Molecular modulators of adipogenesis as treatment options for obesity

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Abstract:

As a risk factor, obesity is a threat to human well-being and related metabolic disorders such as diabetes mellitus and dyslipidemia. adipogenesis is defined as the proliferation and maturation of adipocyte predecessor cells to adipocyte. As the adipogenesis process decides adipocyte production, it may be considered a therapeutic target for obesity and obesity-related disorders. White adipose tissue abnormal expansion increases the size and number of adipocytes. For that reason, this review aims to spot the molecular mechanisms implicated in adipogenesis that lead to application in the therapeutic targets.

Keywords: adipogenesis, signaling pathways, anti-obesity treatment, obesity

Introduction

Globally, about 39 % and 13% of adults are overweight, obese, respectively (1, 2). As obesity has a strong relation with metabolic disorders as diabetes mellitus. It is considered a key factor for human well beings (3). Reactive oxygen species excessive production and malfunction of the antioxidant system lead to an increment in oxidative stress level, which is coupled with obesity (4)

In addition to energy storage, adipose tissue also considered an endocrine organ that produces adipokines, which involved in reactive oxygen species, ant-oxidative ability, and secretion of

 doi:10.20944/preprints202106.0620.v1

pro-inflammatory cytokines. Therefore, obesity stimulates the oxidative stress level via chronic inflammation, mitochondrial oxidation of fatty acids, and over-utilization of O2 metabolism (5).

As a risk of obesity and obesity-related disorders, focusing on bodyweight controlling mechanisms has a key health advantage. The mechanism of obesity is still inadequately documented, and there are very few valuable treatment options for obesity deterrence strategies (6).

In adipocytes, energy is stored in the form of lipids. Unwarranted storage of adipose tissue leads to obesity. As a tissue, adipose tissues are classified as brown and white adipose tissues, which involved in energy balance via lipid homeostasis and thermogenesis regulation during cold stress conditions, respectively. Uncharacteristic extension of white adipose tissue related to obesity involves hypertrophy and hyperplasia in adipocytes. Too much storage of fat by itself does not damage the adipose tissue function. However, if the amount of fat accumulated beyond the adipose tissue storage capability, it may be deposited in other organs like the liver and kidney, which interferes with their functions. As the obesity progression increases, adipose tissue turns out to be more inflamed, deteriorating the white adipose tissue functionality suppleness, which results in metabolic imbalance such as lipidemia (7-10).

Adipogenesis modulators as options of obesity treatment

As a complex process, adipogenesis is the conversion of pre-adipocytes to mature adipocytes. Since about 10 % of body fat cells need restoration per year, adipogenesis is a key physiological process to refurbish adipose tissue's anatomical nature (11).

In the adipogenesis process, the pluripotent cells transformed into unipotent pre-adipocyte, and then pre-adipocytes specialized into mature adipocytes. As it is known in an embryological description, the pluripotent cells are the origin for all cells through Signaling molecules the

 doi:10.20944/preprints202106.0620.v1

pluripotent cell related to preadipocytes undergo anatomical and physiological changes so as to prevent differentiation to other cell types (12).

To conduct research on adipose tissue anatomy, the 3T3-L1 cell lines used as a model, which indicate the conversion of pre-adipocytes into mature fat cells. Through the activation of the pre-adipogenic factor, the 3T3-L1 cell lines undergo a structural change and revealed a gene expression profile in white adipose tissue (13).

In in vitro research work, the adipogenesis process passes in four phases of growth seize, mitotic clonal expansion, early differentiation, and late differentiation (14).

Following the growth arrest of 3T3-L1 pre-adipocytes, the pre-adipocytes specialization is tempted via hormones insulin, which promotes cells to engage in glucose utilization and store as fat, and dexamethasone, which encourage genes that have roles in the activation of transcription factors in adipogenesis (15-17).

Mitotic clonal expansion is an essential precondition for pre-adipocyte differentiation. Throughout Mitotic clonal expansion, cells are inhibited from engaging into the S- phase of cell division. Therefore, the pre-adipocytes differentiation would be interrupted via the regression of transcription factors expression and regulators of adipogenesis (18)

To unwind the double-stranded DNA, via cell mitosis, the transcription factors can easily access the genes concerned in the differentiation process. Thus, sustaining cells at a certain checking point of cell division phases might be considered as a successful option to prevent adipogenesis progression (19).

In the early preadipocytes differentiation, the preadipocytes have circular in shape, while in the terminal preadipocytes differentiation rather than round in shape; there are also maturities in function as metabolic activation for protein section, lipid synthesis, adipocytes functional modifications (Figure 1)(20).

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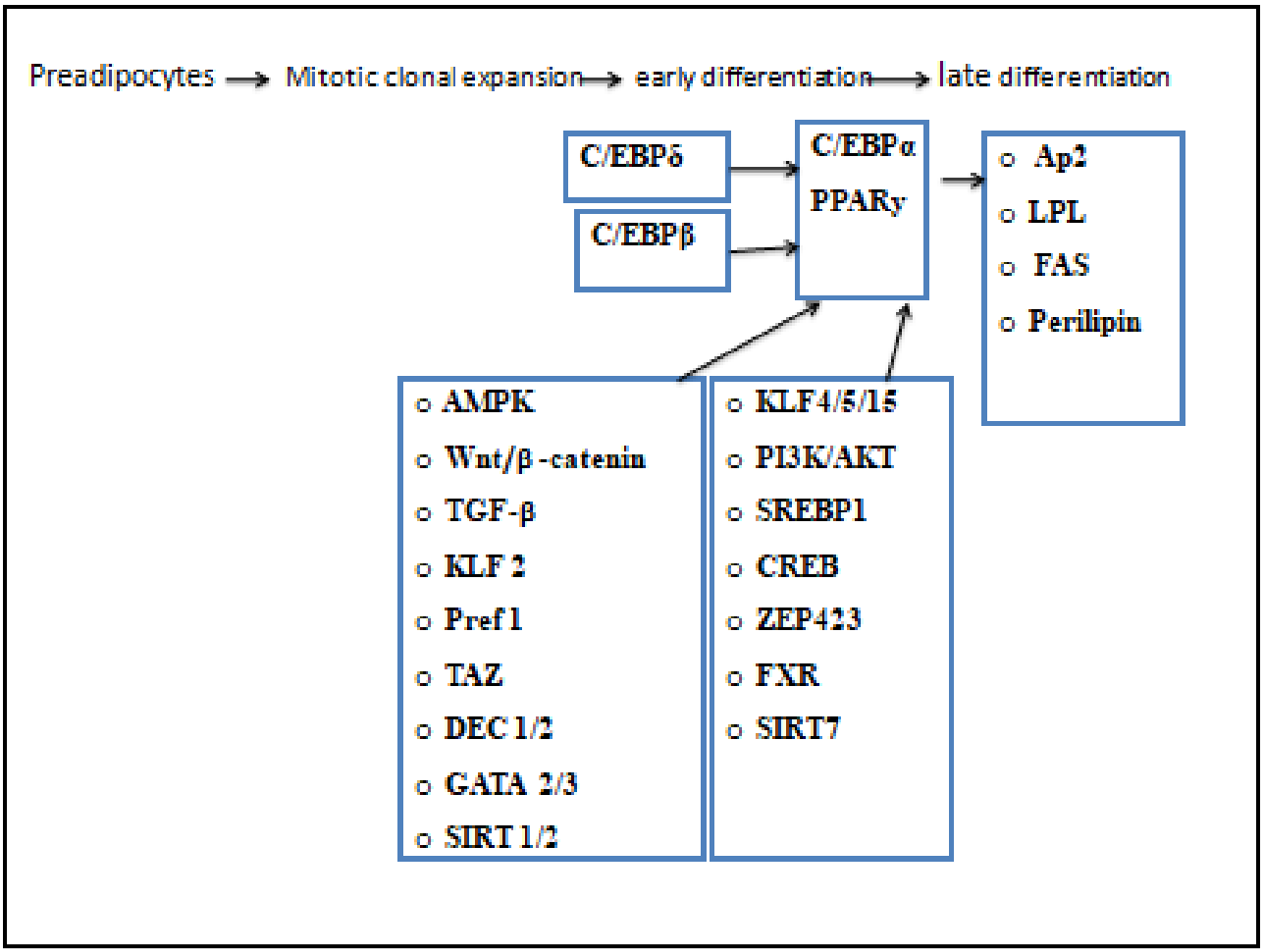

Figure 1 various steps of molecular modulators of activation for adipogenesis that showed therapeutic options for obesity

To sum up, in different stages the adipogenesis is stringently controlled through the transcriptional factors cascade like a transient high expression of CCAAT/enhancer-binding proteins, C/EBPδ, C/EBPβ, C/EBPα. Therefore, these factors considerately encourage the differentiation and stimulation of many adipocyte-specific genes, together with lipoprotein lipase, adipocyte protein 2, fatty acid synthase, and perilipin in the final stage of differentiation (21).

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Transcription Factors in Adipogenesis

Transcription factors are vital to modulate the adipogenesis process. Of these, CCAAT/Enhancer-Binding Proteins C/EBPβ, and C/EBPδ are the primary transcription factors induced immediately after prompt in adipogenic combination. The presence of transcription factor, C/EBPβ, in the nucleus makes easy of DNA-binding and leads to transcriptional process activation of PPAR and C/ EBPα (22). However, the C/EBPβ level decreased nucleus, and then DNA –binding interrupts and leads to interference of gene expression in C/EBPα and PPAR (23).

Therefore, the eccentricity of the transcription factor, C/EBPβ, possibly will be a key prospective target for obesity therapeutic options, as its early transcription factors handling prevent the next cascade, and the repress final adipocytes specialization. Moreover, there are also C/EBP subsets, as a homologous protein that Integration with C/ EBPα and C/EBPβ, it forms a heterodimer, which not involves in bind DNA. So it prevents gene expression in the adipogenesis process (24)

Peroxisome Proliferators-Activated Receptor γ

As a gene expression control factor, PPARγ modulates adipogenesis, lipid metabolism, and inflammation processes. And also, its isoform, PPARγ2, is plentifully activated in the adipose tissue, and it is vital for the adipogenesis process (25). Therefore, PPARγ is a target for obesity therapeutic options.

As a Heterodimer, the PPARγ attaches to an explicit DNA sequence with the retinoid X receptor and controls the intention transcription of genes (26).

Studies illustrated that insulin and corticosteroid provokes the activation of PPARγ mRNA whereas TNFα suppresses the activation of PPARγ (27, 28)

Cell Signaling mechanisms in adipogenesis

In adipogenesis physiological processes, there are many cell signaling transduction mechanisms includes bone morphogenic protein signaling, Hedgehog signaling, AMP-activated protein

 doi:10.20944/preprints202106.0620.v1

kinase pathways, Wnt signaling pathways, the insulin, and protein kinase B, and mitogen-activated protein kinase pathways.

PI3K/AKT and MAPK/ERK Signaling Pathways

During the early phases of pre-adipocytes differentiation, the hormonal stimulation cocktail triggers PI3K/AKT and MAPK/ERK signaling transduction pathways. Within a cytoplasm of the cell, the MAPK pathway system is imperative for modulating cell proliferation and specialization while ERK expression is vital for the stimulation of mitotic clonal expansion and adipogenesis(29). In 3T3-L1 cell lines of preadipocytes, the suppression of the PI3K/AKT pathway system prevents adipogenesis (30)

Conversely, a range of researches revealed that the PPAR is phosphorylated via MAPK pathways and decreases its transcriptional commotion and that activation of MAPK upset 3T3-L1 adipocytic differentiation (31).

Therefore, comprehensible clarification of MAPK/ERK signaling pathway sound effects on adipogenesis possibly will supply therapeutic targets obesity.

Wnt/β-Catenin Signaling Pathways

Wnt signaling pathways prevents the expression of PPARγ and C/EBPα that reserves the adipocytes precursor cells, preadipocytes, in an undifferentiated stage rather than to being mature adipocytes. As a physiological mechanism, Wnt signaling deregulation division, and interrupting PPARγ and C/EBPα expression, inhibits adipogenesis. Therefore, disruption of Wnt signaling leads to the adipogenesis process (32).

The phosphorylated glycogen synthase kinase deteriorates the β-catenin that represses the Wnt signaling. However, the Wnt signaling endorses β-catenin constancy location, grounds the interruption of C/EBPα and PPARγ. Hence, the β-catenin stability via wnt signaling is a key target for adipogenesis prevention (33)

AMP-Activated Protein Kinase Signaling Pathway

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When the cellular ATP concentration level is minimal, through the phosphorylation process there is the activation of AMPK, enhances fatty acid oxidation, and prevents fatty acid synthesis (10). As AMPK prevention of energy-consuming process as of adipogenesis, it can be used as one of the options for obesity therapeutic target site(34). Furthermore, an adipogenic inhibition effect of AMPK is arbitrated by repressing the PPARγ through modulation of p38 MAPK, which enhances PPAR phosphorylation and holds back the transcriptional role (35).

Bone Morphogenic Protein Signaling Pathway

As superfamily members of TGF-B factors, BMPs exhibit wide-ranging impacts on adipogenesis mechanisms. Hence, Generally, TGF-β interrupts the premature adipocytes specialization via networking with C/EBP and suppresses transcriptional motion (36)

The bone morphogenic protein subfamily phosphorylates R-Smads, which binds to Smad 4, promotes the transcriptional role of the Smad protein in the nucleus. BMPs can also activate the p38MAPK signaling cascade, which regulates mitochondrial biogenesis and glucose utilization (44). Moreover, BMP-2 activated to unregulated PPARγ (37).

Hedgehog Signaling Pathway

The activation of the Hh signaling path impairs adipogenesis and lipid storage. The adipocyte differentiation is downregulated. Hh protein inhibits adipogenesis by reducing the expression of C/EBPα, PPARγ, and aP2, whereas inhibition of Hh signaling using increases adipogenic differentiation in 3T3-L1 (38).

Other Regulators of Adipogenesis

Positive and negative Regulators of Adipogenesis

As revealed in table 1 and 2, there are many factors are identified as positive and negative regulators of adipogenesis.

Table 1: positive molecular regulator of adipogenesis

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Regulators	Mechanism of action
KLF5,KLF9,and KLF15	• induced by C/EBPδ/β during the early stages of adipogenesis • binds directly to the PPARγ2 promoter, and cooperates with C/EBPs(22,31,39-41)
SREBP1	• Regulates the expression of FAS and LPL and increases the activity of PPARγ. • Promotes adipogenesis(42)
CREB	• lipid accumulation and the expression of PPARγ and fatty acid-binding protein (FABP).(43)
ZFP423,	• blocks PPARγ expression and adipogenic differentiation • promote adipogenesis of non adipogenic NIH -3T3 cell lines • its inhibition in 3T3-L1 cells blocks PPARγ expression and adipogenic differentiation.(44,45)
FXR	• nuclear hormone receptor that inducing PPARγ2 and C/EBPα expression • promotes adipocyte differentiation(46)

Abbreviations: KLF: Kruppel-Like Factor Family, **SREBP1**: Sterol Regulatory Element-Binding Protein 1, **CREB**: Cyclic AMP Response Element-Binding Protein, **ZFP423**: Zinc Finger Protein 423, **FXR**: Farnesoid X Receptor, **LPL:** lipoprotein lipase, **AP2**: adipocyte protein 2, **FAS**: fatty acid synthase, **PPARγ** Peroxisome Proliferators-Activated Receptor γ

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Table 2 negative molecular regulation of adipogenesis

regulators	Mechanism of actions
KLF2	• inhibition of PPARγ, C/ EBPα, and SREBP1 expression • represses adipogenesis(47)
Pref 1	• Preventing lipid accumulation and expression of PPARγ, C/EBPα FAS, and aP2. • inhibits adipocyte differentiation(48)
TAZ	• PPARγ activity repression • suppresses adipocyte differentiation • adipogenic differentiation(49)
DEC 1 &2	• inhibit the transcriptional activity of C/ EBPβ/α • abundantly expressed in pre-adipocytes (50)
GATA 2 and 3	• suppression of PPARγ expression through PPARγ promoter or the formation of protein complexes with C/EBPα and C/EBPβ • contribute to adipocyte differentiation • inhibits adipogenesis by trapping cells in the pre-adipocyte stage(51,52)
SIRT1&2	• inhibits adipogenesis and keeps cells at the pre-adipocyte stage • an inhibitory effect on adipogenesis by FOXO1 deactivation and subsequent PPARγ transcriptional activity repression(53,54)
SIRT7	• PPAR expression and proper adipocyte differentiation.(55)

Abbreviations: SIRT: Histone deacetylase Sirtuin: **DEC**: differentiated embryo chondrocyte: **TAZ**: transcriptional-coactivator with PDZ-binding motif, **Pref 1:** pre-adipocytes factor

In recent times, scholars have been offered an attention to obesity and obesity associated researches as effective genes expression profiles in adipogenesis. The Micro-RNAs, a small single non- coded RNA molecules such as miR-21, miR-29b, miR-144-3p, miR148a, miR-210, and miR-205-5p augment the adipogenesis via meddlesome with the activation of anti-adipogenic signaling pathways like transforming growth factor-β, Tumor necrosis factor -α, and Wnt signaling pathways .In contrast, through the transcriptional factors of C/EBPs and PPARγ

mechanisms the miRNAs like miR-27a and b, miR-31, miR-128-3p, miR-130a and b; miR- 146a-5p, miR-155, and miR-540 restrain the adipocyte differentiation (11). Furthermore, the miRNAs such as, miR- 103 and miR-107 can control the size of the pre-adipocyte cells in white adipose tissue, unswervingly repressing the activation of Wnt3a, hence enhancing the programmed cell death in pre-adipocytes (56). Therefore, to evaluate the therapeutic approach obesity, the MiRNAs possibly will be used as clinical biomarkers.

Conclusion

Now days, adipogenesis is a vital process that consists of various transcription factors, signaling molecules for the development of obesity and obesity-associated metabolic diseases. Therefore, targeting on these different molecules and signaling pathways would be considered as an important option for obesity therapy.

Ethical considerations: None applicable

Acknowledgment: As it is a review article, all potential contributors of published research papers were accredited.

Funding For this review: No funding sources

Conflict of interests: None

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