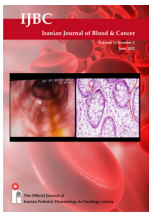
Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir



Review

Visfatin: an adipokine that plays a crucial role in increasing the risk of cancer

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ARTICLE INFO

Article History:
Received: 6/12/2021
Accepted: 4/6/2022

Keywords:
Visfatin
Gastric cancer
Breast cancer
Prostate cancer
Colorectal cancer
Leukemia
Thyroid cancer

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Abstract

Obesity is an important public health problem worldwide. Epidemiological studies have demonstrated that obesity is associated with an increased risk of several cancer types. Also, obesity is associated with an increase in cancer mortality. Biological mechanisms and the relationship between obesity and cancer are complex and not well understood. Studies on the role of adipose-derived factors in cancer development may be the mechanistic link between obesity and cancer risks. Visfatin or pre-B cell enhancing factor (PBEF) or nicotin-amide-phosphoribosyl-transferase (Nampt) is an important hormone protein that is mainly produced by adipose tissue, and has three major functions: growth factor, cytokine, and nicotinamide-phosphoribosyl-transferase, therefore, increasing of visfatin has several effects. Recently, studies have shown that over-expression of visfatin is important in the carcinogenesis of several types of cancers. This review aimed to summarize findings from both experimental and epidemiological studies investigating the association between visfatin levels and cancer risk.

Please cite this article as: Mohammadi M, Hedayati M. Visfatin: an adipokine that plays a crucial role in increasing the risk of cancer. IJBC 2022; 14(2): 68-74

Abbreviations: PBEF, pre-B cell enhancing factor; Nampt, nicotinamide phosphoribosyl transferase; NAD, nicotinamide adenine dinucleotide; STAT3, signal transducer and activator of transcription 3; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; PI3K, Phosphoinositide 3-kinase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; hTERT, Human Telomerase reverse transcriptase; C-Abl, or ABL1, cellular Abelson tyrosine kinase1; SIRT1, Sirtuin 1; SDF-1, stromal cell-derived factor-1; CRC, colorectal cancer; ROS, Reactive oxygen species; EMT, epithelial mesenchymal transition; Dox, doxorubicin; MDR1, multidrug resistance 1; BMI, body mass index; FTC follicular thyroid carcinomas; PTC, papillary thyroid carcinomas; DTCs, Differentiated thyroid carcinomas; HCC, hepatocellular carcinoma; EC, endometrial cancer; SCC, squamous cell carcinoma; CTCL, cutaneous T-cell lymphoma; BC, bladder cancer.

1. Introduction:

The prevalence of obesity is growing which is an important public health problem worldwide. According to the WHO report in 2016, more than 1.9 billion adults aged 18 years and older were overweight. The worldwide prevalence of obesity more than doubled between 1980 and 2016, of these over 600 million adults were obese. Epidemiological studies have demonstrated that obesity is associated with an increased risk of several cancer types, including gastric, colon, endometrium, pancreas, postmenopausal breast, esophagus, bladder, kidney, liver, and hematological malignancy [1]. Biological mechanisms and the relationship between obesity and cancer are complex and not well understood. Different effective factors include obesity-related hormones, and adipokines, growth factors, modulation of energy balance and calorie restriction, inflammatory processes, and multiple signaling pathways that affect cancer cell promotion and progression [2]. This review will focus on the role of visfatin as one of the important adipocytokines that in previous studies have shown over-expression of it, is important in the carcinogenesis in several types of cancers.

2. Visfatin biology

Visfatin is a 52-kDa peptide that in humans is encoded by the NAMPT gene. First, described in the extracellular space in 1994. The extracellular and secretory form of this protein is an enzyme in the nicotinamide adenine dinucleotide (NAD+) salvage pathway that converts nicotinamide to nicotinamide mononucleotide to enable NAD+ biosynthesis therefore another names is extracellular nicotinamide phosphoribosyl-transferase (eNampt). Also, known as the pre-B cell enhancing factor (PBEF), a growth factor for early B cell maturation and inhibits neutrophil apoptosis [3]. Three different biological names with three different functions for a single protein have made it unique. Three major functions of this protein are growth Factor, cytokine and nicotinamide phosphoribosyl-transferase therefore increasing visfatin has several effects. As yet visfatin receptor has not been identified but a study on diabetes has indicated that visfatin receptor phosphorylation and intracellular signaling can regulate insulin secretion from pancreatic beta cells and affects a variety of metabolic and stress responses [4, 5]. Bone marrow, liver, muscle, brain, kidney, spleen, testis, lung, breast, prostate, colon [6-8], and gastric tissues express this protein but are preferentially expressed in the visceral fat of both humans and mice, and plasma levels of visfatin increase during the development of obesity.

3. Role of visfatin in carcinogenesis

Circulating visfatin is enhanced in many cancers, especially obesity-associated malignancies that it is associated with a bad prognosis. Many studies provided evidence that visfatin may be a novel risk factor as well as a surrogate clinical marker in cancer therapeutics. In a recent meta-analysis study, we indicated a significant association between high circulating visfatin levels, and increased risk of various cancers [9]. According to the results of studies, visfatin could be implicated in the initiation, progression, invasion and metastasis of various cancers [10]. Studies demonstrated that visfatin can enter the cytosol, and nucleus and promote the progression of inflammation, angiogenesis and energy metabolism [11, 12].

The association between visfatin and cancer development has been studied in cultured cells and animal models. Several studies suggest that visfatin has a pro-inflammatory effect produced by adipose tissue macrophages [13] and could mediate macrophage survival in obesity by IL-6/ signal transducer and activator of transcription 3 (STAT3) cell survival pathway, thus might play a role in obesity-associated tumorigenesis [14].

Several studies have shown that visfatin can regulate a variety of different signaling pathways such as signal transducer and activator of transcription 3 (STAT3), PI3K/Akt, and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) [15]. Also, several studies have shown metastasis and angiogenic effects of visfatin by up-regulating matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) activity through activation of ERK1/2 and p38 signaling pathways [16-18]. Also, two known inhibitors of visfatin (CHS828 or GMX1777 and FK866 or APO866) have been evaluated as anticancer in the clinic [19].

These data together indicate that the pro-inflammatory, anti-apoptotic and angiogenic functions of visfatin, might play a potential role in the association between obesity and cancer, although further studies will be necessary to demonstrate specific molecular mechanisms of visfatin on tumor development.

4. Role of visfatin in cancer: epidemiological studies

Human epidemiological studies on the relationship between visfatin and obesity, as well as the relationship between visfatin and cancers, revealed inconsistent results that are as follows:

4.1. Gastric cancer

Gastric cancer as a major health concern is the third leading cause of cancer death worldwide [20]. According to the studies, obesity promotes the growth of gastric cancer through complex molecular mechanisms such as adipokine, hormonal, inflammatory, and immunological changes [21].

Few studies, in human, have been investigating the association of visfatin with gastric cancer. The case-control studies found that high levels of visfatin were associated with increases in gastric cancer risk [22, 23]. Higher serum visfatin and visfatin mRNA levels have been observed to be poor prognosis predictors in patients with gastric cancer [24]. The previous study showed that gastric cancer cells secrete and express visfatin endogenously which acts on gastric cancer cells in an autocrine manner [25].

Overall, visfatin plays an important role in gastric carcinogenesis by overexpression of VEGF, MMP2, MMP9, and NF-κB [24, 26]. Also, visfatin induces endogenously gastric cancer cell proliferation and increases telomerase (hTERT) gene expression, as an oncogene [27]. To confirm direct visfatin effects on gastric carcinogenesis in studies showed that the specific Nampt inhibitor FK866 repressed gastric cancer cell proliferation and significantly decreased expression of VEGF, MMP2, MMP9, and NF-κB [24, 28].

4.2. Breast cancer

Breast cancer is the most common female malignancy, and is the second cause of cancer death in women worldwide. Obesity is associated with an increased risk for the initiation and development of breast cancer particularly in postmenopausal women. Visfatin has been reported to be associated with breast cancer progression, but the interaction between the visfatin increasing and clinic pathologic factors in breast cancer progression status require further investigation. Several studies examining the link between circulating visfatin levels and breast cancer risk demonstrated that high preoperative serum visfatin level is associated with more malignant cancer behavior as well as poor patient survival [29-33].

Studies have shown that visfatin plays an important role in breast carcinogenesis. Kim et al. showed that visfatin by overexpression of matrix metalloproteinases 2, matrix metalloproteinases 9, and vascular endothelial growth factor genes, may function in metastasis and angiogenesis of breast cancer [34]. Behrouzfar et al. reported that extracellular visfatin produces Nicotinamide-adenine-dinucleotide (NAD) that causes upregulation of Sirtuin 1 (SIRT1)activity and p53 deacetylation explains the relationship between visfatin and breast cancer progression[35]. Gholinejad et al. showed that visfatin induces breast cancer cell proliferation through AKT/PI3K and ERK/MAPK activation and protects against apoptosis in these cells [36].

Hung et al. reported that extracellular visfatin promoted malignant behavior and metastasis in breast cancer through activation of the cellular Abelson tyrosine kinase (c-Abl, also known as ABL1) and signal transducer and activator of transcription 3 (STAT3) [37]. Park et al. showed that the visfatin-Notch1 axis (Notch signaling is an evolutionarily conserved cell-cell communication pathway and plays a critical role in various physiological and pathological processes) contributes to breast tumor growth through the activation of the NF-κB pathway [38].

In addition, of studies on visfatin roles in breast carcinogenesis, some studies with visfatin inhibition tried to breast cancer cell growth regulation. Alaee et al. showed that FK866 could effectively inhibit NAD+ biosynthesis and induce programmed cell death in Estrogen Receptor-Positive MCF-7 breast cancer cells [39]. Hesari et al. reported that miR-206 reduced NAMPT expression at the protein level, leading to a significant decrease in the intracellular NAD level and subsequent decline in cell survival and induction of apoptosis. Targeting the NAMPT-mediated NAD salvage pathway by miR-206 might provide new insight into the possible molecular mechanism of breast cancer cell growth regulation [40]. Kim et al. showed that, curcumin down-regulates visfatin gene expression in human breast cancer cells by a mechanism that is NF-κB dependent [41].

4.3. Colorectal cancer

Colorectal cancer (CRC) is a major public health

concern, as it is one of the leading causes of cancer deaths in the Western world and developed countries [42]. Epidemiologic studies have reported a positive association between obesity and colorectal cancer also; obesity may play a role in colorectal cancer recurrence, treatment outcomes, and survival. Alteration of adipokines is thought to be an important link between obesity and colorectal cancer.

Several studies examining the link between circulating visfatin levels and colorectal cancer risk demonstrated that an increased level of visfatin was a strong risk factor for both early and advanced colorectal cancer in patients and stage progression significantly correlated with visfatin levels [43-45]. In another study, Neubauer et al. reported that visfatin upregulation in colorectal tumors, in normal tissue and whole blood of colorectal cancer patients, is associated with metastasis, hypoxia, IL1β, and anemia [46].

Visfatin plays an important role in colorectal carcinogenesis. Ghaemmaghami et al. showed that colorectal cancer cells secrete and express visfatin endogenously, that act on colorectal cancer cells in an autocrine manner [6]. Huang et al. found that visfatin stimulation led to an increase in the expression and secretion of stromal cell-derived factor-1 (SDF-1) in colorectal cancer cells that was mediated by β1 integrin. Also, they showed that visfatin increased NF-κB- and AP-1-DNA-binding activities in colorectal cancer cells that have important roles in CRC progression [47].

Buldak et al. showed that visfatin induces a decrease in cell viability and an increase in apoptosis of human colorectal cancer cell line with an effect on the level of ROS as well as the antioxidant capacity that provide greater insight into the association between visfatin level and its endocrine action in colorectal carcinoma cells [48]. Yang et al. reported that visfatin can significantly promote the in vitro migration and invasion of CRC cells with induction epithelial-mesenchymal transition (EMT) via Akt/GSK-3β/β-catenin signals [49].

Zhang et al. demonstrated that miR-26b inhibits visfatin expression at the protein and mRNA levels by binding to the visfatin 3'-UTR. They found a statistically significant inverse correlation between miR-26b and visfatin expression that was observed in the patient's tissue and colorectal cell line samples[50]. Yan et al. showed that visfatin mediates the doxorubicin (Dox)-resistant of CRC cells via up-regulation of multidrug resistance 1 (MDR1) and indicated that targeted inhibition of visfatin might be helpful for overcoming Dox resistance of CRC therapy [51].

4.4. Prostate cancer

Prostate cancer is the second most common male malignancy and is the fifth leading cause of cancer mortality among men worldwide. Several large studies have found an increased obesity and body mass index (BMI) in adulthood to be associated with an increased risk of the development of prostate cancer [52-54].

Few studies, in human, have been investigating the association of visfatin with prostate cancer. The relationship between visfatin levels and clinical stage and grading of tumors in prostate cancer is unclear and needs to be further explored.

4.5. Thyroid cancer

Thyroid carcinomas are the most common malignancies of the endocrine system. Environmental and lifestyle factors, for example, radiation, iodine intake, nitrates as well as obesity, and diabetes are known as thyroid cancer risk factors. Many studies have provided data on the association between obesity and thyroid cancers.

Studies in thyroid disorders and cancers have shown changes. Sawicka-Gutaj et al. showed that visfatin mRNA expression increased in thyroid malignancies with more advanced tumor stage and metastatic disease [55]. In another study, Shackelford et al. reported that NAMPT (visfatin) expression was low in benign thyroid nodules, moderately increased in follicular thyroid carcinomas (FC), and more highly expressed in papillary thyroid carcinomas (PTC) and well-differentiated thyroid carcinomas (TCs). They suggested that NAMPT inhibitor therapy may be useful in thyroid cancers to other treatments [56].

4.5. Leukemia

Leukemia is a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. The epidemiological data regarding the link between overweight and obesity, as defined by body mass index (BMI), and the risk of developing leukemia has revealed conflicting results [57]. Several

studies indicate that obesity is associated with an increased risk of developing leukemia [58-60].
Clinically and pathologically, leukemia is subdivided into a variety of large groups that in several studies have been reported visfatin to be associated with these cancers' progression.
Siviero-Miachon et al. showed that visfatin is a positive predictor of bone mineral density in young survivors of acute lymphocytic leukemia. [61]. Audrito et al. reported that both intracellular and extracellular NAMPT levels are increased in the cells and plasma of chronic lymphocytic leukemia (CLL) patients. They suggested that extracellular NAMPT (visfatin) is a critical element in the induction of an immunosuppressive and tumor-promoting of CLL [62].
Some studies have focused on FK866 (as a specific inhibitor of visfatin) effectiveness on leukemic cells. Grohmann et al. reported that inhibition of NAMPT sensitizes by FK866, and SIRTUIN2 was decreased and accumulation and acetylation of the downstream target p53 were enhanced in leukemia cells. They suggested inhibition of NAMPT sensitizes leukemia cells through the SIRT2-p53 pathway [63]. Thakur BK et al. showed that FK866 is a specific inhibitor of NAMPT that induces apoptosis of leukemic cells and has an anti-leukemic effect by effect on the p53 acetylation pathway [64]. Dan et al. found that visfatin and sirtuin 2 participate in the aberrant proliferation and survival of leukemic cells by deacetylation of protein kinase B/AKT, and suggest that the protein kinase B/AKT/ glycogen synthase kinase-3 β/β-catenin pathway is a target for inhibition of visfatin or sirtuin 2 [65].

4.6. Visfatin and other cancers

The association between visfatin and other cancers has not been extensively investigated. Although plasma visfatin is elevated in a variety of human malignancies, including hepatocellular carcinoma (HCC), endometrial cancer (EC), squamous cell carcinoma (SCC), pancreatic cancer, cutaneous T-cell lymphoma (CTCL), and bladder cancer (BC) [66-71]. The relationship between visfatin levels and clinical stage and grading of tumors in some of these cancers is unclear and needs to be further explored.

5. Conclusion

There is increasing evidence that Nampt/PBEF/visfatin may have pathophysiological effects that extend beyond its traditional roles in the regulation of NAD biosynthesis and energy homeostasis; in particular, its role in cancer, which regulates cell growth, migration, and gene expression, has received considerable experimental and epidemiological supports.
Although epidemiological studies generally support the linkage between visfatin levels and cancer risk, there are not enough studies examining the correlations between visfatin and the molecular subtypes of cancers. Further investigations are needed to provide novel insights into the potential role of visfatin as a mediator of obesity in cancer progression, which may enhance our understanding of tumor progression and allow for the discovery of novel biomarkers or therapeutic targets for cancer treatments.

Acknowledgements

The study was funded by the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences. We are grateful to all individuals who participated in this project.

Declaration of interest

The authors declare no conflicts of interest regarding the publication of this paper.

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