Chapter

Adipocytokines: Are They the Theory of Cancer Progression?

Rowyda Nawwaf Al-Harithy

Abstract

Adipocytokines have gained significant attention in the scientific community over the past few decades. They are a family of enzymes, hormones, growth factors, proteins, and other bioactive molecules that are important regulators of many processes. Adipocytokines are predominantly produced by preadipocytes and mature adipocytes to act through a network of autocrine, paracrine, and endocrine pathways. Leptin (LEP) is the first adipocytokine discovered that has a role in modulating adiposity and has been shown to exert pleiotropic effects on many metabolic pathways through the leptin receptors (LEPRs). LEP has pro-tumoral roles; it promotes angiogenesis, proliferation, survival of tumor cells, and inhibits apoptosis. To exercise its role in tumorigenesis, LEP-LEPR signaling and epithelial-mesenchymal transitions (EMTs) play a significant role. LEP is an oncogenic factor mainly due to its proinflammatory and proangiogenic effects. In angiogenesis, LEP acts directly as an endothelial growth factor or indirectly through cellular pathways, such as STAT3/ERK1/2, JAK2/STAT3, MAPK/ERK, PI3K/AKT, p38, p53, MAPK, and Wnt/β-catenin.

Keywords: adipocytokines, leptin, inflammation, angiogenesis, cancer

1. Introduction

Adipose tissue is a complex, dynamic, and heterogenic endocrine organ with diverse homeostatic processes [1]. During the past few decades, the structural and functional principles of adipose tissue have evolved considerably to get to today's concept [2]. In the human body, the adipose tissue is restricted in depot sites and varies in cellular composition and character. Adipose tissue can be classified by morphology into white, brown, beige, pink, and yellow [3]. Our understanding of their importance started with identifying a range of adipose tissue products and their functions. Since then, much has been learned about how adipose tissue communicates with other organs of the body. More recently, its functions have been reported to be highly influenced by bioactive molecules with widespread systemic effects contributing to numerous physiological and pathological processes [4]. The white adipose depots are considered a specialized organ representing the largest endocrine tissue in humans. It can be broadly classified by location into subcutaneous and visceral. In its different locations, it shows different metabolic profiles with different functions. In general, they are responsible for storing chemical energy formatted as triglycerides packed in unilocular lipid droplets. The white adipocytes, especially in the visceral area, secrete

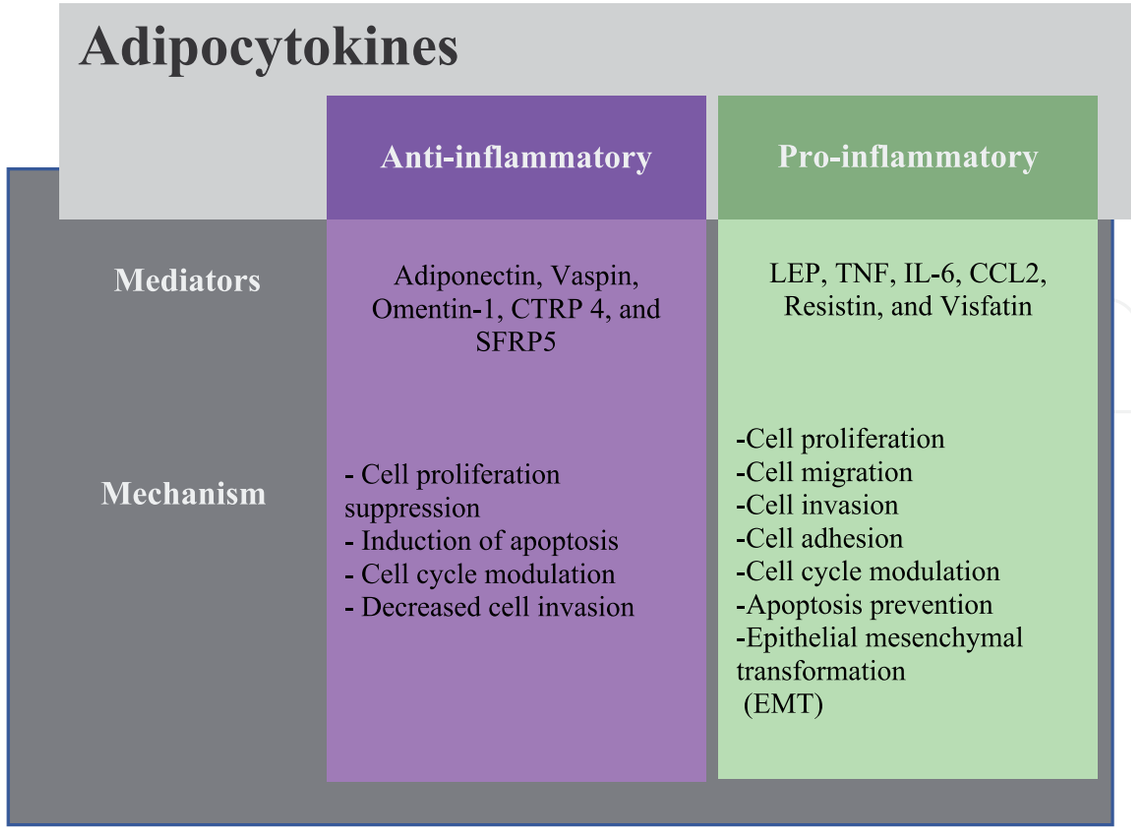

Figure 1.
Adipocytokines and their mechanisms as an anti-inflammatory and proinflammatory.

abundant mediators, including exosomes, miRNA, lipids, inflammatory cytokines, and peptide hormones that participate in the process of interorgan communication via paracrine and endocrine modes [5].

White adipose tissue comprises many different cell types; approximately 40–50% of the cells are adipocytes, with the rest represented by the stromal vascular fraction (SVF) of cells, including preadipocytes, fibroblasts cells, endothelial cells, vascular progenitor cells, mesenchymal stem cells, and a variety of immune cells (macrophages, natural killer cells, B-lymphocytes, and T-lymphocytes) [6]. Adipocytes, specific to white adipose tissue, are plastic and respond to changes in metabolism by altering their size, number, and their exerted functions [7, 8]. The white adipose tissue multifarious composition renders white adipose tissue an important mediator of metabolism and inflammation [9]. White adipose tissue influences metabolism through maintaining energy homeostasis, adipocyte differentiation, and insulin sensitivity. It also affects inflammation through its actions in the immune system as pro- and anti-inflammatory mediators (**Figure 1**). This function is controlled by numerous adipocytokines, other cytokines, chemokines, and growth factors [10]. While the term adipokine is commonly used to refer to adipose tissue-derived proteins, adipocytokines are mainly, but not solely, produced by adipocytes.

2. Adipocytokines

The word adipocytokine is derived from the Greek root meaning fat cell movement. Adipocytokines are produced exclusively or substantially by preadipocytes and mature adipocytes, hence their name. They are biologically active molecules

that are important regulators for many physiological processes. Adipocytokines are heterogeneous in structure and function, which is mainly affected by the specific anatomical location of the producing adipocytes. Adipocytokines have the ability to act locally or distally as inflammatory, immune, or hormonal signalers. They can be categorized in terms of their function as metabolic factors, proinflammatory factors, proangiogenic factors, and extracellular matrix components. Adipocytokines are secreted in response to different triggers; their involvement has been noted in insulin action, endothelial cell function, blood pressure, appetite, hemostasis, reproduction, angiogenesis, and immunity [11].

The year 2022 marks the 35th anniversary of adipocytokines. The breakthrough discovery of the first adipocytokine, adipsin, followed by tumor necrosis factor (TNF), leptin (LEP), and adiponectin led to the widespread recognition of adipose tissue as an endocrine organ. Adipsin (also known as complement factor D) was identified as an adipokine in 1987 [12]. In 1993, TNF was identified as a proinflammatory adipocytokine in the models of diabetes and obesity, becoming pioneering evidence for a functional link between obesity and inflammation [13]. The identification and cloning of LEP in 1994 followed by that of adiponectin in 1995 were an inflection point into the endocrine era [14, 15]. LEP and adiponectin are the classic adipocytokines of visceral adipose tissue and clearly the two most widely studied adipocyte products. LEP is acknowledged as an adipose tissue-specific secreted protein that regulates food intake and energy. Adiponectin, also known as ACRP30, AdipoQ, and gelatin-binding protein-28, has anti-inflammatory actions on the liver, the heart, the kidneys, muscle cells, and pancreatic β cells, to name a few [16–18]. It plays roles that are most likely relevant to cognitive dysfunction, namely, synaptic regulation, insulin sensitivity, neuroinflammation, neuroprotection, and neurogenesis [19, 20].

Adiponectin and LEP's detailed mechanisms of action at the cellular level of their target organs and their mutual effects on each other remain ambiguous. Despite extensive research on the topic, much more regarding LEP and adiponectin, their relationship to each other and to the body remains to be discovered. However, it is important to note that the ratio of adiponectin to LEP has been proposed as a marker of adipose tissue dysfunction [21, 22]. On review of the literature, LEP is found to be the most studied in the context of cancer risk and progression (**Figure 1**).

3. Leptin

Friedman and his colleagues discovered LEP in 1994 and named it after the word "leptos," which means thin in Greek reference to its demonstrated effect on the body. In humans, LEP is encoded by the LEP gene that is located on chromosome 7 7q31.3 and consists of three exonic regions with two intronic regions. It is a nonglycosylated adipocytokine consisting of 146 amino acids. LEP is a multifunctional adipocytokine primarily secreted by the white adipocytes. LEP is also produced by other tissues, such as the stomach, placenta, and mammary glands [23–26]. The past 25 years of research on LEP have provided important insights into the intricate network that links nutrition, metabolism, reproduction, endocrine regulation, inflammation, and immune function [27–29]. LEP is a key regulator of the adipose organ, and its main task is to regulate energy balance, which is possible by lowering the appetite. The essential characteristics of LEP are listed in **Table 1**.

Adipocytokine	Characteristics
Leptin (LEP)	Signals through leptin receptor isoform b (LEPRb)
	Binds short and soluble leptin receptor isoforms (LEPRa, LEPRc)
	Regulates bone mass
	Regulates reproduction
	Regulates body weight gain
	Regulates immune cell functions
	Regulates food intake and energy expenditure
	Regulates glucose tolerance and insulin sensitivity
	Regulates brain sympathetic output to different tissues
	May regulate body temperature
	May regulate hematopoiesis
	Induce epithelial-mesenchymal transition
	Promote adipogenesis
	Increases adipocyte lipolysis
	Increases angiogenesis
	Increases brown adipose tissue activity
	Increases skeletal muscle cell glucose uptake
	Increases adipocyte, hepatocyte, and skeletal muscle cell fatty acid oxidation
	May increase adipose tissue stromal cell proliferation
	May increase white adipose tissue browning
	Decreases adipocyte glucose uptake
	Decreases adipocyte, hepatocyte, and skeletal muscle cell lipogenesis

Table 1.
The functions of leptin.

LEP expression in the adipose tissue is influenced by a variety of hormones, including insulin, glucocorticoids, catecholamines, and cortisol, and several other metabolic factors, including TNF-α, fatty acids, and glucose [30–33]. Recently, a fat-specific long noncoding RNA (lncRNA) has been identified to interact with redundant enhancers and regulate LEP expression [34]. LEP deficiency or resistance is associated with the dysregulation of cytokine production, increased susceptibility to infections, autoimmune disorders, malnutrition, and inflammatory responses. The elevated levels of serum LEP have been unequivocally correlated with an increased risk of developing various tumor forms, including testicular, breast, prostate, colon, and pancreatic cancers [35–40]. The short-, medium-, and long-term regulatory actions of LEP are supported by its specific LEP receptor (LEPR). The LEPR is a class I cytokine receptor and structurally a transmembrane receptor encoded by the *LEPR* (*OBR*) gene on chromosome 1p31.3 [41–43]. In humans, there are at least four splice variants of the LEPR gene that have been identified and categorized as long (LEPRb), short (LEPRa, and LEPRc), and secretive (LEPRe) isoforms. The isoforms have different lengths of intracellular C-terminal domains. The LEPRb contains the full intracellular domain 303 amino acids, and the short isoforms contain 32–40 amino

acids. Although long and short isoforms share a sequence of 29 amino acids proximal to the transmembrane region, the LEPRe isoform lacks both transmembrane and cytoplasmic domains [44, 45]. The long LEPR contains the full intracellular domain to fully induce intracellular signaling necessary for the activation of critical second messenger pathways and normal leptin action. The LEPR isoforms are distributed in almost all peripheral tissues and seem to mediate the transport of LEP. In humans, the effects of LEP can be detected at various sites given that LEPR are found in the brain, heart, placenta, lung, liver, muscle, kidney, pancreas, spleen, thymus, prostate, testes, ovary, small intestine, and colon [46]. Therefore, LEPR locations demonstrate LEP's importance in human molecular processes. The signaling events that follow the binding of LEP to its LEPRs have been studied extensively and characterized at the biochemical and molecular levels in many systems and, more recently, in relation to immune responses [47].

4. Leptin and cancer

LEP is the most studied adipocytokine, particularly in metabolism and obesity-related cancers. It is well established that LEP has pro-tumoral roles; it promotes angiogenesis, proliferation, survival of tumor cells, and inhibits apoptosis [48]. To exercise its role in tumorigenesis, LEP-LEPR signaling and epithelial-mesenchymal transitions (EMTs) play a significant role in tumor initiation, progression, metastasis, and chemoresistance. The function of the leptin axis in cancer is through LEP-LEPR singling. The binding of LEP to LEPR induces the activation of several signaling pathways, such as JAK/STAT3, PI3K/AKT, and MAPK/ERK. Cumulative research demonstrated high levels of LEP and LEPR expression in cancer cells. LEP and LEPR levels are usually missing in epithelial breast tissue but are found in abundance in breast cancer [49]. Other cancers that show high levels of LEP and LEPR include hepatocellular carcinoma [50], lung cancer [51], prostate cancer [52], colorectal cancer [53], melanoma [54], ovarian cancer [55] renal carcinoma [56], and breast cancer (**Figure 2**) [57]. It was also demonstrated that the upregulated level of LEP correlates with clinical and prognostic outcomes in multiple cancer types such as the presence of remote metastasis of breast cancer and the short survival of its patients. The level of LEP expression is influenced by numerous physiological mechanisms, which are noted to be associated with fat mass. One of such mechanisms is the ability of inflammatory cytokines, i.e., TNF-α, interleukin-1 (IL-1), and leukemia inhibitory factor, to induce adipocytes to produce LEP and increase the expression of its mRNA synthesis [58]. Another factor is the genetic variations in the *LEP* gene and/or *LEPR* gene that modulates LEP level [59, 60]. The genetic variations in these genes have been specifically linked to the progression of prostate, breast, gastric, and lung carcinomas [61–63]. Since the proposal of LEP as an EMT inducer a decade ago, research has proven it to be very important in driving the cellular process to aggressive cancer phenotypes. EMT is a complex reprogramming cellular process allowing epithelial cells to acquire mesenchymal characteristics, an important role in the tumor microenvironment (TME). This change enhances migratory and invasive capability and has been demonstrated to be essential in the metastatic spread of several cancer types, including prostate, lung, liver, pancreatic, and breast cancers [64, 65]. EMT programs were also found to stimulate the production of LEP by cancer cells, suggesting a signaling loop in tumor progression. Other important signaling molecules involved in the process

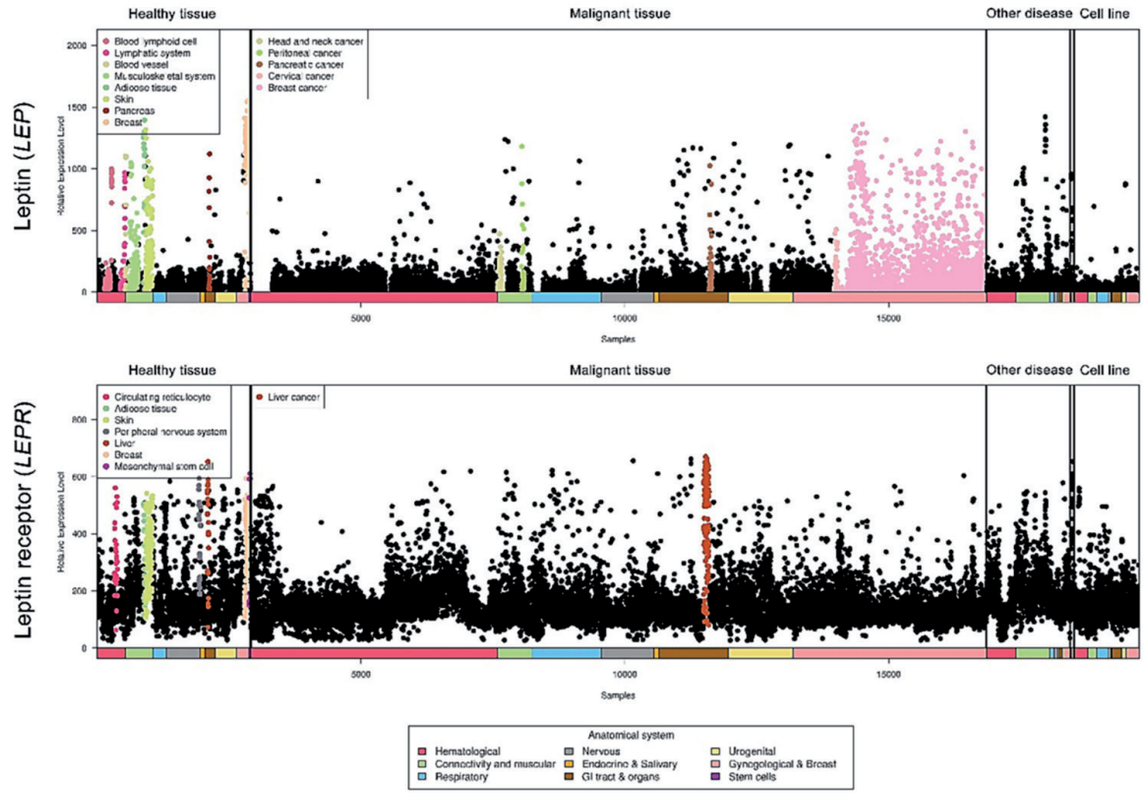

Figure 2.
LEP and LEPR expression in a pancancer panel. From Lin and Hsiao [49].

include integrins, growth factors, and cytokines, such as IL-8, IL-6, and TNF-α, which are often secreted by tumor stroma [66, 67]. Literature has also documented that EMT programs can stimulate the production of proinflammatory factors. Olea-Flores demonstrated the mechanism by which LEP promotes EMT programming, through Src and FAK activations that control the secretion and activation of metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9). Leptin promotes the expression of EMT-related transcription factors and invasion in a Src and FAK-dependent pathway in MCF10A mammary epithelial cells [68]. In a recent review, Tsung-Chieh and Michael indicated that cancer cells and the tumor microenvironment express LEP and LEPRs and suggested that the potential leptin autocrine/paracrine signaling loop could affect tumor progression [49].

Other studied theories on the involvement of LEP in carcinogenesis were described to be mediated by LEPR activation of PI3K, ERK1/2, and Jak2/Stat3 signaling pathways. These pathways regulate the expression of cancer-related genes, such as cyclin D1, cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and potentiate several procarcinogenic processes, including angiogenesis, migration, and mesenchymal transformation [69, 70]. Additionally, *in vitro* studies have documented the antiapoptotic and mitogenic effects of LEP on different cancer cell lines. Zhang and his team have shown that LEP can play the role of being an antiapoptotic by regulating the expression of proteins involved in the apoptotic pathway. They observed that LEP decreases the apoptotic potential of adipose tissue by increasing the Bcl2 and decreasing proapoptotic Bax and CD95 protein expression [71]. More importantly, LEP has been studied as an oncogenic factor due to its proinflammatory and proangiogenic effects.

5. Role of leptin as a proinflammatory factor

The immune system response, acute and chronic inflammation, is called into action when other homeostatic mechanisms are inadequate. Inflammatory mediators play a significant role, adjacent in importance to mutations and epigenetic alterations. In tumor initiation, LEP plays a pleiotropic role in the immune response and can appropriately be considered, both structurally and functionally, as a proinflammatory cytokine. LEP regulates both innate and adaptive immune responses through the modulation of immune cells' survival and proliferation as well as its activity [72–74]. LEP has a modulatory impact on the course of inflammation, affecting the expression of proinflammatory cytokines and their receptors. In the innate immune response, LEP enhances the secretion of TNF-α, a proinflammatory mediator, and interacts with interleukin1beta (IL1β) [75]. IL1β has the ability to increase the levels of cytokines, such as Interleukin 6 (IL6), Interleukin 8 (IL8), and prostaglandin E2 (PGE2), by its mechanism on nitric oxide synthase-2 (NOS2) through the JAK2, PI3K, MAP2K1/MEK1, and MAPK14/p38 signaling pathways [76]. These cytokines also regulate the expression of LEP, creating a signaling loop that supports sustaining a chronic proinflammatory state [77]. In the adaptive immune response, LEP promotes the alteration of memory T-cells immune response toward T helper-1 cells, as well as escalating CD4+CD25– T-cell proliferation and reducing the autophagy process during T-cell receptor (TCR) stimulation by triggering MTOR signaling pathway and upregulating the synthesis of B-cell lymphoma 2 (BCL2) [78]. LEP controls the crosstalk between innate and adaptive immunity by affecting dendritic cell number, maturation, cytokine production, and capacity to induce CD4+ T-cell proliferation [79]. Chronic infectious, immune, and metabolic diseases may lead to LEP resistance, increasing LEP levels and further fueling the inflammatory state. LEP's involvement in the immune and inflammatory response has become increasingly evident and, in turn, is important in cancer.

6. Role of leptin as an angiogenic growth factor

Angiogenesis, a hallmark of cancer, refers to the formation of new blood vessels from preexisting ones. It is a vital process that plays a role in normal physiological as well as pathological processes. Angiogenesis enables tumor growth and metastasis through a multistep progression commencing with endothelial cell migration, proliferation, invasion, and ultimately novel capillary formation. Though the basic steps of angiogenesis are similar in all tissue, it is likely that the vascular network of each organ will be established through tissue-specific key mechanisms. Angiogenesis requires a balance between proangiogenic and antiangiogenic factors; changes in equilibrium can lead to oncogenic angiogenesis.

White adipose tissue is embedded in a dense vascular network and is the most vascularized tissue in the human body. The hypervascularization of the white adipose tissue indicates the presence of an intimate interplay between both the vascular and adipose compartments. The functions of adipose vasculature are summarized in **Table 2**. It has been previously noted that the white adipose tissue regulates the production of various adipocytokines, but it also releases angiogenic factors; therefore, it influences and modulates angiogenesis as well as vascular structure [80–82]. Scientific research has been able to narrow the culprits of angiogenic growth in white

	Adipose vasculature functions
1	Providing nutrients and oxygen essential for the maintenance of adipocyte survival and functions
2	Removing metabolic products from adipose tissue
3	Paracrine regulation of adipocyte functions through the production of various factors and cytokines from vascular cells
4	Transporting adipose-tissue-derived growth factors, adipokines, and cytokines for removal of tissues globally regulating physiological functions via the endocrine mechanism
5	Transporting non-adipose-tissue derived growth factors, cytokines, and hormones for modulating adipocyte functions and growth
6	Alteration of the adipose microenvironment such as hypoxia and acidosis, which control adipocyte function, preadipocyte differentiation, and adipose tissue mass
7	Supplying circulating stem cells from non-adipose tissues to adipose tissues
8	Supplying adipocyte vessel wall stem and precursor cells that can eventually differentiate into mature adipocytes
9	Supplying other cell types such as inflammatory cells that secondarily affect adipocyte function
10	Preparation of adipose niche formation during embryonic development by the vasculature

Table 2.
Adipose vasculature functions in the modulation of adipocyte functions.

adipose tissue to two possibilities: first, in response to signals initiating from neighboring adipocytes that are undergoing proliferation and enlargement; the other possibility is through metabolic signals produced locally or distally. These two possibilities are not mutually exclusive, and probably tissue expansion involves both local signals arising from expanding adipocytes and distant signals reflecting the developmental and metabolic state of the whole organism. It has been acknowledged that adipogenesis, angiogenesis, and vascular remodeling are tightly related and regulated processes. Dysfunction in the regulation of one or more of these processes leads to changes in vessel growth, vascular permeability, remodeling, adipose mass, and function, which will ultimately cause pathological angiogenesis or vascular regression [83].

In white adipose tissue, LEP was found to be an important proangiogenic factor or an angiogenesis inducer [84]. In 1998, Sierra-Honigmann and colleagues produced one of the first studies to demonstrate that leptin-induced cell proliferation, cell survival, and 3D matrix formation of capillary-like tubes mimicking vascular endothelial growth factor (VEGF) 165 [85]. This supported the notion that LEP is an endothelial growth factor. LEP is able to act as a direct factor to induce the angiogenic potential of endothelial cells evident by the presence of LEPR on endothelial cells. Both *in vivo* and *in vitro* studies have demonstrated the activation of endothelial LEPR by LEP, leading to capillary tube formation [86]. The indirect involvement of LEP in angiogenesis has been explored immensely. Garonna *et al*. showed that leptin enhances endothelial cyclooxygenase-2 (COX-2) expression and causes rapid VEGFR2 phosphorylation through the activation of P38 MAPK/AKT/COX-2, which is needed for leptin-stimulated neoangiogenesis [87]. LEP increases the levels and activity of enzymes involved in angiogenesis through metalloproteinase-2 (MMP-2) and MMP-9 activity [82]. Additionally, LEP has been shown to upregulate and act synergistically with the key angiogenic mediators like fibroblast growth factor (FGF)-2, VEGF, and its receptor VEGFR, resulting in stimulation of blood-vessel growth [88]. The VEGF

and VEGFR have a special signaling transduction system that plays a significant role in the process of oncogenic angiogenesis. *In vitro* and *in vivo* findings have implicated the role of VEGFR in the facilitation of angiogenic growth and endothelial cell tube development [89]. LEP can upregulate VEGF expression and function, VEGF can, in turn, activate LEP demonstrating the functional interplay between both cytokines. The increase in the presence of both cytokines could generate and amplify a proangiogenic environment. Moreover, crosstalk between LEP and VEGF has been noted in other tissues, such as in cancerous breast tissue; LEP activates HIF-1α and NF-κB to upregulate VEGF [89]. Additionally, LEP is involved in tumor angiogenesis-related signaling pathways such as STAT3/ERK1/2, JAK2/STAT3, MAPK/ERK, PI3K/AKT, p38, p53, MAPK, and Wnt/β-catenin [90]. Less studied are the Akt and Wnt signaling pathways' effect on the proliferation and angiogenic differentiation of endothelial cells, though LEP's involvement was demonstrated [91]. Furthermore, distinct mechanisms, regulated Wnt-responsive GSK-3β and growth factor/Akt responsive GSK-3β, suggest that GSK-3β has a crucial role in the crosstalk between the Akt and Wnt signaling pathways [92]. However, the underlying cellular mechanism remains to be elicited. Of note, tumor angiogenesis is closely associated with the tumor microenvironment and is regulated by a variety of proangiogenic factors and/or angiogenic inhibitors. The genetic and epigenetic alterations of angiogenesis-associated genes might result in angiogenesis dysfunctions and promote tumorigenesis.

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Author details

Rowyda Nawwaf Al-Harithy
King Abdulaziz University (KAU), Jeddah, Saudi Arabia

*Address all correspondence to: dr.alharithy@gmail.com

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