Review Article
Middle East Journal of Cancer; October 2017; 8(4): 171-177

Visfatin and its Role in Breast Cancer

Robab Sheikhpour

Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract

Breast cancer, the most common cancer in women, is a leading cause of cancer death among women worldwide. Obesity is associated with increased risk of breast cancer. Discovery of biomarkers that can be used for diagnosis, prognosis, and predictors of breast cancer is very important. Visfatin, a new adipokine found in visceral fat, plays a main role in metabolic and stress responses. There is an association between elevated expression of visfatin with malignant behavior and adverse prognosis in breast cancer. Visfatin promotes malignancy via signaling pathways that include Ras, Raf, MEK1/2, ERK, phosphoinositide 3-kinase (PI3K), Akt, and NF-κB. Visfatin up-regulates G1-S phase cell cycle progression through up-regulation of mRNA levels of cyclin D1 and CDK2. Visfatin plays a main role in metastasis and synthesis of genes that play a significant role in tumor-related angiogenesis such as vascular endothelial growth factor, progression and tumor invasion such as matrix metalloproteinases in cancer. Visfatin may increase breast cancer cell growth and metastasis capability through c-Abl and STAT3 activation (two oncoproteins). According to the results of these studies, visfatin expression appears to be associated with virulent behavior and its inhibition may be an effective treatment for breast cancer patients.

Keywords: Breast cancer, Visfatin, NF-κB

Introduction

Cancer is one of the most fatal diseases in humans with an annual mortality rate of 30000 individuals in Iran.[1] Breast cancer (BC) is the most common cancer in women and a leading cause of cancer deaths among women worldwide.[1,2] Of note, the incidence of BC is increasing.[3] Several factors that include cytokines, metabolic parameters, environmental factors, reproductive history, and heredity are important in BC development.[4-6] Currently, there are no adequate serum biomarkers for early BC detection. Therefore, the discovery of biomarkers useful for diagnosis, prognosis, predictive, and therapeutic targets for BC is very important.[7] Visfatin, as a pre-B cell enhancing factor (PBEF),[8] is a new adipokine found in the visceral fat that plays a main role in stress responses and cellular energy

♦Corresponding Author:
Robab Sheikhpour, PhD
Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Tel: +98 9131522462
Email: r.sheikhpour@yahoo.com

Middle East Journal of Cancer

Received: December 3, 2016; Accepted: April 8, 2017

Table 1. Relation between visfatin and obesity.

Study	Results	Reference No.
Berndt et al. (2005)	Visfatin plasma concentration had a positive correlation with visceral visfatin mRNA expression and body mass index (BMI).	33
Pagano et al. (2006)	Visfatin was associated with BMI in the investigated disease.	28
Zahorska-Markiewicz et al. (2007)	Serum concentration of visfatin was significantly higher in obese women when compared to controls.	34
Shea et al. (2007)	An association existed between visfatin and the investigated disease with obesity.	35
Kovacikova et al. (2008)	Visfatin was associated with BMI.	36
Malavazos et al. (2008)	BMI >30 in obese patients was associated with disease.	37
Nakajima et al. (2010)	Visfatin levels increased with obesity.	38
Kim et al. (2010)	The level of visfatin increased with obesity.	8
Dalamaga et al. (2012)	One parameter that determined serum visfatin level in PBC cases was BMI.	7
Romacho et al. (2013)	Increased circulating levels of visfatin were reported in obese patients.	12
Assiri et al. (2015)	A positive correlation existed between visfatin and BMI.	9
El-Benhawy et al. (2015)	A high level of serum visfatin was independent of BMI.	39
Nourbakhsh et al. (2015)	Visfatin levels increased in obese people and were associated with insulin resistance (IR).	40
Hung et al. (2016)	High serum visfatin levels had a significant association with BMI.	13
Liang et al. (2016)	Elevated visfatin serum levels increased weight.	41

metabolism as nicotinamide phosphoribosyl transferase (Nampt).[7] There is an association between elevated expression of visfatin with malignant behavior and adverse prognosis in BC.[9] Few studies have evaluated the relationship between visfatin levels and BC, and its molecular basis remains poorly understood. Hence, this review aims to evaluate the role of visfatin in BC patients.

Visfatin

The visfatin gene has been placed on the long arm of chromosome 7 (7q22.2).[10] Visfatin was discovered in adipocytes by Chang et al. in 2005.[11] Visfatin, a multifaceted molecule, is known as a 52 KDa adipocytokine.[12,13] It also acts as a pro-inflammatory cytokine[14] and inflammation increases visfatin synthesis.[12] Visfatin is ubiquitously generated in many tissues and several cells such as synovial fibroblasts,[15] articular chondrocytes,[16] or monocyes.[17] Pro-inflammatory cytokines that include tumor necrosis factor alpha (TNFα) or interleukin (IL)-1β, by lipopolysaccharide (LPS) and dexamethasone regulate expression of visfatin.[18-20] It exists in both intracellular and extracellular states.[13] The action of intracellular visfatin as a rate-limiting enzyme is the biosynthesis of nicotinamide adenine dinucleotide (NAD). NAD+ is a ubiquitous coenzyme that performs an important role in redox reactions and carries electrons from one reaction to another.[21] It receives electrons from other molecules and becomes NADH. Therefore, it seems that Nampt/visfatin as a regulator of NAD+ metabolism can play a main role in the control of basic processes.[21] Visfatin release outside of cells shows dual roles in enzyme-like activity on extracellular NAD formation and cytokine-like activity through a putative receptor-mediated pathway.[4] In both the intracellular and extracellular states it can be involved in tumor development and cancer progression.[13]

Contradictions exist regarding the insulin mimetic effect and protective role of visfatin against development of insulin resistance (IR).[22] Some studies report that visfatin can bind to insulin receptors in a place separate from insulin and act as an insulin mimetic, increasing glucose uptake and metabolism in myocytes and adipocytes, and block the gluconeogenesis

pathway. These functions of visfatin cause hypoglycemia. Studies report an association between visfatin and insulin levels,[23,24] however others report no such association.[25-28]

Relation between obesity and visfatin in breast cancer (BC)

Visfatin may be a promising predictor for obesity, IR, and metabolic syndrome.[29-32] Table 1 shows the relation between obesity and visfatin.

Obesity and related metabolic alterations are associated with increased risk for cancer, particularly BC.[8] Obese postmenopausal women compared to non-obese women had a higher overall risk of BC.[42] Although the relation between obesity and BC is complex and not understood,[43] a number of parameters can contribute to this process.

Role of visfatinin in breast cancer (BC)

Visfatin is over-expressed in many inflammatory diseases that include atherosclerosis, rheumatoid arthritis, osteoarthritis (OA), metabolic syndrome, and sepsis.[15-17,44,45] Visfatin also promotes malignancy and is related to a worse clinical prognosis.[46] Elevated expression of visfatin is associated with adverse prognosis of BC.[47] Therefore, visfatin may show a new link with BC pathophysiology.[47,48] Table 2 lists studies that have reported the role of visfatin in BC.

Signaling pathways of visfatin

Although studies have shown the role of serum visfatin as a biomarker13 in BC, the relation between visfatin levels and BC risk is unclear. The molecular basis for this link is not understood. Visfatin up-regulates G1-S phase cell cycle progression through up-regulation of mRNA levels of cyclin D1 and CDK2.[8] Visfatin has been shown to increase expressions of matrix metalloproteinases MMP2 and MMP9 mRNA, and vascular endothelial growth factor (VEGF).[54] Therefore, it seems that visfatin can play a main role in metastasis, as well as synthesis of genes that play a significant role in tumor-related angiogenesis (VEGF as a pro-angiogenic protein),[7] and progression and tumor invasion (MMP in BC).[52]

Park et al. have reported that visfatin increased NF-κB p65 and Notch1 levels. NF-κB p65 is a positive regulator of Notch1 stimulated by visfatin in BC cells.[52] Notch1 was inhibited via NF-κB signaling pathway inhibition. It has not been determined if NF-κB directly or indirectly mediates the stimulation of Notch1 expression.[52] Visfatin, via Notch1 signaling activation, promoted BC. Reduction of visfatin and Notch1 suppressed cell proliferation and stimulated apoptosis.[53] However, over-expression of active Notch1 increased tumor formation in murine mammary tissue.[53] Therefore, increased expression of Notch1 has been shown to correlate with poor overall survival in BC patients. It seems that Notch1 can be as a prognostic biomarker for the pathogenesis of BC and a new therapeutic target.[53]

Hung et al. reported that extracellular visfatin increased BC cell growth and metastasis capability through c-Abl and STAT3 activation (two important oncoproteins).[13] They reported that imatinib, a tyrosine kinase inhibitor, and Stattic as STAT3 inhibitor might be useful to treat BC patients who have elevated levels of visfatin.[13]

It has been shown that numerous signaling pathways such as PI3K,[54] p38 MAPK,[55]

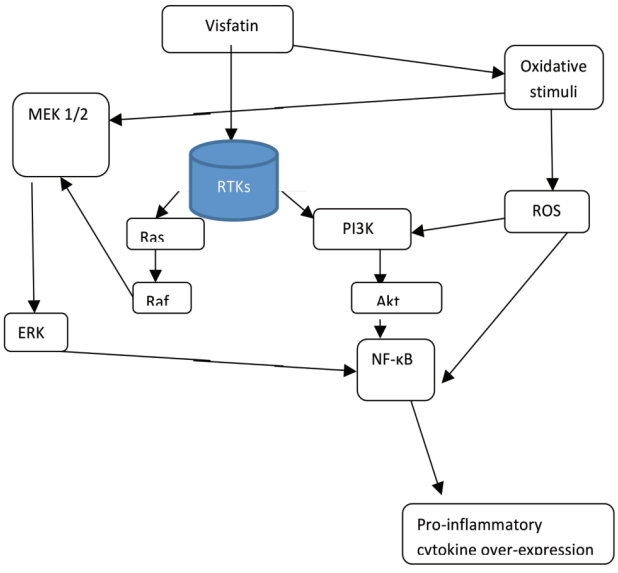

Figure 1. Visfatin signaling pathway which leads to pro-inflammatory cytokine over-expression by oxidative stress and receptor tyrosine kinases (RTKs).[59]

Table 2. Different studies that discussed the role of visfatin in breast cancer (BC).

Study	Results	Reference No.
Folgueira et al. (2005)	Visfatin was expressed in human BC tissue.	49
Yonezawa et al. (2006)	Visfatin was expressed in MCF-7 BC cells.	50
Kim e al. (2010)	Visfatin motivated proliferation of MCF-7 human BC cells.	8
Moschen et al. (2010)	The level of visfatin as a pro-inflammatory adipocytokine increased in various inflammatory conditions and was correlated with the degree of inflammation.	51
Dalamaga et al. (2011)	A significantly greater mean level of visfatin existed in BC patients compared to the control group.	4
Lee et al. (2011)	Visfatin highly expressed in human BC cells both *in vitro* and *in vivo*.	47
Kim et al. (2012)	Visfatin increased the invasion of MDA-MB-231 human BC cells.	52
Dalamaga et al. (2012)	Higher visfatin expression in BC tissue correlated with increased malignant cancer behavior.	7
Park et al. (2014)	Visfatin stimulated BC proliferation and invasion.	53
Li et al. (2014)	Women with high serum levels of visfatin had significantly shorter overall survival compared to those with low serum levels of visfatin.	3
Assiri et al. (2015)	Visfatin increased lymph node metastasis in postmenopausal BC.	9
El-Benhawy et al. (2015)	High levels of serum visfatin were seen in BC patients compared to controls.	39
Hung et al. (2016)	High serum visfatin levels were associated with advanced tumor stage, increased tumor size, lymph node metastasis, and poor survival in BC patients.	13

ERK1/2,[56] JNK,[57] STAT3,[58] AKT,[59] NF-κB[52] can contribute to activation of downstream target gene transcription induced by visfatin. Some studies reported that STAT3 as a downstream target gene transcription for visfatin does not contribute to cancer progression.[59] Figure 1 shows visfatin signaling pathway which leads to pro-inflammatory cytokine over-expression by oxidative stress and receptor tyrosine kinases (RTKs).[59]

Visfatin and oxidative stress

Several metabolic pathways such as aerobic metabolism in the mitochondrial respiratory chain can generate reactive oxygen species (ROS) and subsequently initiate and progress several types of cancers.[60] Reactive oxygen species can affect many signals such as growth factors and mitogenic pathways.[60] The role of visfatin in inflammation, progression, and oxidative stress is emerging.[59] Visfatin is a strong marker for inflammation and dysfunction.[21]

Visfatin can increase expressions of inflammatory adhesion molecules including vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule 1(ICAM-1) in vascular endothelial cells in a ROS-dependent manner via NF-κB signaling.[61] Therefore, these studies have shown that visfatin increased oxidative stress and inflammation through NF-κB activation and other stress-related signaling pathways in a cell-type dependent manner.[61] Visfatin, by stimulation of PI3K, caused activation of NF-κB and pro-inflammatory answer.[59,62] Other studies have reported that visfatin activates members of the MAPK signaling pathway involved in stress responses, including ERK[62] and p38.[61,62] Marseglia et al. have reported that nicotinamide phosphoribosyltransferase (NAMPT) / visfatin can act as a cytokine, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, IL-1β, IL-6, and IL-13 which up-regulate in several acute and chronic inflammatory neonatal diseases.[21] However Buldac reported that visfatin increased cytokine production via increased intracellular ROS levels.[60]

Lipid peroxidation increased in the presence of visfatin.[60] Visfatin could interact with protein

mediated oxidative stress and inflammation including ND1, ferritin light chain, and interferon-induced transmembrane protein 3 (IFITM3) which led to increased levels of ROS.[63]

Conclusion

According to the result of these studies, it seems that visfatin expression is associated with virulent behavior. Its inhibition may be effective therapy for breast cancer patients.

Conflict of Interest

No conflict of interest is declared.

References

1. Sheikhpour R. Role of ghrelin in cancer. *Iranian J Blood Cancer.* 2016; 8(1): 1-4.
2. Sheikhpour R, Hekmat Moghadam H. The effect of estrogen on p53 protein in T47D breast cancer cell line. *Razi J Med Sci*. 2015;22(133):51-8.
3. Li XY, Tang SH, Zhou XC, Ye YH, Xu XQ, Li RZ. Preoperative serum visfatin levels and prognosis of breast cancer among Chinese women. *Peptides*. 2014;51:86-90.
4. Dalamaga M, Karmaniolas K, Papadavid E, Pelekanos N, Sotiropoulos G, Lekka A. Elevated serum visfatin/nicotinamide phosphoribosyl-transferase levels are associated with risk of postmenopausal breast cancer independently from adiponectin, leptin, and anthropometric and metabolic parameters. *Menopause.* 2011;18(11):1198-204.
5. Lee WL, Cheng MH, Chao HT, Wang PH. The role of selective estrogen receptor modulators on breast cancer: from tamoxifen to raloxifene. *Taiwan J Obstet Gynecol.* 2008;47(1):24-31.
6. Yoo HJ, Lim MC, Son Y, Seo SS, Kang S, Kim SH, et al. Survival outcome in endometrial cancer patients according to hereditary predisposition. *Taiwan J Obstet Gynecol.* 2015;54(1):24-8.
7. Dalamaga M, Archondakis S, Sotiropoulos G, Karmaniolas K, Pelekanos N, Papadavid E, et al. Could serum visfatin be a potential biomarker for postmenopausal breast cancer? *Maturitas*. 2012;71(3):301-8.
8. Kim JG, Kim EO, Jeong BR, Min YJ, Park JW, Kim ES, et al. Visfatin stimulates proliferation of MCF-7 human breast cancer cells. *Mol Cells.* 2010;30(4):341-5.
9. Assiri AM, Kamel HF, Hassanien MF. Resistin, visfatin, adiponectin, and leptin: risk of breast cancer in pre- and postmenopausal saudi females and their possible diagnostic and predictive implications as novel biomarkers. *Dis Markers.* 2015;2015:253519.
10. Ogawa H, Damrongrungruang T, Hori S, Nouno K, Minagawa K, Sato M, et al. Effect of periodontal treatment on adipokines in type 2 diabetes. *World J Diabetes.* 2014;5(6):924-31.
11. Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. *Diabetes Metab Res Rev.* 2011;27(6):515-27.
12. Romacho T, Villalobos LA, Cercas E, Carraro R, Sánchez-Ferrer CF, Peiró C. Visfatin as a novel mediator released by inflamed human endothelial cells. *PLoS One.* 2013;8(10):e78283.
13. Hung AC, Lo S, Hou MF, Lee YC, Tsai CH, Chen YY, et al. Extracellular visfatin-promoted malignant behavior in breast cancer is mediated through c-Abl and STAT3 activation. *Clin Cancer Res*. 2016;22(17):4478-90.
14. Li XY, Tang SH, Zhou XC, Ye YH, Xu XQ, Li RZ. Preoperative serum visfatin levels and prognosis of breast cancer among Chinese women. *Peptides*. 2014;51:86-90.
15. Brentano F, Schorr O, Ospelt C, Stanczyk J, Gay RE, Gay S, et al. Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. *Arthritis Rheum*. 2007;56(9):2829-39.
16. Gosset M, Berenbaum F, Salvat C, Sautet A, Pigenet A, Tahiri K, et al. Crucial role of visfatin/pre-B cell colony-enhancing factor in matrix degradation and prostaglandin E2 synthesis in chondrocytes: possible influence on osteoarthritis. *Arthritis Rheum*. 2008;58(5):1399-409.
17. Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A, et al. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation.* 2007;115(8):972-80.
18. Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest.* 2004;113(9):1318-27.
19. Kralisch S, Klein J, Lossner U, Bluher M, Paschke R, Stumvoll M, et al. Hormonal regulation of the novel adipocytokine visfatin in 3T3-L1 adipocytes. *J Endocrinol.* 2005;185(3):R1-8.
20. Kralisch S, Klein J, Lossner U, Bluher M, Paschke R, Stumvoll M, et al. Interleukin-6 is a negative regulator of visfatin gene expression in 3T3-L1 adipocytes. *Am J Physiol Endocrinol Metab*. 2005;289(4):E586-90.
21. Marseglia L, D'Angelo G, Manti M, Aversa S, Fiamingo C, Arrigo T, et al. Visfatin: New marker of oxidative stress in preterm newborns. *Int J Immunopathol Pharmacol.* 2016;29(1):23-9.

22. Siahanidou T, Margeli A, Kappis A, Papassotiriou I, Mandyla H. Circulating visfatin levels in healthy preterm infants are independently associated with high-density lipoprotein cholesterol levels and dietary long-chain polyunsaturated fatty acids. *Metabolism*. 2011;60(3):389-93.
23. López-Bermejo A, Chico-Julià B, Fernàndez-Balsells M, Recasens M, Esteve E, Casamitjana R, et al. Serum visfatin increases with progressive beta-cell deterioration. *Diabetes.* 2006;55(10):2871-5.
24. Lewandowski KC, Stojanovic N, Press M, Tuck SM, Szosland K, Bienkiewicz M, et al. Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. *Diabetologia.* 2007;50(5):1033-7.
25. Chen CC, Li TC, Li CI, Liu CS, Lin WY, Wu MT, et al. The relationship between visfatin levels and anthropometric and metabolic parameters: association with cholesterol levels in women. *Metabolism*. 2007;56(9):1216-20.
26-. Malamitsi-Puchner A, Briana DD, Boutsikou M, Kouskouni E, Hassiakos D, Gourgiotis D. Perinatal circulating visfatin levels in intrauterine growth restriction. *Pediatrics.* 2007;119(6):e1314-8.
27. Sun G, Bishop J, Khalili S, Vasdev S, Gill V, Pace D, et al. Serum visfatin concentrations are positively correlated with serum triacylglycerols and down-regulated by overfeeding in healthy young men. *Am J Clin Nutr.* 2007;85(2):399-404.
28. Pagano C, Pilon C, Olivieri M, Mason P, Fabris R, Serra R, et al. Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. *J Clin Endocrinol Metab*. 2006;91(8):3165-70.
29. Sandeep S, Velmurugan K, Deepa R, Mohan V. Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians. *Metabolism*. 2007;56(4):565-70.
30. Malavazos AE, Ermetici F, Cereda E, Coman C, Locati M, Morricone L, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. *Nutr Metab Cardiovasc Dis.* 2008;18(8):523-30.
31. Hallschmid M, Randeva H, Tan BK, Kern W, Lehnert H. Relationship between cerebrospinal fluid visfatin (PBEF/Nampt) levels and adiposity in humans. *Diabetes.* 2009;58(3):637-40.
32. Zhong M, Tan HW, Gong HP, Wang SF, Zhang Y, Zhang W. Increased serum visfatin in patients with metabolic syndrome and carotid atherosclerosis. *Clin Endocrinol (Oxf).* 2008;69(6):878-84.
33. Berndt J1, Klöting N, Kralisch S, Kovacs P, Fasshauer M, Schön MR, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes.* 2005;54(10):2911-6.
34. Zahorska-Markiewicz B, Olszanecka-Glinianowicz M, Janowska J, Kocełak P, Semik-Grabarczyk E, Holecki M, et al. Serum concentration of visfatin in obese women. *Metabolism.* 2007;56(8):1131-4.
35. Shea J, Randell E, Vasdev S, Wang PP, Roebothan B, Sun G. Serum retinol-binding protein 4 concentrations in response to short-term overfeeding in normal-weight, overweight, and obese men. *Am J Clin Nutr.* 2007;86(5):1310-5.
36. Kovacikova M, Vitkova M, Klimcakova E, Polak J, Hejnova J, Bajzova M, et al. Visfatin expression in subcutaneous adipose tissue of pre-menopausal women: relation to hormones and weight reduction. *Eur J Clin Invest.* 2008;38(7):516-22.
37. Malavazos AE, Ermetici F, Cereda E, Coman C, Locati M, Morricone L, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. *Nutr Metab Cardiovasc Dis.* 2008;18(8):523-30.
38. Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, et al. Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Sci.* 2010;101(5):1286-91.
39. El-Benhawy SA, Abd El Moneim NA, Ebeid SA. Serum adipocytokines (visfatin and resistin): New biomarkers of breast carcinogenesis. *Middle East J Cancer.* 2015;6(4):253-64.
40. Nourbakhsh M, Nourbakhsh M, Gholinejad Z, Razzaghy-Azar M. Visfatin in obese children and adolescents and its association with insulin resistance and metabolic syndrome. *Scand J Clin Lab Invest.* 2015;75(2):183-8.
41. Liang Z, Wu Y, Xu J, Fang Q, Chen D. Correlations of serum visfatin and metabolisms of glucose and lipid in women with gestational diabetes mellitus. *J Diabetes Investig.* 2016;7(2):247-52.
42. Sheikhpour R, Taghipour Sh. Evaluation of polymorphism codon 72 gene p53 and resulted protein in breast cancer patients. *Breast Cancer Disease*. 2014;7(3):1-10.
43. Sinicrope FA, Dannenberg AJ. Obesity and breast cancer prognosis: weight of the evidence. *J Clin Oncol.* 2011;29(1):4-7.
44. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, et al. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol.* 2007;178(3):1748-58.
45. Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest.* 2004;113(9):1318-27.
46. Yang J, Zhang K, Song H, Wu M, Li J, Yong Z, et al. Visfatin is involved in promotion of colorectal carcinoma malignancy through an inducing EMT mechanism. *Oncotarget.* 2016;7(22):32306-17.
47. Lee YC, Yang YH, Su JH, Chang HL, Hou MF, Yuan

SS. High visfatin expression in breast cancer tissue is associated with poor survival. *Cancer Epidemiol Biomarkers Prev.* 2011;20(9):1892-901.
48. Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, et al. Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Sci.* 2010;101(5):1286-91.
49. Folgueira MA, Carraro DM, Brentani H, Patrão DF, Barbosa EM, Netto MM, et al. Gene expression profile associated with response to doxorubicin-based therapy in breast cancer. *Clin Cancer Res.* 2005;11(20):7434-43.
50. Yonezawa T, Haga S, Kobayashi Y, Takahashi T, Obara Y. Visfatin is present in bovine mammary epithelial cells, lactating mammary gland and milk, and its expression is regulated by cAMP pathway. *FEBS Lett.* 2006;580(28-29):6635-43.
51. Moschen AR, Gerner RR, Tilg H. Pre-B cell colony enhancing factor/NAMPT/visfatin in inflammation and obesity-related disorders. *Curr Pharm Des.* 2010;16(17):1913-20.
52. Kim SR, Park HJ, Bae YH, Ahn SC, Wee HJ, Yun I, et al. Curcumin down-regulates visfatin expression and inhibits breast cancer cell invasion. *Endocrinology.* 2012;153(2):554-63.
53. Park HJ, Kim SR, Kim SS, Wee HJ, Bae MK, Ryu MH, et al. Visfatin promotes cell and tumor growth by upregulating Notch1 in breast cancer. *Oncotarget.* 2014;5(13):5087-99.
54. Adya R, Tan BK, Punn A, Chen J, Randeva HS. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. *Cardiovasc Res.* 2008;78(2):356-65.
55. Wang P, Xu TY, Guan YF, Su DF, Fan GR, Miao CY. Perivascular adipose tissue-derived visfatin is a vascular smooth muscle cell growth factor: role of nicotinamide mononucleotide. *Cardiovasc Res.* 2009;81(2):370-80.
56. Kim SR, Bae SK, Choi KS, Park SY, Jun HO, Lee JY, et al. Visfatin promotes angiogenesis by activation of extracellular signal-regulated kinase 1/2. *Biochem Biophys Res Commun.* 2007;357(1):150-6.
57. Liu P, Li H, Cepeda J, Xia Y, Kempf JA, Ye H, et al. Regulation of inflammatory cytokine expression in pulmonary epithelial cells by pre-B-cell colony-enhancing factor via a nonenzymatic and AP-1-dependent mechanism. *J Biol Chem.* 2009;284(40):27344-51.
58. Nowell MA, Richards PJ, Fielding CA, Ognjanovic S, Topley N, Williams AS, et al. Regulation of pre-B cell colony-enhancing factor by STAT-3-dependent interleukin-6 trans-signaling: implications in the pathogenesis of rheumatoid arthritis. *Arthritis Rheum.* 2006;54(7):2084-95.
59. Buldak RJ, Polaniak R, Buldak L, Mielanczyk L, Kukla M, Skonieczna M, et al. Exogenous administration of visfatin affects cytokine secretion and increases oxidative stress in human malignant melanoma Me45 cells. *J Physiol Pharmacol.* 2013;64(3):377-85.
60. Buldak RJ, Gowarzewski M, Buldak L, Skonieczna M, Kukla M, Polaniak R, et al. Viability and oxidative response of human colorectal HCT-116 cancer cells treated with visfatin/eNampt *in vitro*. *J Physiol Pharmacol.* 2015;66(4):557-66.
61. Oita RC, Ferdinando D, Wilson S, Bunce C, Mazzatti DJ. Visfatin induces oxidative stress in differentiated C2C12 myotubes in an Akt- and MAPK-independent, NFkB-dependent manner. *Pflugers Arch.* 2010;459(4):619-30.
62. Adya R, Tan BK, Punn A, Chen J, Randeva HS. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signaling pathways: novel insights into visfatin-induced angiogenesis. *Cardiovasc Res*. 2008;78(2):356-65.
63. Zhang LQ, Adyshev DM, Singleton P, Li H, Cepeda J, Huang SY, et al. Interactions between PBEF and oxidative stress proteins-a potential new mechanism underlying PBEF in the pathogenesis of acute lung injury. *FEBS Lett.* 2008;582(13):1802-8.