



Review

Insights into the role of endostatin in obesity

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ABSTRACT

Objective: The role of endostatin has come out as an emerging remedy in control and treatment of numerous metabolic disorders. This review highlights the intricate role in obesity and its associated complications.

Key findings: Through recent studies and reports the role of various epigenetic markers in the treatment of obesity has been revealed. Neovascularization and adipogenesis produce various angiogenic factors including leptin, angiopoietins, VEGF (Vascular endothelial growth factor) and TGF- β (Transforming growth factor beta) during expansion of adipose tissue via paracrine signaling pathway, therefore angiogenesis has been recognized as a major therapeutic target of obesity. It has been stated that endostatin has been identified as a potent inhibitor of adipogenesis and dietary-induced obesity. However, the mechanism of endostatin is still unclear but its act on Sam68 RNA in preadipocytes by binding to it and this in turn prevents the interaction of Sam68 to intron 5 in mTOR resulting in decreases the expression of mTOR. Moreover, it has been demonstrated that the antiangiogenic property of endostatin prevents obesity and its related metabolic disorders, including insulin resistance, glucose intolerance, and hepatic steatosis and inhibit the combined functions on angiogenesis and adipogenesis.

Summary: The present review focus on the intrinsic role of endostatin as an emerging remedy in the treatment of obesity and its related complications demonstrating their use in the inhibition of angiogenesis event, adipogenesis and provide protection against the release of angiogenic factors.

1. Introduction

Approximately 60% of adults in United States and half of the population in rest of the world are obese (Korner and Aronne, 2013). Periodic evidence has revealed that about 15% of children in developed countries are obese and this phenomenon is expected to increase significantly. Obesity is recognized as a major risk factor for the development of various disease such as stroke, hypertension, cancer, gall-bladder disease, dyslipidemia, type2 diabetes mellitus and metabolic syndrome (Friedman, 2000; Kopelman, 2000; Roth et al., 2004). All of these obesity related disease are responsible for vascular dysfunctions. For example, during hypo vascularization and hyper vascularization there is development of diabetes, cancer. Although certain amount of fat is required for survival such as during starvation In time excessive intake of food leads excessive deposition of fat in adipose tissue causes overexpression of white adipose tissue which in turns lead to enlargement of adipocytes through adipogenesis, resulting in obesity (Spiegelman and Flier, 2001; Ravussin and Bogardus, 1989; Seeley and Woods, 2003). The excessive storage leads to secretion of free fatty

acids that regulate oxidative stress in the endothelium and mitochondria. This also affects adipose as well as non-adipose tissue accounting for its vital role in liver and pancreas (Evans et al., 2004; Hutley and Prins, 2005). The excessive secretion of free fatty acids prevent clearance of serum from body by inhibiting lipogenesis causes lipotoxicity results in insulin receptor dysfunction and it also decreases the secretion of insulin from pancreatic β cells (Pan et al., 1997; Boden et al., 1994).

Adipose is the endocrine organ composed of capillary network and it regulates the production of hormones free fatty acids, growth factors such as leptin, adiponectin, VEGF, IL-6, TNF- α , and angiopoietins (Bouloumié et al., 2002; Crandall et al., 1997a; Silverman et al., 1988a). Proliferation of adipocyte is regulated by various transcriptional factors, such as peroxisome proliferator-activated receptor- γ (PPAR- γ) and CCAAT/enhancer-binding proteins (C/EBPs) (Cristancho and Lazar, 2011; Rosen et al., 2000). Both C/EBP- β and PPAR- γ are considered as the proximal regulator of adipogenesis, that maintains the expression of adipocyte-specific genes (Tang and Lane, 2012; Tontonoz and Spiegelman, 2008). In an experiment conducted on mice model revealed that Sam68 (Src-associated substrate in mitosis; 68 kDa) mice contain a

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lean phenotype that inhibit adipogenesis by regulating RNA splicing of mammalian target of rapamycin (mTOR) (Huot et al., 2012). Sam68 is a member of the signal transduction activator of RNA (STAR) family, that regulates splicing of RNA and its metabolism and mRNA recruitment. Sam68 mice induces an error in the RNA splicing of mTOR by retaining intron 5 that results in defects in adipogenesis.

Recent studies revealed that various angiogenesis inhibitors produce an anti-obesity effect by inhibiting angiogenesis in adipose tissue as angiogenesis is responsible for development of obesity and its related metabolic disorder (Daquinag et al., 2011; Rupnick et al., 2002a; Kim et al., 2010). Endostatin is one such agent that has been identified as inhibitor of angiogenesis as it has both anti angiogenic and anti-proliferative properties. Endostatin is a naturally occurring 20-KDa –C terminal fragment obtained by proteolytic cleavage from collagen XVIII and its carboxylic terminal. However the mechanistic role of endostatin in adipogenesis and dietary-induced obesity is still unclear. Endostatin protect dietary induce obese mice and its related complications including insulin resistance, glucose intolerance, by inhibiting angiogenesis and adipogenesis. Various new therapeutic approaches have been made for the treatment of obesity and its related disorders by exerting anti-obesity and anti-adipogenic effects.

2. Pathological role of angiogenesis and adipogenesis in obesity

Angiogenesis is a physiological process in which new blood vessel generate from preexisting vessels by various inflammatory mediator responses and it is accompanied by the process of proliferation (Coronato et al., 2012). The event of neovascularization occurs due to vascular proliferation, activation and relocation of endothelial cell, although it emphasizes on two factors namely proangiogenesis and anti-angiogenesis that maintain the equilibrium throughout the normal physiological process of the body. The proangiogenesis components are required for upregulation of neovascularization events, which is necessary for fetus development and in organ restoration. Additionally, antiangiogenic components downregulate neovascularization by restricting the overgrowth of tissues, cells and blood vessels and also necessary during repression of proangiogenic component, eventually resulting in tumorigenesis. During the regulation of angiogenesis in morbid state overexpression of proangiogenic components cause the differentiation of endothelial cells and release of inflammatory mediators which in turn lead to generation of blood vessels, an event called neovascularization (Qaziet al., 2009).

Adipogenesis is regulated by various transcription factors, such as CCAAT/enhancer-binding proteins (C/EBP) β , C/EBP α , and peroxisome proliferator-activated receptor γ (PPAR γ). Recent study revealed that overnutrition result in the stimulation of (mTOR)/ribosomal S6 kinase (S6K1) (Jia et al., 2014a) that interact with PPAR γ -C/EBP α transcriptional factors that leads to adipogenic proliferation. Additionally, mTOR/S6K1 signaling pathway promotes cellular growth and stress responses by mediating mTOR and mTORC2 signaling pathway. Accumulating evidence proved that mTORC1 and its complexes regulate adipogenesis and lipogenesis and it is regulated by both mTOR/S6K1-dependent and mTOR/S6K1-independent signaling pathway that result in defects in adipogenesis. Furthermore, mTORC2 plays a vital role in adipogenesis by controlling protein kinase B activity in adipogenesis, but this process is dispensable in the regulation of the function of the mature adipocyte (Yoon et al., 2013; Haissaguerre et al., 2014).

3. Functional link between angiogenesis and adipogenesis

Adipose tissue formation is associated with micro vessel growth during embryogenesis (Crandall et al., 1997b). Both adipocytes and endothelial proliferate into adipocytes depending upon exposure to different environments (Planat-Benard et al., 2004). Human adipose tissue-derived stem cells proliferate into endothelial cells and promotes

(Cao et al., 2005). Brown adipose tissue (BAT) has a high thermogenic expenditure but it remains inactive in obesity (Himms-Hagen and Desautels, 1998; Tonello et al., 1998). Neovascularization is necessary for BAT hyperplasia, that depend on activation of mitosis in brown fat cells and endothelial cells to form vessels (Bukowiecki et al., 1980) while white adipose tissue (WAT) can be converted into BAT during chronic exposure to cold. However, transformation of BAT into WAT might result in regression of capillary networks. Data conducted over the years revealed that adipose tissue promote wound healing and revascularize ischemic tissues (Beck, 1935). In a study conducted on chick and mouse shown that media obtained from preadipocytes and tissue homogenates promotes angiogenesis in the chick chorioallantoic membrane (CAM) and in the mouse cornea Silverman et al. (1988b); Castellot et al., 1982; Goldsmith et al., 1984).

4. Endothelial and adipocytes

It has been stated that endothelial cells communicate with adipocytes through paracrine signaling pathways and cell-cell interactions (Hutley et al., 2001). During the development of embryos, the fat organs are formed at the perivascular site. Furthermore preadipocytes are differentiate by PPAR- γ , that help in regulation of angiogenesis in adipocytes. However, overexpression of PPAR- γ leads to impaired development of angiogenesis and adipocytes. Recent study revealed that VEGF (vascular endothelial growth factor) regulate preadipocytes differentiation, although inactivation of VEGFR-2 signaling system inhibits both angiogenesis and preadipocyte differentiation (Fukumura et al., 2003; Panigrahy et al., 2002; Ren et al., 2002; Rosen et al., 1994).

Accumulating evidence state that adipose tissue produces various MMPs (matrix metalloproteinases) such as MMP-2 and -9 (Bouloumié et al., 2001), that regulate angiogenesis by releasing VEGF (Bergers et al., 2000). Additionally upregulation of MMP-3, -11 and -14 and downregulation of MMP-7 and -24 induces adipogenesis by expanding adipose tissue (Christiaens and Lijnen, 2006). In a study conducted on MMP-3 deficient mice fed high-calorie diet-induced obesity result in increase in density of adipose blood vessel which in turn modulate angiogenesis (Maquoi et al., 2003). However, treatment of high fat diet-fed mice with galardin, inhibit angiogenesis, leads to reduction in obesity (Lijnen et al., 2002).

During expansion of adipose tissue, hypoxia plays a vital role in the formation of capillary network. As hypoxia occurs adipose tissues produce angiogenic factors including VEGF, leptin and TNF- α which stimulate neovascularization (Fitzpatrick and Graham, 1998). Therefore, it has been recognized that expansion of adipose tissue is associated with hypoxia, which result in angiogenesis by stimulation of various growth factors.

5. Adipose tissue derived angiogenic factors

Adipose tissue produces various angiogenic factors such as leptin, VEGF, FGF-2 (Fibroblast growth factor), HGF (Hepatocyte growth factor), IGF (Insulin like growth factor), TNF- α (Tumor necrosis factor-alpha), TGF- β (Transforming growth factor beta), placental growth factor (PlGF), resistin, tissue factor (TF), neuropeptide Y (NPY). Additionally, adipocytes produce non-protein lipid molecules such as monobutyrin that regulates angiogenesis in the adipose tissue. Inflammatory mediators such as macrophages produce TNF- α , VEGF, FGF-2, IL-1b, IL-6, and IL-8 that result in angiogenesis (Wellen and Hotamisligil, 2003, 2005).

Leptin is an angiogenic factor that stimulates food intake and thermogenesis. However, overexpression of leptin result in obesity, diabetes, and infertility. It has been stated that binding of leptin with its OB-Rb receptor stimulates Stat3 pathway and corneal neovascularization in vivo (Sierra-Honigmann et al., 1998). Although leptin activate MMP-2 and MMP-9 that induces angiogenesis and regulate JAK pathway that upregulates expression of VEGF (Suganami et al., 2005;

Park et al., 2001). Interestingly, vascular activity is regulated by FGF-2– and VEGF to promote neovascularization but inhibition of FGF-2 result in functional impairment in angiogenesis (Cao et al., 2001). Leptin increases vasodilation in adipocytes by regulating eNOS activity and maintain blood flow rate (Winters et al., 2000). Additionally, leptin induces vascular formation in other tissues including placenta, mammary glands, and skeletal muscles (Henson and Castracane, 2000; Matsui et al., 2007).

VEGF plays a vital role in the growth of tissues and adipocytes is the major contributor for the production of VEGF. Recent study conducted on mice has shown that subcutaneous fat has increased level of VEGF (Zhang et al., 1997) and inactivation of VEGF leads to inadequate adipose tissue development. Although resistin, initiates proliferation of endothelial cells. IGF-1 maintain integrity of capillary network in adipocytes (Hanet al, 2003). In obese mice, both angiogenic factor TGF- β and TF are increased in adipocytes and stimulate neovascularization (Hotamisligilet al, 1993; Lebrin et al., 2005) and other angiogenic factors such as VEGF-B, VEGF-C, have been correlated with BMI (Silha et al., 2005).

6. Adipose tissue derived angiogenesis inhibitors

Adipose tissue produces various angiogenesis inhibitors. Adiponectin is one such endogenous angiogenesis inhibitors is higher in the blood circulation of individual and decrease the progression of diabetes and atherosclerosis (Arita et al., 1999) and have been inversely correlated with BMI which activate (Brakenhielm et al., 2004a) caspase-triggered endothelial cell apoptosis that in turn lead to decrease regulation of adipogenesis (Maeda et al., 2002).

Recent study revealed that expansion of adipose tissue result in regulation of angiogenesis, so to counteract this phenomenon angiogenic inhibitors are required to restrict further vessel growth. Various endogenous angiogenesis inhibitors are endostatin, thrombospondin 1 (TSP-1), and soluble VEGFR-2 are produced at high levels in overweight and obese individuals. Additionally, an elevated level of PlGF has been found in adipocytes and this PlGF inhibit regulation of VEGF-induced angiogenesis (Inuzuka et al., 1999; Seida et al., 2003). Although expansion of subcutaneous adipose tissue produces excessive amount of proteases such as MMPs that break collagen XVIII into endostatin, thus endostatin inhibit the regulation of angiogenesis. Therefore various endogenous angiogenesis inhibitors are upregulated in order to maintain a homeostatic state of the adipose tissue by restrict the growth of vessels and proangiogenic activity.

7. Role of endostatin in inhibition of angiogenesis

Endostatin is a naturally occurring 20-KDa –C terminal fragment obtained by proteolytic cleavage from collagen XVIII and its carboxylic terminal. It has been stated that administration of endostatin decrease expansion of adipose tissue, inhibit regulation of angiogenesis and suppress tumor activity (Mucci et al., 2009) by interfering with the action of angiogenic factors such as vascular endothelial growth factor (VEGF). Endostatin is an endogenous inhibitor of angiogenesis. It interfere with TNF α activation of c-Jun N –terminal Kinase and blocks the pro-angiogenic factors required for angiogenesis (Shichiri and Hirata, 2001; Yin et al., 2002). It inhibit the expansion of endothelial cells through disruption of cell-matrix adhesions and cell-cell adhesions. In vitro studies have shown that endostatin inhibit the expansion of endothelial cells in blood vessel (Folkman and Kalluri, 2004) and in animal it invade the activity of angiogenesis and growth of tumors.

In a study conducted Wang et al. (2015) suggesting that endostatin bind with Sam68RNA in preadipocytes prevent interaction of Sam68RNA with mTOR intron5, causing decrease in expression of mTOR which result in inhibition adipogenesis, angiogenesis, and dietary-induced obesity. Therefore, it has been concluded that endostatin prevent obesity and its related disorders, such as insulin

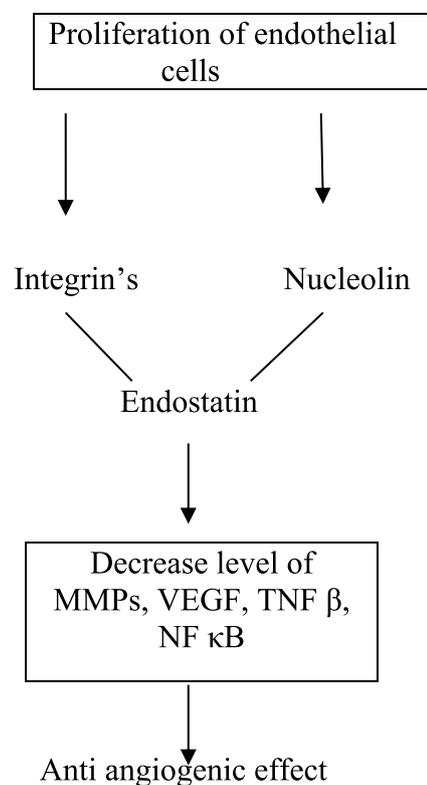


Fig. 1. The signaling pathway by which endostatin suppresses angiogenesis cell migration, pro-angiogenic factors PlGF (placental growth factor), TGF (tissue growth factor), VEGF and TNF β , NF κ B (nuclear factor kappa B).

resistance and glucose intolerance.

Endostatin has both anti-obesity and antiangiogenic property as it has become a new approach for anti-obesity therapy and treatment of the cardio renal metabolic syndrome. For example, hyperglycemia and insulin resistance induces regulation of reactive oxygen species and oxidative stress that leads to impairment of myocardial angiogenesis (Kim et al., 2012; Hayden et al., 2008). Additionally, overexpression of angiogenesis result in various diseases, including cancer, diabetes complications, hypertension, metabolic syndrome and stroke. Recent study revealed an FDA-approved drug rapamycin inhibits mTOR signaling pathway that has been used for coating coronary stents, treating cancer, and suppressing the immune response and also rapamycin prevent dietary-induced obesity by inhibition of angiogenesis and adipose tissue expansion by inhibiting mTOR signaling pathway by causing error in mTOR (Jia et al., 2014b). (See Fig. 1).

8. Therapeutic intervention of obesity by endostatin

Overexpression of adipogenesis and angiogenesis has led therapeutic intervention of obesity by targeting the vasculature. Data conducted over the years revealed various angiogenesis inhibitors, that are TNP-470, angiostatin and endostatin, have been studied on both genetically obese and high-calorie diet-induce obese animals (Brakenhielm et al., 2004b). Additionally administration of angiostatin, endostatin, and TNP-470 in both genetically obese and high-calorie diet-induce mice results in weight reduction as well as loss of adipocytes by decreasing the proliferation of endothelial cells (Rupnick et al., 2002b). Although immunohistochemical analysis has revealed that vascularity of the adipose tissue is reduced in animals treated with angiogenesis inhibitors. Furthermore the angiogenesis inhibitor TNP-470 leads to increase in insulin sensitivity and prevent the development of type II diabetes in obese animals.

9. Conclusion

Chronic overnutrition and lack of physical exercise leads to excess storage of adipose tissue which play a significant role in the development of type 2 diabetes, stroke, cancer and cardiovascular disease. The overexpression of adipose tissue in high calorie diet induced obesity result in hyperplasia of adipocytes, and these processes are accompanied by the proliferation of endothelial cells from re-existing blood vessels with neovascularization (Manrique et al., 2013). Normal angiogenesis is maintain by the balance between angiogenic factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor- β , as well as angiostatic factors, such as angiostatin, endostatin but in case of obesity, adipocytes promotes expansion of endothelial cells that result in overgrowth of vessel. Therefore, endothelial cells interacts to regulate angiogenesis and this result in expansion of capillary network (Soumya et al., 2013). Despite this, elevated levels of serum leptin prevent deposition of fat in adipocytes via inhibiting angiogenesis. Various investigation are done to inhibit angiogenesis by studying several antiangiogenic agents including endostatin, angiostatin om genetic and dietary induce obese mice that might block the functions of angiogenic factors, leading to shrinkage of the fat mass. Although, antiangiogenic agents provides a new therapeutic approach for the prevention and treatment of obesity. As more antiangiogenic agents become available for experimental and clinical applications, they provide an opportunity to test this possibility in the near future.

Conflicts of interest

The author declare that there are no conflicts of interest.

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