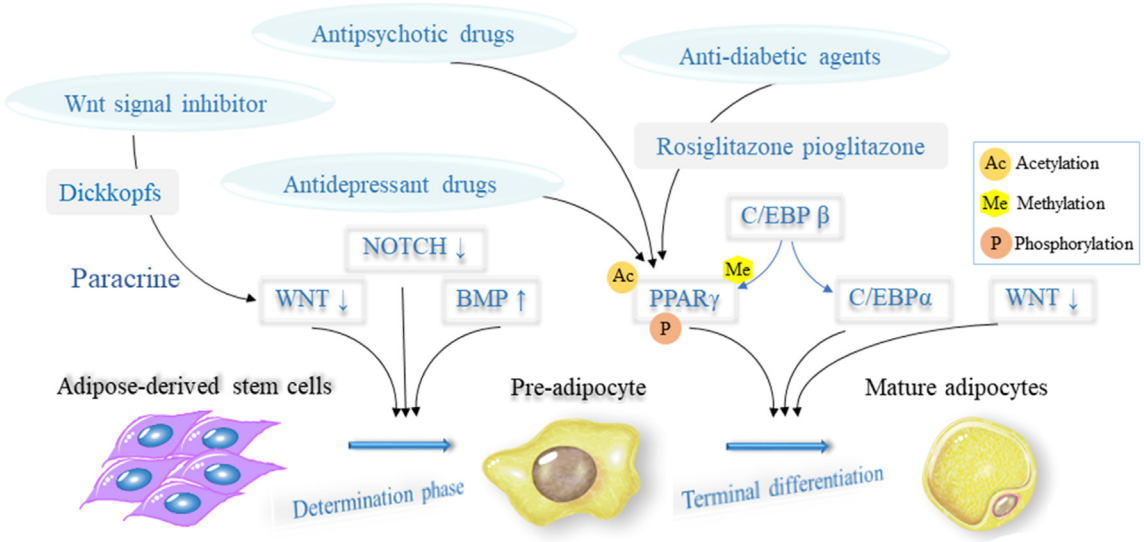

Figure 4 The mechanism of obesogen on ADSCs.

antipsychotic drugs such as olanzapine belong to the class of obesity factors.[93–96] These endocrine interfering substances promote the differentiation of ADSCs into mature adipocytes by activating the superoxide proliferator, the central regulator of peroxisome proliferator activated receptor gamma (PPARγ).[97,98] A research team found through animal experiments that ADSCs taken from white adipose tissue injected with tributyltin (TBT) or rosiglitazone before birth showed a clear tendency to differentiate into adipocytes, and this trend became extremely significant, after being treated with obesity factors *in vitro*.[99]

Obesogen could directly regulate ADSC-related signal pathways to regulate the expression of related genes such as their targeted differentiation and dryness maintenance, so that the body undergoes stable and heritable changes. Careful experiments have found that the methylation level of the gene encoding fatty acid binding protein 4 (FABP4) was reduced in ADSCs taken from mice exposed to obesity factors during the embryonic period, without *in vitro* induction, making these ADSCs become easier to differentiate into fat cells. At the same time, the methylation levels of AP2 and PPARγ, which encode adipogenesis-related genes, had also changed, causing the body to produce more adipose precursor cells and ADSCs that tend to differentiate into adipocytes.[99] In addition, Wnt signaling antagonists Dickkopf-1 (DKK1) treatment can promotes ADSC differentiation and increases adipocytokine secretion via the canonical Wnt signaling pathway. This means that inhibiting or knocking down DKK-1 maybe a novel way to prevent obesity-related diseases.[100]

The effect of obesity on ADSCs

Once the body fat level of mammals and humans exceeds the normal threshold to reach the obesity level, the body's internal environment would be in a relatively abnormal stable state and many indicators would no longer fluctuate. In such a condition, in order to maintain the abnormal homeostasis of individuals with obesity, the ADSCs in body adipose tissue (especially visceral adipose tissue) could change in many ways to meet this abnormal balance.[101,102] Studies have shown that obesity can cause changes in the pluripotency, proliferation, differentiation, and energy metabolism of ADSCs (Fig. 5)[103].

Animal experiments detecting the ADSCs taken from different tissues of obese mouse model fed with a high-fat diet found that compared with individuals with normal body index, the content of ADSCs in the subcutaneous adipose tissue increased. However, its telomerase activity decreased, the length of telomeres was shortened, and proliferation ability was weakened, accompanied by a decrease in the content of OCT4, SALL4, SOX15 and KLF4.[104–107] These studies show that the self-renewal ability of ADSCs from individuals with obesity was decreased. Moreover, its ability to differentiate into adipocytes and osteoblasts *in vitro* was also enhanced, while the chondrogenic ability was decreased.[108] In addition, studies using similar animal models found that the expression of AP2, C/EBPα, PPARγ and other adipogenesis-related genes in ADSCs of obese animal decreased significantly, and the adipogenic potential showed an upward trend; however, the ability to differentiate into endothelial cells has shown a downward trend.[109] Clinical studies confirmed that an increase in body mass index would reduce the proliferation ability of human subcutaneous ADSCs, and the ability to induce bone formation *in vitro* was affected.[110] The content of $CD90^+$ ADSCs in the vascular matrix of the subcutaneous adipose tissue of individuals with obesity was lower than that of normal individuals, and the differentiation ability and angiogenesis ability of these cells were significantly lower than individuals with normal body fat content.[111] The ADSCs in visceral adipose tissue of individuals with obesity became easier to differentiate into adipocytes, so as to increase the number of adipocytes and meet the body's demand for excess energy storage.[112,113] Individuals with obesity were involved in the maintenance of dryness of visceral adipose tissue ADSCs, cell differentiation and apoptosis and other related microRNA expression levels were significantly up-regulated.[114,115] The decreased multi-differentiation ability of ADSCs derived from visceral adipose tissue in morbidly individuals with

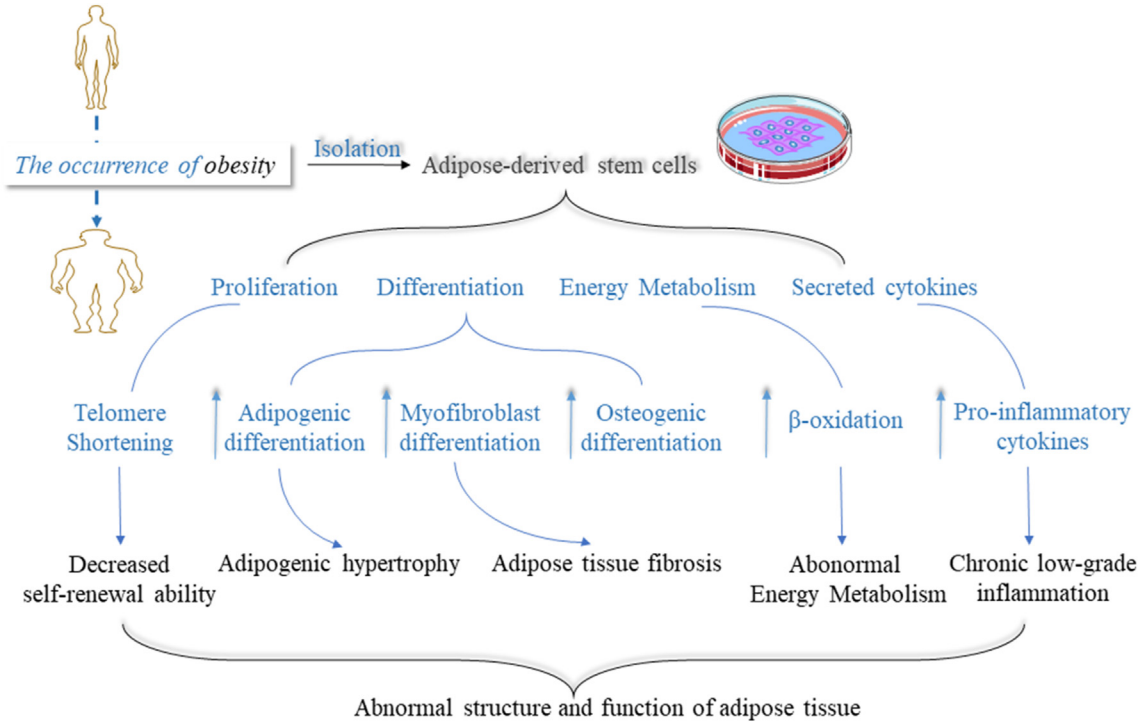

Figure 5 The effect of obesity on ADSCs.

obesity may be related to the dysregulation of Wnt and Notch related signaling pathways.[116,117] The above changes were similar to the current research conclusions that many hypercholesterolemia, diabetes, and hypertension-related diseases can damage the function and reduce the number of BMSCs. It has been mentioned in previous studies that ADSCs derived from $CD34^+$ visceral adipose tissue from obese (ob/ob) mice secreted high levels of monocyte chemotactic protein-1, compared with ADSCs derived from subcutaneous adipose tissue, which would enhance the body's chronic inflammatory response caused by obesity.[118] The stemness, monoline directed differentiation ability, and inflammation related gene transcription profiles of ADSCs obtained from subcutaneous white adipose tissue of individuals with obesity also changed, which promoted the differentiation of these cells into adipocytes, and the expression level of inflammation-related genes would be up-regulated with the loss of stemness.[119–121]

The process of self-renewal and differentiation of stem cells is accompanied by adaptive regulation of energy metabolism in cells. When cells differentiate into mature functional cells, the energy metabolism of cells is converted from glycolysis as the main feature to oxidative phosphorylation (OXPHS).[122] Studies have found that the mitochondrial function of ADSCs from individuals with obesity is abnormal.[123] When glucose is used as the substrate, the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of ADSCs are lower than those of non-obese group; and when fatty acids are used as the substrate, the OCR of ADSCs is higher, which shows that ADSCs from individuals with obesity use fatty acid β-oxidation as a source of energy. At the same time, the number of mitochondria in ADSCs from obese mice increased, and the level of reactive oxygen species also increased significantly, which is the same as that in individuals with obesity.[124]

ADSCs are a trenchant edge in the treatment of obesity

Obesity often involves pathologies of multiple systems.[47] The strong plasticity of ADSCs is expected to provide a new treatment approach for obesity and related metabolic syndrome. Under certain conditions, ADSCs could differentiate into a variety of cells across the germ layer, and could also treat lipid metabolism disorders of metabolic syndrome, insulin resistance, hypertension, hyperglycemia, atherosclerosis, low-grade inflammation and other diseases through direct participation in repairing damage, anti-inflammatory, cell protection, anti-apoptosis, immune regulation and other paracrine effects (Fig. 6).[125]

Abnormal blood lipid composition caused by energy intake exceeding energy expenditure is the mechanism that triggers obesity.[126] Studies have systematically evaluated the effects of ADSCs in the treatment of obesity, confirming that ADSCs have a positive effect in the treatment of obesity in terms of body mass, glucose metabolism homeostasis, lipid distribution, non-alcoholic fatty liver disease and systemic inflammation.[127,128] However, the proliferation ability of ADSCs was affected by age. ADSCs from young donors showed higher proliferation ability, and the repair and regeneration characteristics of ADSCs were related to their own diseases.[129] This also means that when the body had certain pathological conditions (such as metabolic disorders), the regeneration ability of ADSCs was

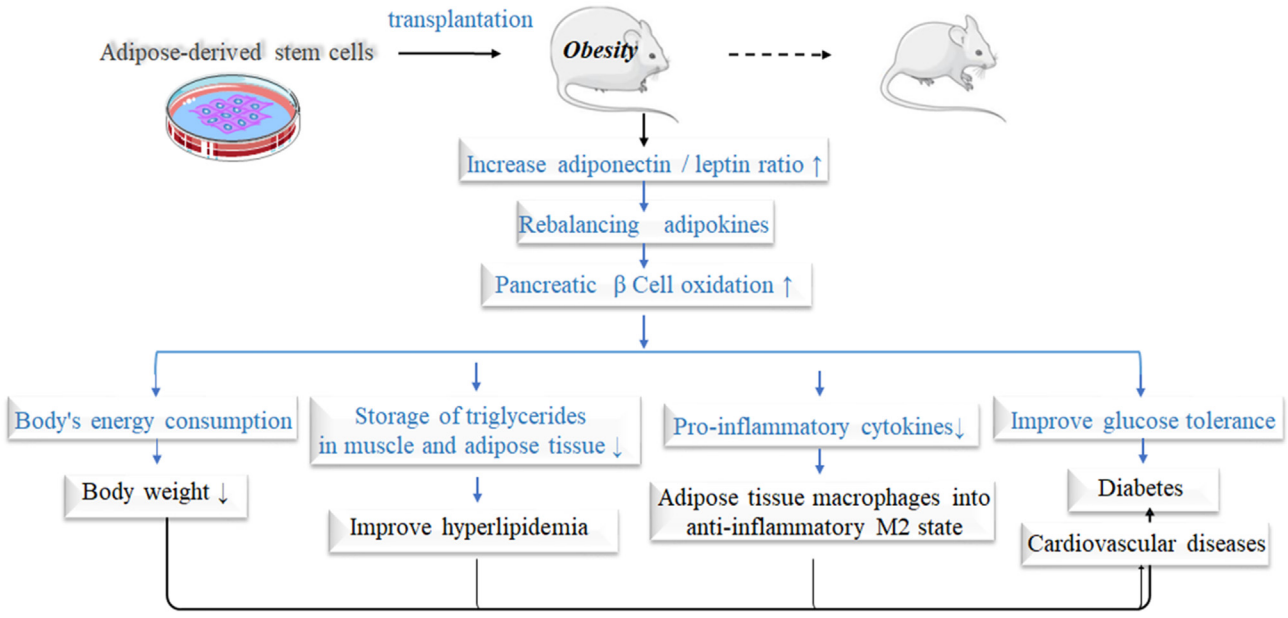

Figure 6 ADSCs are a trenchant edge in the treatment of obesity.

significantly affected, and their therapeutic potential was reduced.[130] The researchers implanted *ex vivo* expanded syngeneic ADSCs into obese mice and found that ADSCs could increase adiponectin secretion, promote fat burning, energy consumption and glucose treatment in adipose tissue, liver and muscle, and increase adiponectin/leptin ratio, thus rebalancing the expression of adipokines in obese mice, further improving leptin resistance and promoting pancreatic β cell oxidation, which promotes the body's energy consumption, reduces the storage of triglycerides in muscle and adipose tissue, and reduces the transport of fatty acids from muscle to liver, ultimately improving hyperlipidemia and reducing body weight.[128,131]

In addition, ADSCs could also relieve obesity through its anti-inflammatory properties.[87,132] Serum levels of inflammatory factors such as TNF-α, IL-6, and IL-1 are increased in individuals with obesity, and the inflammatory factors in adipose tissue, especially monocyte chemotactic protein-1 and TNF-α, are also correspondingly increased, which promotes the infiltration of inflammatory cells in fat, causing insulin resistance.[132] It is critically important to understand that obesity is associated with macrophage accumulation in adipose tissue.[133,134] It has been reported that diet-induced obesity activates adipose tissue macrophages (ATM) into pro-inflammatory M1 macrophages that produce a variety of pro-inflammatory cytokines such as TNF-α and IL-6, which contribute to the development of diabetes and atherosclerosis.[135,136] ADSC administration lowered the expression of pro-inflammatory cytokines and significantly reduced the levels of inflammatory mediators in HFD-fed mice. Infusion of ADSCs in obese mice found that ADSCs reduced IL-1, IL-6, TNF-α and other related inflammatory factors levels in serum and adipose tissue and inhibited the inflammatory response to reduce obesity.[87,131] Owing to their immunomodulatory and anti-inflammatory properties, researchers postulate that ADSC infusion produced significant anti-diabetic effects via soluble factors in part through directing ATM into anti-inflammatory M2 state and subsequently suppressing the secretion of pro-inflammatory mediators, thus ameliorating the inflammatory microenvironment.[87,137,138] In summary, ADSCs could effectively treat obesity-related diabetes in animal models and prevent cardiovascular diseases, which may be partly due to the weakening of inflammatory mediators. Therefore, ADSCs may provide promising therapeutic potential in combating obesity-related diseases in patients.

Conclusion and outlook

ADSCs have received extensive attention due to their advantages such as easy acquisition, multi-directional differentiation potential, nutritional function, and immunomodulatory properties. The change of adipose tissue function is closely related to the occurrence of obesity. Therefore, the relationship between the change of ADSCs in adipose tissue and the occurrence and development of obesity has begun to become a new focus of research. There are still many problems to be solved on the road ahead.

At present, the separation and *in vitro* amplification technologies of ADSCs are quite mature, and the basic research and clinical trials of ADSCs used in the treatment of obesity have also achieved certain results. However, there are still many problems to be solved for the wide application in obesity and metabolic syndrome. First of all, there is no best answer for the dosage, frequency, timing of transplantation, and which transplantation route can achieve the best therapeutic effect. Secondly, although stem cell transplantation can improve insulin resistance and atherosclerosis, regulate glucose and lipid metabolism, and promote cardiovascular and renal system repair, when the above-mentioned lesions are gathered in an individual as a component of metabolic syndrome, will such a good therapeutic effect still occur? There is also a lack of research evidence to support whether stem cell transplantation can improve the accumulation of abdominal fat. Furthermore,

stem cells that enter the blood circulation, especially stem cells transplanted through the venous system, will be trapped by other organs before homing to the target cells. What is the ratio of trapped stem cells? How long can they stay after reaching the target organ? What is the long-term effect? There is no definite conclusion. And in the microenvironment of damaged tissues and organs, how to migrate and differentiate needs to be solved by further animal experiments. However, as far as the current research results are concerned, the multi-directional differentiation and high proliferation of ADSCs make it a non-negligible status and broad application prospects for the treatment of metabolic syndrome involving multiple systems.

Now it has reached the point of a "severe obesity epidemic". Ten years ago, there were only a handful of people in China who heard of stem cells. In 2006, China's investment in stem cell field was very limited, and total investment was even less than that of some state projects in the United States.[139] In order to improve and speed up the pace of stem cell research in China, my country has successively provided financial support for many major key projects of stem cell research from different levels.[140,141] At present, medical staff in my country also show a high level of cognition on stem cell research.[142] In addition to individual efforts, in order to avoid the severe obesity epidemic, various governments can introduce new policies to slow and stop weight gain on a global scale, and fast and rigorous assessments must be implemented, including smart food policies and improved health care training.

Author contributions

H.Y., and C.S. contributed to the research design of this review. H.Y., CW. L., YZ. L. and RQ. T. contributed to the writing of this review.

Conflict of interests

The authors declare that they have no competing interests.

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