



Stem Cell and Obesity: Current State and Future Perspective

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Abstract

Obesity as a worldwide growing challenge is determined by abnormal fat deposition, which may damage general health. Weight loss and control of related risk factors like type2 diabetes, dyslipidemia, hypertension, cardiovascular diseases, and metabolic syndrome is an important concern in obesity management. Different therapeutic approaches such as lifestyle change, medications, and surgery are introduced for obesity treatment. Despite of gaining partially desirable results, the problem

is remained unsolved. Therefore, finding a new approach that can overcome previous limitations is very attractive for both researchers and clinicians. Cell-based therapy using adipose-derived stromal cells seems to be a promising strategy to control obesity and related syndromes. To attain this aim, understanding of different type of adipose tissues, main signaling pathways, and different factors involved in development of adipocyte is essential. Recently, several cell-based methods like stem cell administration, brown adipose tissue

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transplantation, cell lysates and exosomes have been examined on obese mouse models to manage obesity and related disorders. Successful outcome of such preclinical studies can encourage the cell-based clinical trials in the near future.

Keywords

Adipocyte · Adipose tissue · Animal models · Cell therapy · Mesenchymal stem/stromal cells · Obesity

Abbreviations

ADAMTS5	A	disintegrin	and	ENG	Endoglin (protein)
		metalloproteinase	with	ERK	Extra cellular receptor kinase
		thrombospondin motif 5		ES	Embryonic stem cell
ADSC		Adipose derived mesenchymal stem cells		EVs	Extracellular vesicles
AKR1B10		Aldo-keto reductase family 1 member B10		FDA	Food and drug administration
aP2		Adipocyte protein 2		FGF10	Fibroblast growth factor 10
ASCs		Adipose derived-stem cells		FPG	Fasting plasma glucose
BAT		Brown adipose tissue		FTO	Fat mass and obesity associated (gene)
BMI		Body mass index		H3K9	Histone H3 lysine 9
BM-MSCs		Bone marrow mesenchymal stem cells		HDL	High-density lipoprotein
BMP4		Bone morphogenic protein 4		HFD	High-fat diet
C/EBP α		CCAAT/enhancer-binding protein		Hh	Hedgehog
(A)/ β / δ		α / β / δ		HOXC8	HomeoboxC8
CB-MSC		Umbilical cord blood-mesenchymal stem cell		IDF	International diabetes federation
CB-plasma		Cord blood plasma		IGF1	Insulin-like growth factor1
CD24		Cluster of differentiation 24		IL6	Interlukine 6
Cidea		Cell death-inducing DFFA-like effector a		LOX	lysyl oxidase
CIT		Cold induced thermogenesis		M-BA	MSC-derived BAT
Cox2		Cyclooxygenase 2		Mef2	Myocyte enhancer factor 2
CRE		cAMP response element		miR-196a	MicroRNA 196a
CXCL3		Chemokine(C-X-C motif) ligand3		miRNAs	MicroRNAs
DIO		Diet-induced obese		MSC	Mesenchymal stem cells
DIT		Diet-induced thermogenesis		Myf5	Myogenic factor 5
Dlk1		Delta like non-canonical notch ligand 1		NICD	Notch intracellular domain
EBF2		Early B cell factor 2		NRs	Number of nuclear receptors
EHMT1		Euchromatic histone lysine methyltransferase 1		Pax7	Paired box 7
				PDGF	Platelet-derived growth factor
				PDGPR α / b	Platelet derived growth factor receptor α / β
				PGC α	Peroxisome proliferator-activated receptor-gamma coactivator α
				PLIN	Perilipin
				PPAR- γ /G	Peroxisome proliferator-activated receptor- γ
				PPRE	PPAR response element
				PRb/Rb	Retinoblastoma protein/retinoblastoma
				PRDM16	PR domain containing 16
				PREF1	Preadipocyte factor 1
				RARE	Retinoic acid response element
				RIP	Receptor interacting protein
				SAT	Subcutaneous white adipose tissue
				SMA	Spinal muscular atrophy
				STAT3	Signal transducers and activators of transcription 3
				TC1	Immune response regulator

TNF α	Tumor necrosis factor α
TRE	Thyroid response element
TGF β	Transforming growth factor beta
UCP1	Uncoupling protein 1
VAT	Visceral white adipose tissue
VEAT	Visceral endothelial adipose tissue
WAT	White adipose tissue
WHO	World health organization
Wisp2	Inducible signaling path-way protein 2
WNT1	Wingless-type MMTV integration family member 1
Zfp516	Zinc finger protein 516
P107	Retinoblastoma-like 1

1 Introduction

Obesity is now a global problem and it is called “Globesity” which means many people around the world suffer from this disease (Pietrabissa et al. 2012). Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health [WHO]. The rate of obesity has risen in recent decades and it is predicted to rise even more because of changing lifestyle and demography. In 2016, more than 650 million adults were obese [WHO]. A review study has estimated the range of overweight and obesity among Iranian adults as 27%–38.5% and 12.6%–25.9% respectively (Jafari-Adli et al. 2014).

Obesity is an important risk factor for type2 diabetes, dyslipidemia, hypertension, cardiovascular disease, and some types of cancers (Matsushita and Dzau 2017; Narayanaswami and Dwoskin 2017; Payab et al. 2014; Payab et al. 2017b). Another associated disorder is Metabolic Syndrome which is defined by IDF as central obesity plus any 2 of these 4 parameters: raised triglycerides, reduced HDL cholesterol, raised blood pressure, raised FPG. Thus, obesity can increase the risk of metabolic syndrome (Pi-Sunyer 2009). The life-threatening increase in obesity evoked some main strategies to control it: lifestyle modification, taking medication, and undergoing surgery (Petroni et al. 2017). These

conventional methods have some considerable advantages for treatment and management of obesity for instance an average weight loss of 7 to 10Kg in 6 months by lifestyle modification, providing additional weight loss and positive effects on several metabolic parameters such as systolic blood pressure and total cholesterol by taking medication and a dramatic weight loss along with the rapid remission of type 2 diabetes mellitus by surgery (Yanovski and Yanovski 2014). Nonetheless, there are a number of limitations in the long-term efficacy and safety of these types of treatments such as return of lost weight, adverse effects and invasiveness respectively (Pories 2008).

Despite all the significant achievements of the mentioned methods, the obesity is still a major health problem which is needed to develop a novel treatment to enhance the effectiveness of obesity treatment. Nowadays, cell-based products propose promising advances in treatment of several disorders. Accordingly, clinical application of different types of stem cells can help scientists and clinicians to treat diseases include diabetes, disc degeneration, neurodegenerative disorders and obesity (Aghayan et al. 2017). Mesenchymal stem cells (MSCs) are multipotent cells which are considered to be common applicable type of stem cells. These cells can be derived from various sources like bone marrow, blood, umbilical cord tissue and adipose tissue and can differentiate into several cell types like chondrocytes, osteoblasts, adipocytes and myoblasts (Augello and De Bari 2010; Tarte et al. 2010). Adipose derived mesenchymal stem cells (ASCs) are considered to be more beneficial, compared to bone marrow derived mesenchymal stem cells: human subcutaneous adipose tissue can be accessed easily and repetitively, the isolation procedure is rather simple, minimally invasive and it provides a large number of isolated cell (Aghayan et al. 2015; Thirumala et al. 2009).

MSCs play an essential role in adipogenesis which is a fundamental part in obesity and this makes them a potential target for therapeutic use (Baptista et al. 2015). In addition, these cells can be used to find a new way of controlling obesity *in vitro* and *in vivo* (Lee et al. 2017; Matsushita

2016). There are complex signaling pathways of adipogenesis from MSCs and many studies have determined the pathways governing MSC adipogenesis and realize therapeutic strategies for obesity (James 2013). Much researches have been carried out into the heterogeneity and properties of different white adipose tissue depots and ASCs to find suitable potentials for treatment of obesity (Cleal et al. 2017). Another research area is MSC differentiation into brown adipocyte which is reported to improve obesity hence this sounds promising to identify therapeutic strategies (Vargas-Castillo et al. 2017). However, our knowledge in these fields is not enough as there are contrasts in many results of related studies. MSCs can hopefully be a therapeutic alternative for obesity and further studies are expected to shed some light on all the complexities and open possibilities for a novel treatment for obesity. The authors in this review are trying to show that what are the ultimate results of the related studies and provide a future direction for more researches leading to clinical application of a safe and efficient type of stem cells for obesity treatment.

2 Adipose Tissue as a Secretory Organ

Adipose tissue can be found in mammals and especially in humans. There are two types of adipose tissue that differ in function, structure, color and position: 1) white adipose tissue (WAT) and itself includes visceral white adipose tissue (VAT) and subcutaneous white adipose tissue (SAT), 2) brown adipose tissue (BAT). Moreover, investigators have discovered another type of adipose tissue, the color of which is between BAT and WAT and it is called beige adipose tissue (brite adipose tissue) (Illouz et al. 2011). All of them are differentiated from an identical origin, MSC. First of all, MSC which can differentiate into adipocyte, osteoblasts, myoblasts, and connective tissue is isolated from various tissues like bone marrow and adipose tissue. Secondly, MSC results in adipoblast that differentiates into brown

and white preadipocyte in the presence of specific stimuli. After that, preadipocyte differentiates into brown or white adipocyte (Fig. 1 ;Esteve Rafols 2014).

Some of the main duties of the adipose tissue are energy storage, shock absorption, thermal insulation. Additionally, adipose tissue acts as a secretory organ. In fact, due to the link between obesity and metabolic syndrome, attention is also drawn to the adipose tissue system. Adipose tissue secretes proteins which are generally called adipokine include leptin, adiponektine, interleukine 6 (IL6) (Anderson et al. 2003), tumor necrosis factor α (TNF α) and resistine (Gao et al. 2018). They can be made by adipocytes and skeletal muscle cells. Adipokines can perform different physiological activities. In fact, they can be transmitted through the paracrine system to various organs such as the lungs, heart, the skeletal muscle, muscle of vessels and influence activities of these organs.

2.1 Different Types of Adipose Tissue

2.1.1 White Adipose Tissue

In WAT fatty particles are stored in the form of triglycerides molecules and triglycerides consist of two parts: glycerol and fatty acids WAT mass increases with obesity. Moreover, obese people should lose weight and WAT mass by changing lifestyle, exercise training, taking medicine such as dietary supplement, including polyphenols with physician prescription but, because of the pharmacological approaches side effects researchers focus on exercise training and changing lifestyle (Sakurai et al. 2012).

Treating white adipocytes with irisin, a hormone secreted by skeletal muscle, and FGF21 induces browning. It was reported that “the beneficial effects of exercise, reduction of diet induced obesity and decrease of insulin resistance in mice” is related to irisin. Stimulating the conversion of white fat to brown fat by irisin in humans was also proposed. FGF21 increases the expression of uncoupling protein 1 (UCP1) and other

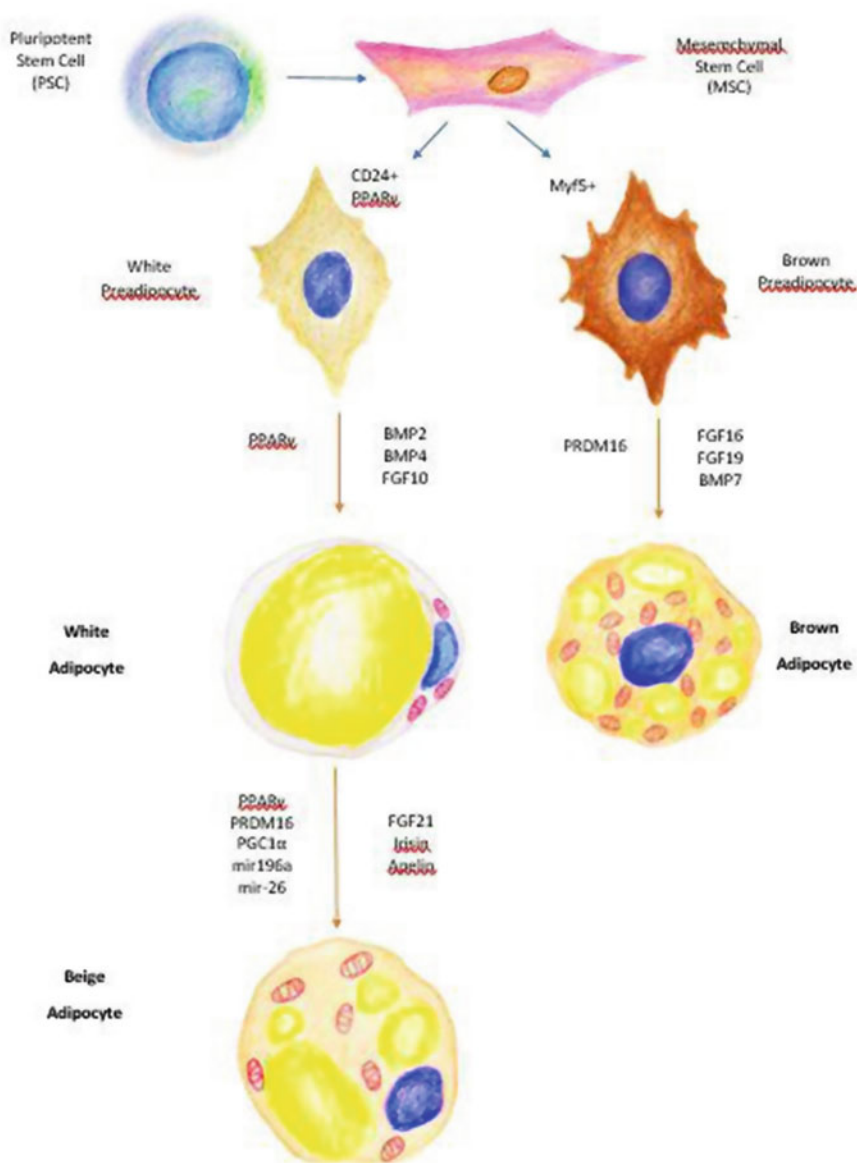


Fig. 1 The development of brown and beige adipocyte (drawn by Rasta Arjmand). Initially, pluripotent stem cell modifies into MSC which can get cluster of differentiation 24 (CD24) and peroxisome proliferator- activated receptor- γ (PPAR- γ) + white preadipocyte and myogenic factor 5 (Myf5) + brown preadipocyte. Secondly, in the face of white preadipocyte and some factors including PPAR- γ , bone morphogenic protein 4 (BMP-4), BMP-2 and fibroblast growth factor 10 (FGF10). Moreover,

WAT can come into beige adipocyte throughout exposure to PR domain containing 16 (PRDM16), FGF21, PPAR- γ , Peroxisome proliferator-activated receptor- γ coactivator α (PGC α), Irisin, apelin, Cyclooxygenase 2 (Cox2), microRNA 196 (MIR196a) and mir28. Brown preadipocyte is induced to be matured into BAT by way of ministration with some factors, for instance: PRDM16, FGF19, FGF16 and BMP-7 (Unser et al. 2015)

brown-fat-related genes in perirenal and inguinal WAT. Adipocytic FGF21 triggers the browning of WAT and activate BAT in response to cold (Lee et al. 2014; Poher et al. 2015).

2.1.2 Brown Adipose Tissue

The role of BAT is fat burning and producing heat in the body. Although the activity of BAT is reduced with age, it does not lose its activity completely and cold exposure can stimulate reactivation of BAT. BAT color is due to differences in the number of mitochondria and nerve fibers in the brown to yellow color range (Vargas-Castillo et al. 2017). The main location of this tissue are sternocleidomastoid muscles, the supraclavicular region, the armpits, the groin muscles, the adrenal glands, between the subscapularis and pectoralis muscles, the para aortic adipose tissue, and around the viscera in the omentum tissue (Aldiss et al. 2017; Harms and Seale 2013; Lidell et al. 2013). The formation of BAT via brown adipogenesis is an important process due to its ability to expend energy as heat with implication in the treatment of metabolic disorders and obesity (Unser et al. 2015).

Adaptive thermogenesis by BAT activation have been described in two ways: 1) cold induced thermogenesis (CIT), 2) diet-induced thermogenesis (DIT) (Silva and Bianco 2008).

2.1.3 Beige Adipose Tissue

UCP1-positive cells have been demonstrated in WAT as the counterpart of BAT cells (Boucher et al. 2016; Brand et al. 2005; Wu et al. 2012). Nowadays, inducible adipose tissue has been intriguing as an alternative therapy for obesity. Beige adipose tissue can be found in diverse zones as supraclavicular, shoulder-blades, axillary, mediastinal, paravertebral, perirenal and peri-aortic regions (Rogers 2015; Wu et al. 2012). There are different methods for development of beige adipocyte, three of which are more significant: “De novo beige adipogenesis, white-to-beige adipocyte trans differentiation, activation of dormant beige adipocytes” (Rui 2017). In these three types of method, inducing inactive beige

adipocytes is motivated by cold exposure, β adrenergic's etc. (Barbatelli et al. 2010; Berkowitz et al. 1998; Rosenwald et al. 2013; Wang et al. 2013; Wu et al. 2012). Beige adipose tissue has offered a new approach in treatment of metabolic diseases. It is similar to both WAT and BAT in rather different ways. Researches have been performed on animal and human subjects investigating to demonstrate the features of this type of adipose tissue.

BAT and brite adipose tissue are distinguished from WAT by their high levels of metabolic rates and thermogenic capacity (Bartelt et al. 2011; Stanford et al. 2013). Mitochondrial energetics, lipid droplet dynamics and metabolic fuel mobilization all influence BAT and beige adipocyte thermogenesis. Also UCP1-mediated thermogenesis is a hallmark of BAT and beige adipocyte. Recent findings illustrate that both of these tissues also do thermogenesis by additional UCP1-independent mechanisms (Rui 2017).

BAT has a common origin with muscles. Both of them are derived from dermomyotom of mesodermal layer. Early B cell factor 2 (EBF2) and BMP7 induce dermomyotom to form brown preadipocyte and PRDM16, CCAAT/enhancer-binding protein β (C/EBP β), EBF2, PPAR- γ , zinc finger protein 516 (Zfp516) play significant role in differentiation brown preadipocyte to brown adipocyte tissue. There are multitude UCP1 in the mitochondria of BAT, that contributes to thermogenesis (Zhang et al. 2016). “UCP1 of BAT dissipates proton gradient generated and catalyzes proton leak throughout the inner mitochondrial membrane” (Vargas-Castillo et al. 2017). This molecular marker is useful to recognize BAT and Beige adipocyte (Rui 2017). UCP1 locates in the inner mitochondrial membrane. Although, there is no UCP1 in brown and beige progenitor cells, but during adipogenesis its expression enhances under the control of genetic program (Rabelo et al. 1996).

Besides the similarity of these three types of adipose tissue they also have some differences which are depicted in Table 1 (Ikeda et al. 2018; Rui 2017).

Table 1 Characteristics of Brown, White and Beige Adipocyte

	Brown adipose tissue	Beige adipose tissue	White adipose tissue
Location	Infants (dedicated ddepots)	Adults (mammels)	Infants and adults
Function	Methabolically active and heat productive	Methabolically active and heat productive	As an energy store
Endocrine function	Neurgulin4, IGF-1 ⁽¹⁾ , FGF21 ⁽²⁾ , interleukin 6	Neurgulin4, IGF-1, FFGF21, interleukin6	Adipokines (leptin-adiponectin)
	Leptin, adiponectin (alittle)	Leptin, adiponectin (alittle)	
Thermogenic process	UCP1-dependent	UCP1-independent	—
Lineage	Myogenic lineage (ENG ⁺ , Myf5 ⁺⁽³⁾ , Pax7 ⁺⁽⁴⁾)	Multiple lineages (SMA ⁺ , PDGFRa ⁺⁽⁵⁾ , PDGFRb ⁺⁽⁶⁾)	—
Continuance	Constitutive	Transient	Constitutive
		(direct transition)	
Heterogeneity	Homogeneous	Heterogeneous	Heterogeneous

+ 1: *insulin like growth factor 1*. 2: *fibroblast growth factor 21*. 3: *myogenic factor 5*. 4: *Paired box 7*. 5: *platelet derived growth factor receptor α* . 6: *platelet derived growth factor receptor β* .

2.2 Factors Secreted from Adipose Tissue

Adipokines influence inflammation within adipose tissue and visceral endothelial adipose tissue (VEAT)(Lehr et al. 2012). As an adipokine, Leptin, was discovered almost simultaneously with the most important adipokine called adiponectin. Leptin is produced by adipocytes and plays an important role in regulating body weight. Accordingly, damaging hypothalamic methabolic circuits is because of the lack of leptin receptor in myeloid cell which cause increasing body weight, enlarging proinflammatory genes to modify 3 T3-L1 adipocyte as another consequence of leptin in adipose tissue (Gao et al. 2018). The studies of leptin till now have been performed on animals especially on mouse but researches on the physiological effects of leptin such as leptin resistance in the brain have not been discovered. Adiponectin has several effects including insulin-sensitizing, anti-inflammatory, anti-atherogenic and anti-carcinogenic activity (especially in breast cancer) (Fève 2013; Payab et al. 2017a). Adipose tissue in obese individuals acts as endocrine and secretory organ and the result is increasing the rate of secretion of pro inflammatory adepokines including TNF α and IL6 (Anderson et al. 2003). IL6 is produced and secreted by adipocytes and muscle cells which is

increased in the plasma following obesity (Carey and Febbraio 2004). TNF α was the first adepokine, the activity of which was being studied and its performance in the human body is still unclear (Halse et al. 2001) It is secreted by the innate immune cells (macrophage) and expressed in adipocyte (Lehr et al. 2012). In the context of the relationship between inflammation and obesity it should be said that obesity is a type of low-grade inflammation (Cao et al. 2008).

2.3 Gene Expression and Adipogenesis

The role of genetics and mechanisms which affect gene function in the process of adipocyte differentiation is absolutely essential and it is considered as an interesting research area to find a novel treatment for obesity. There has been a great effort to identify genetic variants affecting obesity traits. The first gene associated to non syndromic obesity is fat mass and obesity associated (FTO) (Herrera et al. 2011). The association of this gene region with obesity explains 1% of BMI heritability. Also, FTO is reported to be involved in decreased lipolytic effect in adipocyte. Further, more gene loci related to obesity and BMI associated variants have been identified (Speliotes et al. 2010). The pattern of fat

distribution, the factors affecting it and the potential risks caused by central and peripheral obesity, need to be fully understood. Accordingly, it was demonstrated that the development or maintenance of specific regional fat depots can be affected by DNA variants. Among 17 novel common obesity loci, 14 loci are related to body fat distribution and some of them are connected with sex in women. In other words, the fat distribution in men and women is influenced by sex-specific genes (Herrera et al. 2011).

There are several genes that regulate the adipogenesis (Fig. 2). BMP family control multiple steps of differentiation processes like adipogenesis. BMP-2 and BMP-4 are adipogenic factor for white fat and direct white adipocyte progenitor cells to white preadipocyte. In contrast, BMP-7 triggers commitment of MSC to brown adipocyte lineage (Chen and Tong 2013; Tseng et al. 2008). In addition to this family, one of the most powerful transcriptional regulators which control the fate of brown fat cells is PRDM16. Over expression of PRDM16 converts skeletal muscle progenitor cells to brown adipocytes (Chen and Tong 2013). Further, it restricts skeletal muscle gene expression in brown fat precursors by its interaction with PGC-1 α and PGC-1 β , as other transcriptional co-regulators. Among many nuclear factors regulating adipocyte differentiation, PPAR γ 2 is a key regulator that triggers differentiation to adipocyte. PRDM16 binds to PPAR- γ and coactivates its function (Seale et al. 2008). In addition to this factor, C/EBPs, a transcription factor family, has some members that induce adipogenesis: C/EBP α , β , δ . C/EBP β and C/EBP δ “are expressed early and transiently” in the adipogenesis process and are induced by cAMP and glucocorticoids respectively (Ming Shi et al. 2000). It was found that ectopic expression of PPAR- γ and C/EBP α alters the program of differentiation of myoblasts and convert them to adipocytes upon hormonal stimulation. This suggests that the mentioned factors have the “dominant role in adipocyte determination and differentiation processes” (Hu et al. 1995).

In addition to the mentioned genes, there are some other genes, which intervene in this process. A gene of vertebrate which has regulatory effect on adipogenesis is called transcriptional and immune response regulator (TC1). It down-regulates PPAR- γ and C/EBP α while it up-regulates the wingless-type MMTV integration family member 1 (WNT1), inducible signaling pathway protein 2 (Wisp2) and delta like non-canonical notch ligand 1 (Dlk1) (Jang et al. 2016). Wisp2 inhibits adipogenesis in both mesenchymal stem cells and preadipocytes (Hammarstedt et al. 2013).

Another gene which can promote expression of PPAR γ 2, *c/ebpb* and *c/ebpd* is chemokine (C-X-C motif) ligand3 (CXCL3), a chemokine produced by different types of cells including adipocytes (Kusuyama et al. 2016).

One of the most compelling topics in this field is about BAT, as the thermogenesis was found intriguing in this type of adipose tissue. The precursor cells of BAT can also differentiate into muscle cell in the presence of some special transcription factors like PPAR- γ , PRDMI6 (which is of great importance in differentiation of adipocytes and is highly expressed in Brown adipocytes) and Euchromatic histone lysine methyltransferase 1 (EHMT1). As it was mentioned before, UCP1 is the hallmark protein for promoting thermogenesis which its transcriptional process is initiated by a number of transcription factors like: thyroid response element (TRE), PPAR response element (PPRE), retinoic acid response element (RARE) and cAMP response element (CRE). All of these factors influence the expression of UCP1 as it was mentioned before that can be summarized: TRE which is activated by triiodothyronine (T3) is a positive regulator of UCP1, the binding of PPRE to PPAR controls UCP1 gene expression related to brown adipose differentiation, RARE triggers UCP1 expression in BAT and CRE seems vital as a mutation in its sites diminishes the UCP1 expression. Recently Zfp516 has been added in the list of transcription factors that binds to UCP1 promoter leading to UCP1 expression (Vargas-Castillo et al. 2017).

2.4 Hypertrophy and Hyperplasia

Extensive adipose tissue growth, which can potentially lead to obesity, generally has two mechanisms: hyperplasia or increasing in fat cell number and hypertrophy or enhancement of fat cell size. In the development of obesity, hyperplasia occurs only in the first stages and it is triggered by hypertrophy. Hypertrophy is used for storing additional fat in the progression and is prior to hyperplasia. A study on C57BL/6 mice fed a high-fat diet explained that hypertrophy is the major cause of increased VAT while hyperplasia due to the presence of higher number of adipose progenitor cells in SAT mostly occurs in this type of adipose tissue (Joe et al. 2009). In an animal study on mice, it was suggested that hyperplasia does not contribute to fat mass increase because it occurs in small cells that have small volume of stored fat, whereas hypertrophy is the main contributor to the increase of fat mass. Studies on genetic and diet effects on these mechanisms in mice has revealed that increase in number of fat cells is affected by genes while enlargement of fat cells is a diet variable (Jo et al. 2009). In regard to the role of obesity in the development of non-insulin-dependent diabetes and relatively, glucose intolerance and insulin resistance, the size of adipocytes might be important as it is positively correlated with glucose intolerance and hyperinsulinemia (Ferrannini and Camastra 1998). Moreover, as the adipocytes get larger, they become more susceptible to inflammation and cell death (Pellegrinelli et al. 2016).

3 Adipose Tissue-Derived Stem Cells and Adipogenesis

3.1 Mesenchymal Stem Cells (MSCs)

MSCs are spindle shape, multipotent cells with self-renewal capacity that can expand thousand folds and differentiate into different cell lineages including adipocyte, osteocyte and chondrocyte (Bianco 2014; Short et al. 2003). MSCs can be isolated from different tissues like bone marrow

(Penforinis and Pochampally 2011), adipose tissue (Gimble and Guilak 2003), umbilical cord (Han et al. 2013), Wharton's jelly (Chatzistamatiou et al. 2014), placenta (Vellasamy et al. 2012), dental pulp (Alkhalil et al. 2015) etc. Regarding to the multipotent capacity, MSCs seem to be substituted injured cells, although more findings are need to confirm this claim (Baksh et al. 2004). Moreover, MSCs secrete various type of growth factors and cytokines that execute significant role in repair, regeneration and immunogenic balance (Caplan and Dennis 2006). Low immunogenicity, as the main characteristic of MSCs, allow the allogenic use of cell products that is very important in cell-based therapies and regenerative medicine (Aggarwal and Pittenger 2005). ASCs are more considerable source in regenerative medicine research and clinical trials.

One of the most significant concern in cell therapy is providing cells from less or non-invasive sources. ASCs can be isolated in large numbers from abandon and waste adipose tissue that obtained by liposuction as less invasive method (Yarak and Okamoto 2010). On the other hand, the superior potential of ASCs is determined in basic and clinical researches (Aghayan et al. 2015).

3.2 Potential Pathways

Adipogenesis is a multi-step process involving expression of some transcription factors resulted in differentiation of fibroblast-like preadipocytes into mature adipocytes (Ali et al. 2013). According to literature, adipogenesis includes two main phases: 1) the determination phase underlying commitment of MSCs into preadipocyte and 2) the terminal differentiation phase that leads to mature adipocyte (Matsushita and Dzau 2017).

The role of MSCs in adipogenesis is complicated and requires cross talking between major signaling pathways. Several different pathways are studied that involved in different phases of adipogenesis. Here, we described some important signaling pathways that present positive or

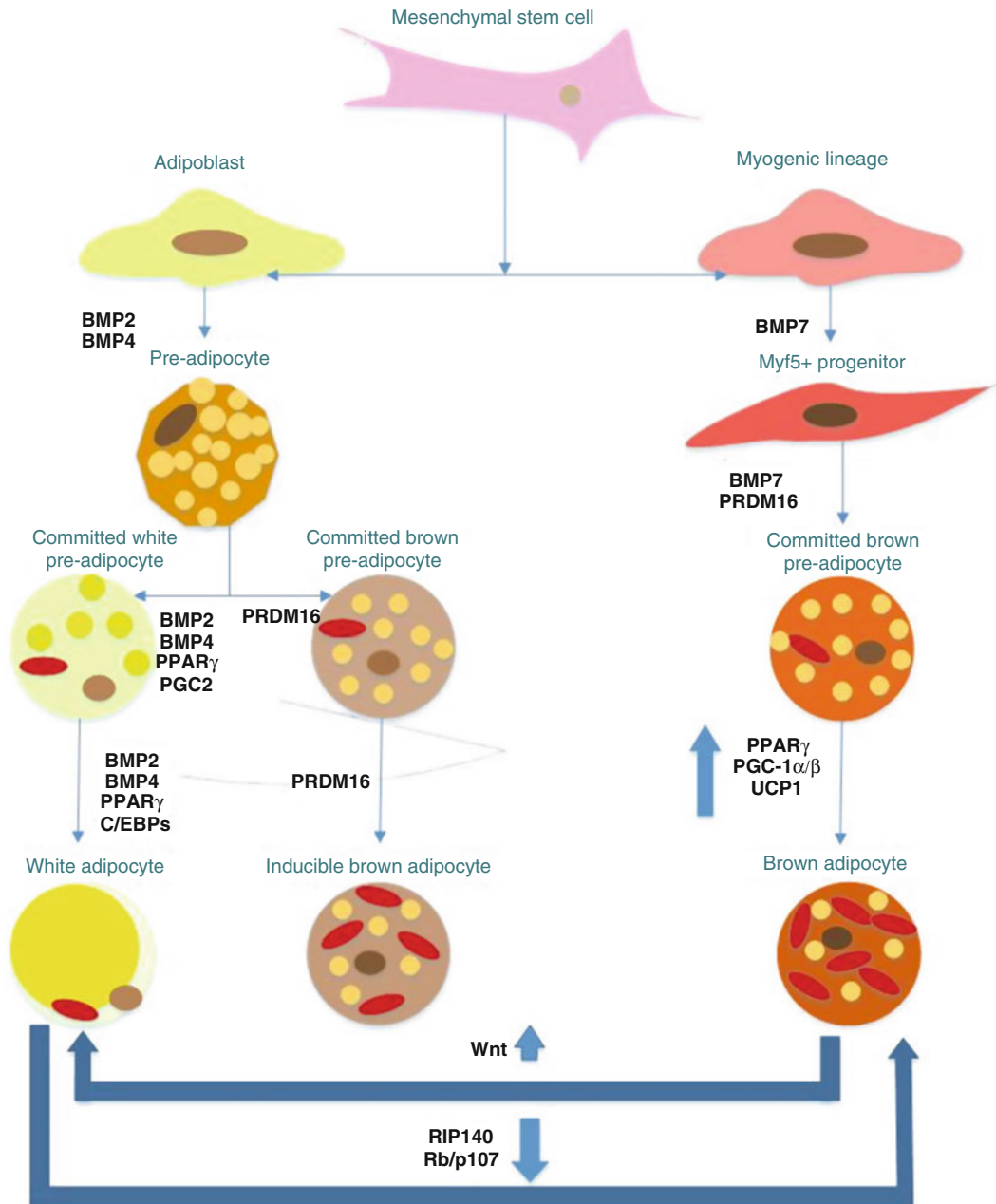


Fig. 2 An Overview of potential mechanisms/pathways underlying MSC white, beige and brown adipogenesis.

Brown adipocyte is known to be arisen from myogenic lineage which is a different origin to white and beige adipocyte lineage (Chen and Tong 2013). In the developmental pathway leading to the differentiations of white and beige adipocyte, BMP-2 and BMP-4 direct adipoblasts or white adipocyte progenitor cells to pre-adipocyte. Then, in the presence of some factors including PPAR- γ , C/EBPs and PGC-2, pre adipocyte forms committed white pre-adipocyte and then white adipocyte. Whereas, PRDM16 activates brown adipogenesis and differentiation of pre-adipocyte to committed brown pre-adipocyte. It can also promote inducible brown adipocyte or beige adipocyte. On the other hand, BMP-7 drives the brown-fat cell fate and it induces PRDM16, which represses skeletal muscle differentiation. Hence, Myf5⁺ progenitors are driven to committed brown adipocytes. PRDM16 acts as a key regulator and co-activates PPAR- γ , which results in subsequent induction of PGC-1 α , PGC-1 β and UCP1 that lead to brown adipocyte (Fruhbeck et al. 2009;

negative regulatory effect on adipogenic differentiation (Fig. 3).

3.2.1 Classic Pathways and Adipogenesis

BMPs are the members of Transforming growth factor beta 1 (TGF- β 1) family performing different roles in the adipogenic differentiation of MSCs (Chen et al. 2016). BMP-2 and BMP-4 can persuade commitment of C3H10T1/2 stem cells as mouse MSC model into adipocyte. BMPs affect adipogenesis mediated by canonical Smad and p38 MAPK pathways, which lead to overexpression of lysyl oxidase (LOX) as a target gene of adipocyte lineage commitment (Huang et al. 2009). BMP-7 stimulates adipogenesis in human MSCs while, BMP-2 shows inhibitory effects on differentiation of human MSCs to adipocytes (Gori et al. 1999).

Wnt signaling pathway is very important in cell proliferation and differentiation. Up to date, 19 molecules of Wnt are recognized that trigger one of the canonical and noncanonical Wnt/calcium pathways by binding to Frizeld family receptors. The outcome of Wnt pathway on commitment of MSC to adipogenic lineage is well studied and the inhibitory effect of both pathways is determined. The canonical pathway suppresses expression of PPAR- γ mRNA, whereas the noncanonical pathway stimulates histone methyltransferases that prevent PPAR- γ activation via histone H3 lysine 9 (H3K9) methylation (Yuan et al. 2016).

Wnt 1 and Wnt 10b inhibit the expression of PPAR- γ in 3 T3-L1 preadipocytes, which resulted in retaining undifferentiated state (Liu and Farmer 2004). The existence of Wnt 3a in 3 T3-L1 cell culture medium can suppress the expression of adipogenic genes via prevention of PPAR- γ

induction (Kawai et al. 2007). Similarly, neutralization of Wnt 5a promote determination of human MSC to preadipocytes by inactivation of PPAR- γ (Bilkovski et al. 2010) and reduction in middle stage adipogenesis was observed after treatment of rat ASCs by 50 ng/mL Wnt5a in the anti- β -catenin and MAPK pathway independent manner (Tang et al. 2018).

Consequently, Wnt signaling pathways act as an adipogenesis blocker, hence Wnt antagonist like secreted frizzled-related protein 1 (SFRP1) can induce invitro adipogenesis and invivo accumulation of adipose tissue (Lagathu et al. 2010). Hedgehog (Hh) signaling pathway controls several biological process during embryogenesis, development, organ patterning, cellular proliferation and differentiation. Treatment of C3H10T1/2 cells whit Hh reduces the amount of adipogenic transcription factors, (Spinella-Jaegle et al. 2001) this effect was emerged via induction of an adipogenic factors like Gata 2 upstream of Hh (Suh et al. 2006). In the case of human ASCs, Hh pathway does not alter the entire number of adipocytes, while adipogenesis has been impaired, with declined lipid accumulation, a reduction in adipocyte specific markers, and appearance of an insulin-resistant phenotype. It seems that Hh signaling affects the late events of human MSC adipogenesis nor the commitment stage. In spite of evidences related to inhibitory effects of Hh on adipogenic differentiation, elimination of this pathway is essential but not adequate to promote adipogenesis in both human and mouse MSCs (Fontaine et al. 2008).

Notch signaling is a highly conserved pathway that regulates cell proliferation, differentiation, cell death and cell fate determination in several cell types. After binding to ligand, two proteolytic cleavages has been occurred and the emerged

Fig. 2 (continued) Yao et al. 2011). Brown adipocyte may change its phenotype into white by up regulation of Wnt which suppresses the characters of brown adipocyte . In the same way, white adipocyte may transform into brown adipocyte by changing the expression of RIP140, Rb, and p107 (Yao et al. 2011). Receptor interacting ptein140 (RIP140)is suggested to repress UCP1 enhancer in brown adipocytes (Rosell et al. 2011). Pocket proteins like retinoblastoma protein (pRb) and Retinoblastoma-like 1(p107) have been shown to alter the adipocyte differentiation and evoke white fat phenotype. Therefore, down regulation of these genes may result in trans-differentiation of white adipocytes to brown adipocytes (Yao et al. 2011)

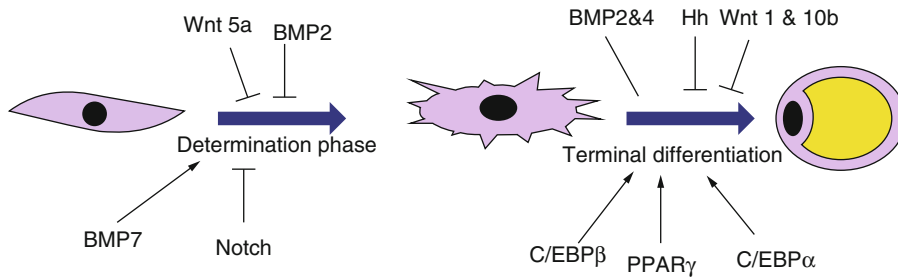


Fig. 3 An overview of positive and negative regulators of MSCs adipogenesis. Adipogenesis pathway can be divided into two main phases: determination phase that characterized by differentiation of MSCs into preadipocytes and terminal differentiation phase that resulted in developing adipocyte phenotype. Several factors are involved in these two different phases of adipogenic differentiation. Among these, Wnt signaling

pathway has been showed negative role in both phases of MSC adipogenic development. On the other hand, PPAR- γ and C/EBP α are two main adipogenic transcription factors that stimulate second phase of adipocyte differentiation. More researches are required to reveal all aspects of MSCs differentiation to adipocytes and knowledge of signaling pathway network improve our comprehension to find new strategies for treatment of obesity

notch intracellular domain (NICD) moves into nucleus to stimulate transcription of target genes (Kopan and Ilagan 2009). The expression of notch gene decreased during adipogenic differentiation of human MSCs and inhibition of notch signaling by γ -Secretase inhibitors enhanced MSCs adipogenesis mediated by autophagy activation involving PTEN-PI3K/Akt/mTOR pathway (Song et al. 2015). However, the role of Notch signaling in adipose progenitor cells proliferation is conversational since the inhibition of Notch leads to decrease in human MSC expansion but increase in mouse 3 T3-L1 preadipocyte cell counting (Shan et al. 2017).

3.2.2 Adipogenesis and Master Transcription Factors

PPAR- γ and C/EBP α are two key transcription factors that regulate adipogenic differentiation. PPAR- γ is a nuclear hormone receptors with two distinct isoforms, PPAR γ 1 and PPAR γ 2, are detected. Overexpression of PPAR- γ in fibroblast cell line by retroviral vectors caused to appearance of preadipocyte features. The mentioned ability indicates the role of PPAR γ 2 in early phase of adipogenesis and adipocyte determination (Tontonoz et al. 1994). Accordingly, embryonic stem cells are successfully generated by homologous recombination and showed that the null clones cannot undergo adipogenic differentiation. Moreover, creation chimeric mice of

PPAR- γ null ES cells demonstrate no distribution of null cells in adipose tissue that prove the *in vivo* role of PPAR- γ in adipogenesis and fat formation (Rosen et al. 1999).

C/EBPs are basic region-leucine zipper proteins comprised of six isoforms: C/EBP α , C/EBP β , C/EBP γ , C/EBP δ , C/EBP ϵ and C/EBP ζ . C/EBP α and C/EBP β are highly expressed transcription factors in liver, lung and adipose tissue (Nerlov 2007). C/EBP β plays an essential role in adipocyte differentiation of 3 T3-L1 cells via inducing the expression of C/EBP α and PPAR- γ genes (Guo et al. 2015).

C/EBP α is vital for adipogenic differentiation, since the expression of C/EBP α antisense RNA in 3 T3-L1 cells interrupts regular differentiation and gene knock out of C/EBP α in mice cause to failure in normal development of adipose tissue (Lin and Lane 1994).

More evidences shows that PPAR γ can induce adipogenesis in the C/EBP α null cells but the ability of C/EBP α to trigger similar condition in the absence of PPAR γ was not proven (Rosen et al. 2002).

3.2.3 Hyperplasia Involved Signaling Pathways

Adipocyte number increasing (hyperplasia) is related to signaling pathways that involved in cell proliferation. Adipogenic differentiation is arrested and cell growth triggered while

hyperplasia occurring in adipose tissue (White and Tchoukalova 2014). *In vivo* studies via *Tc1*^{-/-} mice showed that hyperplasia is regulated in stem cell levels and ASCs revealed more proliferative capacity and adipogenesis activity (Jang et al. 2016).

Abdesselem et al. suggested that reduction of sirtuin 1 expression in preadipocytes followed by hyperacetylation of c-Myc leads to uncontrolled fat hyperplasia so, Sirt1/c-Myc signaling pathway might be more studied as a potential therapeutic pathway for obesity (Abdesselem et al. 2016). Moreover, Wnt-β catenin may be the master pathway regulating adipose hyperplasia, and the induction of this pathway beside cross-talking with glucocorticoid-related signalings alter the activity of preadipocytes. Such alteration is appeared in disruption of adipocyte differentiation and increasing cell proliferation (Wong et al. 2016). Furthermore, activation of the protein kinase C which stimulated by endothelin-1 can improve *invitro* preadipocyte expansion and *invivo* hyperplasia. On the other hand, Extracellular receptor kinase(ERK)-dependent pathway inhibits the hypertrophy in 3 T3-L1 adipocytes after endothelin-1 treatment (Lien et al. 2016).

The study of transcription factors and signaling pathways involved in adipogenesis can introduce negative or positive regulators in adipogenic differentiation. Such knowledge might paved the path to plan a new approach in controlling obesity.

4 Therapeutic Use of Adipose Tissue-Derived Stem Cells (Adscs) in Obesity

4.1 Experimental Background

Obesity, which is the excess accumulation of adipose tissue, can be concluded from adipogenic differentiation of MSCs. Therefore, this pandemic disease can be managed by inhibiting this process. In this regard, different factors were investigated to promote an alternative therapy of obesity such as IGF-1, glucorticoids and prostaglandins which have stimulatory effects

on adipogenesis and androgens like testosterone and dihydrotestosterone, growth hormone and inflammatory cytokines as adipogenesis inhibitors (Ali et al. 2013; Matsushita and Dzau 2017; Zerradi et al. 2014).

4.1.1 *Invitro* Experiments

Due to the importance of BAT and thermogenesis, several studies have focused on the BAT and induction of preadipocytes to brown adipocytes. Generally, two main approaches could be used to increase BAT mass and activity: 1) *invivo* infusion of small molecules and growth factors to spark BAT growth, 2) *exvivo* cell based approach in which progenitor cells are differentiated into brown adipocytes more and then the brown adipocytes will be implanted in patients (Cypess and Kahn 2010). According to several studies, some genes especially BMP7, persuade preadipocytes differentiation to form BAT. BMP-7 treatment in the brown adipocyte cell line arouses the expression of genes including PGC-1α and PGC-1β which are involved in mitochondrial biogenesis and function. Also, treating multipotent C3H10T1/2 cells with BMP-7 shows an increased expression of UCP-1, C/EBPα, β and δ, PPAR-γ and adipocyte protein 2(aP2) (Tseng et al. 2008). In a similar way, when PRDM16 is expressed in white fat cell progenitors, it provokes PGC-1α, UCP-1, and type2 deiodinase expression, then, the brown fat phenotype is activated (Seale et al. 2007).

Interestingly, umbilical cord blood-MSc (CB-MSc) has indicated a low potential for adipogenic differentiation, while the adipose tissue and bone marrow-MSCs are able to develop adipogenic phenotype. Gene expression analysis verified a higher average expression of preadipocyte factor 1 (PREF1), which has been demonstrated to inhibit adipocyte formation, in CB-MSc compared to the other MSc sources. On the other hand, PPARγ, perilipin (PLIN), adiponectin (ADIPOQ) and C/EBPA were upregulated in adipose tissue-and BM-MSCs, resulted in adipogenic differentiation. However, the mRNA levels of these genes were remained unchanged in CB-MSc. Although, treating ASCs with umbilical cord blood plasma (CB-plasma)

caused adipogenesis inhibition due to high concentration of Pref-1, but siRNA knock down of PREF1 did not induce adipogenesis. Indeed, endogenous PREF1 expression has not an essential function in impaired adipogenesis in CB-MSCs whereas, Pref-1 in plasma seems to mediate inhibition of adipogenesis (Karagianni et al. 2013).

Additionally, the adipogenic differentiation of MSCs cultured in the presence of TGF- β and cAMP-enhancing agents revealed that this cytokine reduces expression of adipogenic genes like PPAR γ , a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS5) and aldo-keto reductase family 1 member B10 (AKR1B10). In more detail, MSCs were cultured in adipogenic differentiation medium and it was depicted that TGF- β blocked adipocyte transformation of MSCs in a dose-dependent manner. Despite of the significant effect of TGF- β in adipogenesis, systematic treatment with this cytokine is not a realistic option as it has strong inhibitory effect on the immune system. Also, It may cause skin fibrosis and toxicity which were indicated in animals. Since FDA has approved some drugs for the mentioned genes, they are potential targets for treatment of obesity though further studies are required (van Zoelen et al. 2016).

Recently, MicroRNAs (miRNAs) have also shown the regulatory potential and they are involved in cell fate decision. For example, miR-17-5p and miR-106a target BMP-2 and increase adipogenic CEP α and PPAR- γ to promote adipogenesis of ASCs (Li et al. 2013). In addition, miRNAs can regulate brown adipogenesis as miR-193b-365 and miR-196a regulate brown adipogenesis positively. The miR-193b-365 is called a key regulator of brown fat development since blocking miR-193b and/or miR-365 impaires brown adipogenesis in primary brown preadipocytes. Also, miR-193b is able to induce differentiation of C2C12 myoblasts to brown adipocytes in adipogenic condition (Sun et al. 2011). Likewise, HomeoboxC8 (HOXC8), a white-fat gene that represses the brown adipogenesis, is down regulated by miR-196a in brown adipogenesis of

WAT-Progenitor cells. It has been demonstrated that the transgenic miR-196a mice have a lower blood glucose level in the glucose tolerance test and a lower insulin level than wild type mice. Also, transgenic mice exhibit a resistance to obesity despite the increased food intake compared to wild types (Mori et al. 2012). On the other hand, miR-27 is down regulated during brown differentiation of WAT. MiR-27a and b are decreased in the beige differentiation of SAT preadipocytes. What is more, inhibition of miR-27 increases the expression levels of Ucp1, Prdm16, Pparg, Ppar α , cell death-inducing DFFA-like effector a (Cidea), Pgc1 α and aP2 in SAT precursors and the brown adipogenic markers in VAT precursors (Sun and Trajkovski 2014). Similarly, miR-133 negatively regulates PRDM16, hence inhibition of miR-133 or its transcriptional regulator Myocyte enhancer factor 2 (Mef2) leads to differentiation of precursors of BAT and SAT to mature adipocytes (Trajkovski et al. 2012; Unser et al. 2015).

Adipokines and adipokine receptors which are expressed in several type of cells have the capacity to affect the adipogenic differentiation. Analyzing the expression of chemokine and chemokine receptor genes in 3 T3-L1 and ST2 cell lines revealed that some mRNAs are highly increased during the differentiation. Among these mRNAs, Cxcl3, which has the greatest effect in adipogenesis, is increased in both 3 T3-L1 preadipocyte differentiation and ST2 MSC in the inducing condition of adipogenesis (Kusuyama et al. 2016).

4.1.2 *In-vivo* Experiments

There are several preclinical studies in the field of obesity treatment which used obese mouse models (Fig. 4). Here, we are reviewing some attempts to develop therapeutic way for obesity with more focus on cell-based therapies.

Rieusset et al. reported that decrease in the activity of PPAR- γ by using its antagonists, protects mice from high-fat diet-induced adipocyte hypertrophy and insulin resistance. *In vitro* inhibition of PPAR- γ prevents adipocyte differentiation and *in vivo* inhibition suppresses full development of WAT and BAT (Rieusset et al. 2002). Additionally, PPAR- γ

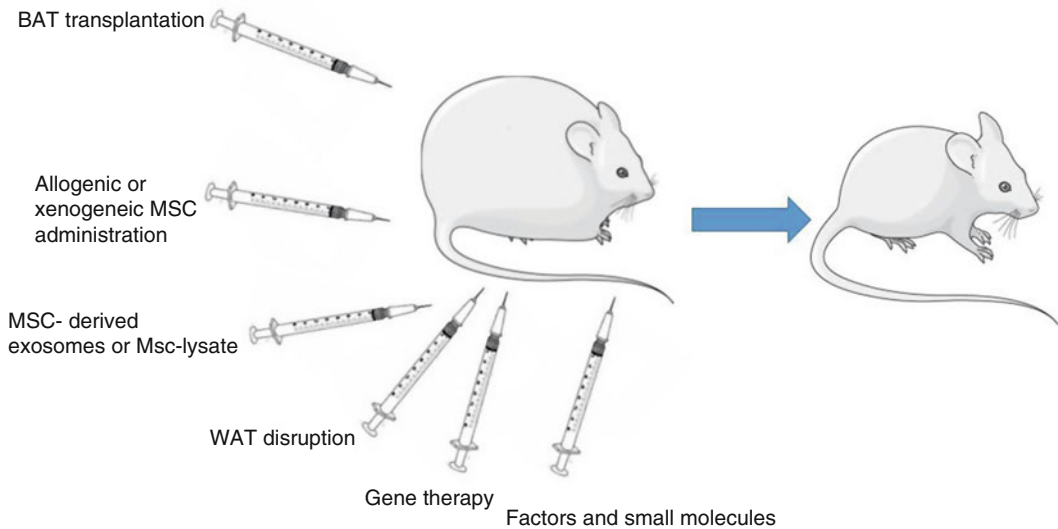


Fig. 4 Several useful methods for obesity treatment in preclinical phase. Different strategies have been investigated to treat feature of obesity in mice model. Administration of cell or derived exosomes, injection of inappropriate factors, transplantation of BAT and disruption of WAT are examples of these strategies. Cell-based

approaches are more considered to develop as the new promising therapeutic strategies in human obesity. Infusion of ASCs or secreted exosomes led to significant improvement of obesity and related syndromes in mouse models

and $C/EBP\alpha$ are up-regulated in ASCs from TC1 deleted mice, whereas the inhibitors of adipogenesis, $Wisp2$ and $Dlk1$ can be down-regulated. This data and the point that $Tc1^{-/-}$ mice has more capacity for adipogenesis than wild types may introduce TC1 as a new regulator of ASCs (Jang et al. 2016). Directing the WAT or preadipocytes to form BAT is also a valuable area of research. For instance, implanting BMP-7 treated C3H10T1/2 cells into athymic nude mice developed a large number of UCP1 positive brown adipocytes and a small portion of white adipocytes (Tseng et al. 2008).

The expansion, metabolism, viability, and regenerative capacities of ASCs is damaged in obese mice and the cell recovery does not happen even after the weight loss (Perez et al. 2016) since ASCs graft seems to be the appropriate therapeutic option for obesity-related disorders.

Cao et al. investigated the anti-obesity influence of allogeneic ASCs in high-fat diet-induced obese (DIO) mouse model. Single dose treatment of ASCs led to the reduction in body weights, decrease of the liver inflammation and level of blood glucose and also triglycerides while, the

levels of HDL and expression of $PPAR-\gamma$ was increased (Cao et al. 2015).

In another study, the anti-obesity effects of ASCs but not umbilical cord-derived MSCs have been proved in both dyslipidemia and obese mouse model. This study showed that administration of ASCs could activate AMPK HSL/ACC1 signaling cascades in adipose tissue. The final outcome of such pathways is determined by lipolysis and WAT browning functions (Liu et al. 2016).

Interestingly, the anti-obesity effects of human ASCs treatment as a xenogeneic source has been studied in obese mouse model. Furthermore, ASCs, ASC-lysate and brown adipocyte differentiated from MSCs (M-BA) are compared to analyze therapeutic their effects. Significantly, M-BA due to 60% expression of $Ucp1$, exhibited the strongest effect on reduction of body weight, triglycerides, cholesterol and increasing the HDL/LDL ratio after injection into high-fat diet (HFD) mice (Lee et al. 2017).

Apart from the agents which were mentioned above, there are other factors affecting adipogenesis including: stem cell microenvironment, surface biochemistry, cell adhesion,

geometric and mechanical characteristics and also co-culture. Cell shape influences adipogenesis, as spheroidal MSCs are more capable for adipogenesis than protruded ones. Dynamic loading like cyclic stretching inhibits adipogenesis while static stretching accelerates adipogenic differentiation. Furthermore, adipogenesis is influenced by neighboring cells and the paracrine interactions between them. As a result, mature adipocytes promote adipogenic differentiation as an example (Unser et al. 2015).

Besides the mentioned approaches, BAT transplantation is another strategy in the cell-based therapy. Two different research groups determined that transplantation of BAT into DIO and HFD mice model enhances glucose tolerance, energy balance, insulin sensitivity and reduces fat mass (Liu et al. 2015; Stanford et al. 2013). Moreover, transplantation of BAT into dorsal subcutaneous region of leptin-deficient Ob/Ob mice as a genetically obese model showed similar effects. Improvement of obesity symptoms like reduction of body weight, upregulation of BAT activity, increasing in insulin sensitivity and thermogenesis was observed. Gaining promising results from preclinical studies could introduce BAT transplantation as a novel option for treatment of obesity and diabetes (Liu et al. 2015).

Beside BAT transplantation strategy, destruction of WAT tissue can be a useful approach in obesity treatment. In this specific case, Anti-angiogenic strategies can be used as a supporting agent since adipogenesis and angiogenesis are very closed and occurred in cell clusters near adipose tissue neovascularisation region (Nishimura et al. 2007). Kolonin et al. designed attractive gene construct by fusion of WAT vasculature receptor and cytotoxic genes. By delivery of such construct to obese mice, WAT tissue is targeted and disrupted and the obesity development reversed via ablation the WAT growth (Kolonin et al. 2004).

Other than all the strategies mentioned above, recently, exosomes have received lots of attention both in basic science and clinic-wise for finding treatment of many diseases. Exosomes are nano vesicles that are secreted from the cells and can act as a key transporter of paracrine factors in angiogenesis, immune regulation and tissue

regeneration (Zhao et al. 2018). Extracellular vesicle produced by adipocytes has been studied and it was found that under hypoxic condition, which can be a result of adipocyte hypertrophy, exosomes were enriched in enzymes and were able to stimulate lipid accumulation in target cells (Sano et al. 2014). Brown and Beige adipocyte exosome production, specifically, is enhanced by cAMP treatment in the mouse (Gao et al. 2017).

The immunomodulatory function of MSC-derived exosome was assessed in a study on C57BL/6 male mice. Exosomes secreted from ASCs of WAT (WAT-derived ASCs) polarized M2 macrophages with highly expressing of Arg-1 (due to transferred Signal transducers and activators of transcription 3 (STAT3) from exosomes) and IL-10 thus reduced the inflammatory ability of macrophages. The macrophages then promoted beiging of WAT, and this is why in obese (HFD-fed) mice treated with ADSC-derived exosomes, WAT inflammation and obesity progression were reduced and metabolic hemostasis was improved (Shang et al. 2015; Zhao et al. 2017).

The angiogenic potential of extracellular vesicles (EVs) was also studied. The data suggested that EVs from ASCs of obese individual have lesser pro angiogenic capacity, indicating that circulating fatty acids in obesity alter the function of ASCs. However, platelet-derived growth factor (PDGF) evokes ADSC EV secretion and enhances angiogenic potential (Lopatina et al. 2014).

5 Future Perspective

The pathway of Adipogenesis is divided into two main phases: the determination phase that is characterized by the differentiation of MSCs into the preadipocytes and the phase of terminal differentiation, which leads to the developing adipocyte phenotype. Several factors in these two different phases are involved in the adipogenic differentiation, such as transcription factors, molecular signals, epigenetics, and etc. Among these, a number of factors play an inhibitory role

and other categories have stimulatory role. The challenge for future studies is the insight into obtaining the key to identifying these factors and their mechanisms in adipogenesis with the potential of providing new therapeutic goals for treatment of obesity and its comorbidities. In-vitro and in-vivo studies currently support stem cells therapies in the treatment of obesity. The results of studies conducted in this review revealed that the use of stem cells (infusion or injection) can significantly suppress obesity and related diseases such as cardiovascular and diabetes and improves dyslipidemia and insulin resistance.

Since autologous stem cells have been used in previous studies, this treatment does not have the risk of rejection and can be ideal for the treatment of obesity.

Also, future research on molecular control of brown or beige adipogenesis may result in new and novel achievements. Intervention studies such as controlling the adipogenicity from MSC to brown adipocyte or from white to brown adipogenesis can be used as a therapeutic strategy for obesity.

The potential effective and safety of stem cell therapy on obesity and its comorbidities must be further studied.

6 Conclusion

In conclusion, stem cell therapy is a therapeutic option for obesity in the future. However, long term studies are required to evaluate the efficacy and safety of stem cells therapy to find new and novel strategies for the treatment of obesity; and further studies in humans are necessary to investigate the results on animal models. This review showed that current studies are promising tools that can answer many questions in this regard.

In the future, one can hope that stem cell therapy can be used in control adipogenesis along with other obesity treatments and promises a new therapeutic approach in clinical applications.

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