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REVIEW

The role of visfatin in cancer proliferation, angiogenesis, metastasis, drug resistance and clinical prognosis

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Abstract: Visfatin, also known as nicotinamide phosphoribosyltransferase or pre-B-cell colony-enhancing factor (*PBEF*), is an adipocytokine secreted by adipocytes, macrophages and inflamed endothelial tissue. Related reports have indicated a positive correlation between the visfatin level and obesity and cancer risk. In addition to its original function, visfatin is multifunctional and plays critical roles in the promotion of several processes relevant to cancer progression including cancer cell proliferation, angiogenesis, metastasis and drug resistance. The relative expression of visfatin and the potential visfatin receptor on a pan-cancer scale was determined based on the transcriptome analysis data in The Cancer Genome Atlas. We further show the clinical association of its signaling axis with the survival of cancer patients, which reveals its prognostic power for specific cancer types. This review illustrates visfatin's biological functions related to cancer progression and demonstrates its clinical significance in predicting outcomes of cancer patients.

Keywords: visfatin, cancer progression, clinical outcome

Introduction

The adipocytokine visfatin is also known as pre-B-cell colony-enhancing factor (*PBEF*), and is secreted by human peripheral blood lymphocytes.[1] Its intracellular form has been recognized for its enzyme function in the nicotinamide adenine dinucleotide NAD^+ salvage pathway where it is designated as nicotinamide phosphoribosyltransferase (NAMPT).[2,3] Recently, increases in both the NAD(H) pool size and the NAD^+/NADH ratio caused by NAMPT were shown to promote colorectal cancer (CRC) progression.[44] Importantly, the abnormal expression of visfatin in many types of cancers and a significant correlation between high circulating visfatin levels and an increase in cancer risk were observed.[5] Furthermore, emerging evidence has demonstrated visfatin expression in a broad range of cancer types along with visfatin-mediated effects on the regulation of several critical factors in processes related to cancer progression including tumor proliferation, angiogenesis, metastasis and drug resistance. In this review, we focus on the biological function of visfatin in cancer and further illustrate its clinical significance including its relative expression level on a pan-cancer scale and its specific correlation with patient survival in various cancer types.

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Expression of visfatin and its potential receptor in cancer

Visfatin was detected in tumors or plasma of patients with variant types of cancers, which indicates its clinical importance in cancer progression. According to the results of a tissue array analysis in oral squamous cell carcinoma, visfatin overexpression was observed.[6] In addition, higher levels of visfatin were detected in tumor tissues from 8 matched pairs of human pancreatic ductal adenocarcinoma (PDAC), and similar findings were obtained in PDAC cells.[7] Breast cancer MDA-MB -231, MDA-MB-468 and MCF-7 cell lines displayed elevated visfatin levels compared with the non-transformed MCF-10A cell line, and an inverse relationship between the visfatin and p73 levels was also proposed.[8] In clear cell renal cell carcinoma (RCC), visfatin expression was higher in tumors as compared to that in the adjacent normal tissues (GSE6344).[9] Patients with thyroid malignancy also exhibited a higher visfatin expression level, and visfatin appeared to correlate with advanced tumor stage and metastasis.[10] Moreover, an increase in visfatin expression was observed in experimental myelomatous bones compared with non-myelomatous bones.[11] A comprehensive analysis using the Xena browser to analyze pan-cancer transcriptome data and matched clinical information was launched by the University of California Santa Cruz.[12] The omics data were mainly generated by microarray experiments and RNA sequencing in combination with cancer patients' follow-up data in The Cancer Genome Atlas (TCGA). The results demonstrated the relative expression levels of visfatin (*NAMPT*) and its potential receptor (*INSR*) after normalization to the pan-cancer scale (Figure 1). A relatively high visfatin level was found in lung squamous cell carcinoma, stomach adenocarcinoma, glioblastoma multiforme, liver hepatocellular carcinoma, lung adenocarcinoma, kidney clear cell carcinoma, esophageal carcinoma, head and neck squamous carcinoma, prostate carcinoma and skin cutaneous carcinoma. In addition, the potential visfatin receptor was relatively highly expressed in adrenocortical cancer, kidney chromophobe, stomach adenocarcinoma, liver hepatocellular carcinoma, kidney clear cell carcinoma, kidney papillary cell carcinoma, breast invasive carcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma and thyroid carcinoma, which indicates the potential pathological role in cancer.

Correlation with clinical outcome

Evaluation of the association of the visfatin level with clinical outcome in various types of cancers has been reported. Visfatin expression was shown to correlate with poor overall survival in melanoma patients.[13] In addition, hepatocellular carcinoma patients with high serum visfatin levels had shorter overall survival times compared with those with low serum visfatin levels ($p<0.001$).[14] In colorectal carcinoma cases, the results of a Kaplan–Meier analysis of 87 patients indicated a statistically negative correlation between visfatin levels and overall survival probability ($p<0.001$).[15] A study of 176 breast cancer biopsy tissues demonstrated that visfatin is a prognosis marker for its association with poor patient survival.[8] Another cohort study in breast cancer further suggested that the combination of high serum visfatin and estrogen receptor-negative status appeared to correlate with the worst disease-free survival ($p<0.001$).[16] The concurrent status of poor survival outcome and high visfatin level was verified in patients with upper tract urothelial carcinoma,[17] gastric cancer,[18] gastric cancer with diabetes,[19] breast cancer[20,21] and bortezomib-resistant myeloma.[22] Furthermore, the gene expression profile, as determined by microarray and RNA sequencing technology, together with clinical follow-up data were retrieved and analyzed through SurvExpress,[23] TCGA[12] and the Kaplan–Meier plotter database,[24] which illustrates the prognostic impact of visfatin (*NAMPT*) and its potential receptor (*INSR*) in specific cancer types (Tables 1 and 2).

Visfatin and proliferation

The role of visfatin in regulating cancer cell proliferation has also been reported. In melanoma cells, NAMPT promotes proliferation and inhibits p53-dependent apoptosis via the E2F2/SIRT1 axis, and this effect was more significant than the NAD^+-driven transcriptional program.[13] Visfatin regulated redox adaptative responses by increasing the activity of anti-oxidative enzyme including SOD, CAT and GSH-Px along with an increase in the proliferation rate via [^{3}H]thymidine incorporation in Me45 human malignant melanoma cells.[25] Visfatin was revealed to preferentially induce the proliferation of HepG2, Hep3B and HuH7 human hepatoma cells compared with normal hepatocyte Hc cells. This biological effect was reversed by PI3K/MEK1/GSK3β pathway inhibitors.[26] In one study, visfatin also promoted breast tumor growth by upregulating Notch1, which contributed to activation of the

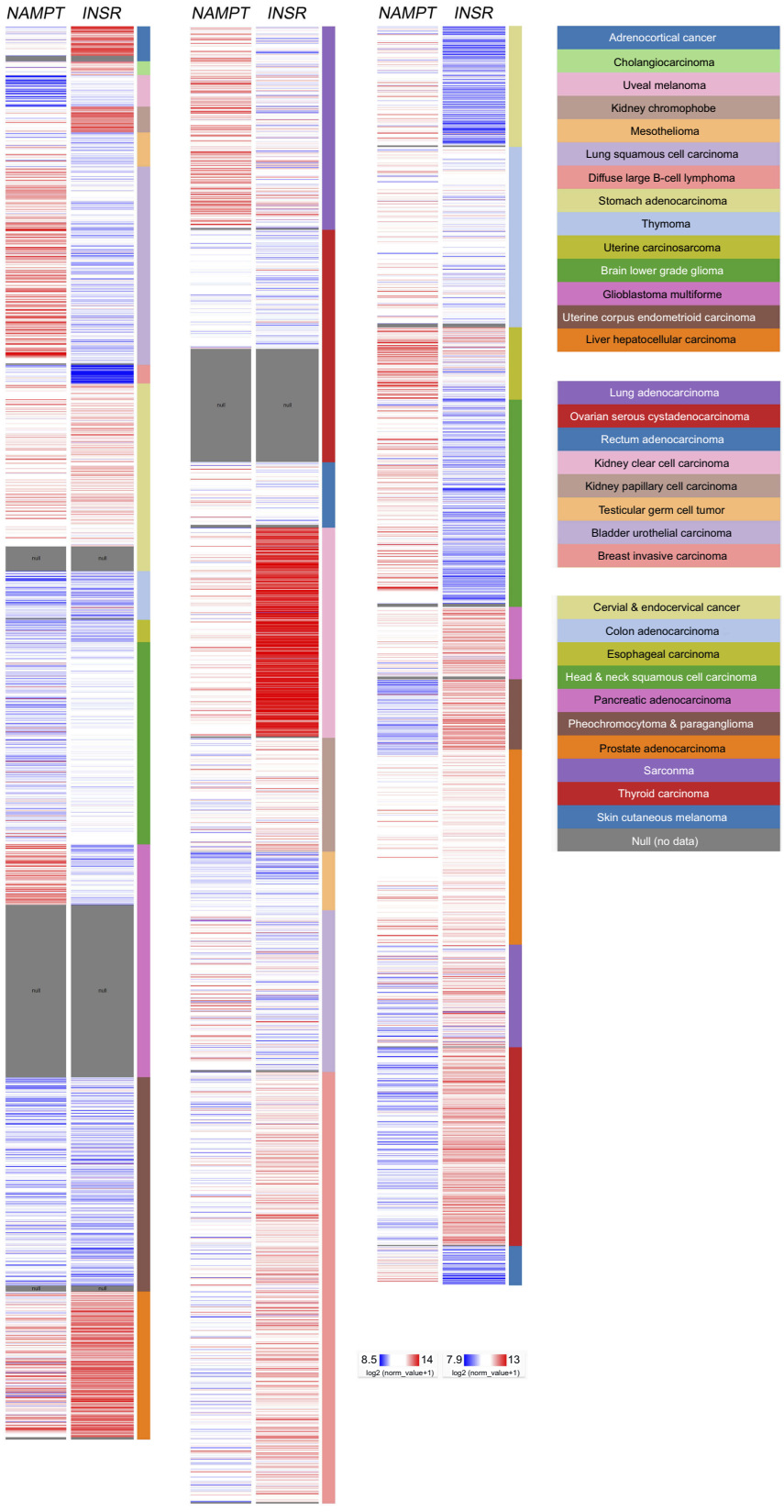

Figure 1 Relative expression of visfatin and potential visfatin receptor in the pan-cancer panel. In The Cancer Genome Atlas pan-cancer dataset, the relative visfatin (*NAMPT*) and potential visfatin receptor (*INSR*) expression levels were presented on a pan-cancer scale. Red color in heat map represents genes with high expression. Blue color in heat map represents genes with low expression.

Table 1 The correlation of visfatin (*NAMPT*) with cancer patient survival

Symbol	Cancer type	Prognosis	Endpoint	*p*-value	Cases	Dataset/cohort	Method	Probe ID
NAMPT	Bladder urothelial carcinoma	–	Overall survival	N.S.	390	TCGA	RNA sequencing	
NAMPT	Glioblastoma multiforme	Poor	Overall survival	0.001	538	TCGA	RNA sequencing	
NAMPT	Breast invasive carcinoma	–	Overall survival	N.S.	962	TCGA	RNA sequencing	
NAMPT	Cervical squamous cell carcinoma	–	Overall survival	N.S.	191	TCGA	RNA sequencing	
NAMPT	Colon and rectum adenocarcinoma	–	Overall survival	N.S.	467	TCGA	RNA sequencing	
NAMPT	Esophageal carcinoma	–	Overall survival	N.S.	184	TCGA	RNA sequencing	
NAMPT	Uveal melanoma	–	Overall survival	N.S.	80	TCGA	RNA sequencing	
NAMPT	Head and neck squamous cell carcinoma	Poor	Overall survival	0.0048	502	TCGA	RNA sequencing	
NAMPT	Acute myeloid leukemia	–	Overall survival	N.S.	168	TCGA	RNA sequencing	
NAMPT	Kidney PAN cancer	Poor	Overall survival	0.0159	792	TCGA	RNA sequencing	
NAMPT	Liver hepatocellular carcinoma	–	Overall survival	N.S.	361	TCGA	RNA sequencing	
NAMPT	Lung adenocarcinoma	–	Overall survival	N.S.	475	TCGA	RNA sequencing	
NAMPT	Ovarian serous cystadenocarcinoma	–	Overall survival	N.S.	578	TCGA	RNA sequencing	
NAMPT	Pancreatic adenocarcinoma	–	Overall survival	N.S.	176	TCGA	RNA sequencing	
NAMPT	Prostate adenocarcinoma	–	Overall survival	N.S.	497	TCGA	RNA sequencing	
NAMPT	Skin cutaneous melanoma	–	Overall survival	N.S.	336	TCGA	RNA sequencing	
NAMPT	Stomach adenocarcinoma	–	Overall survival	N.S.	352	TCGA	RNA sequencing	
NAMPT	Testicular germ cell tumors	–	Overall survival	N.S.	133	TCGA	RNA sequencing	
NAMPT	Thymoma	Poor	Overall survival	0.0226	118	TCGA	RNA sequencing	
NAMPT	Thyroid carcinoma	–	Overall survival	N.S.	489	TCGA	RNA sequencing	
NAMPT	Uterine corpus endometrioid carcinoma	–	Overall survival	N.S.	332	TCGA	RNA sequencing	
NAMPT	Breast cancer	Poor	Relapse-free survival	0.0022	3951	E-MTAB-365, E-TABM-43, GSE: 11,121, 12,093, 12,276, 1,456, 16,391, 16,446, 16,716, 17,705, 17,907,	Array	217739_s_at

(*Continued*)

Table 1 (Continued).

Symbol	Cancer type	Prognosis	Endpoint	*p*-value	Cases	Dataset/cohort	Method	Probe ID
NAMPT	Ovarian cancer	Poor	Post progression survival	0.043	782	18,728, 19,615, 20,194, 20,271, 2,034, 20,685, 20,711, 21,653, 2,603, 26,971, 2,990, 31,448, 31,519, 32,646, 3,494, 37,946, 41,998, 42,568, 45,255, 4,611, 5,327, 6,532, 7,390, 9,195 GSE: 14,764, 15,622, 18,520, 19,829, 23,554, 26,193, 26,712, 27,651, 30,161, 3,149, 51,373, 63,885, 65,986, 9,891, TCGA (N=565)	Array RNA sequencing	217739_s_at
NAMPT	Lung cancer	–	Post progression survival	N.S.	344	CAARRAY, GSE: 14,814, 19,188, 29,013, 30,219, 31,210, 3,141, 31,908, 37,745, 43,580, 4,573, 50,081, 8,894, TCGA (N=133)	Array RNA sequencing	217739_s_at
NAMPT	Gastric cancer	Good	Post progression survival	<0.0001	499	GSE: 14,210, 15,459, 22,377, 29,272, 51,105, 62,254	Array	217739_s_at

Note: Survival data were collected from SurvExpress, The Cancer Genome Atlas (TCGA) and Kaplan–Meier plotter database.
Abbreviations: NAMPT, nicotinamide phosphoribosyltransferase (visfatin); N.S., no significance; GSE, Gene Expression Omnibus (GEO) Series.

NF- B pathway.[27] Furthermore, visfatin induced proliferation of breast cancer MCF-7 and MDA-MB-231 cells, whereas the effect was further inhibited by treatment with AKT and ERK1/2 inhibitors.[28] Induced MCF-7 cell proliferation as well as an increase in both extracellular and intracellular NAD concentrations using visfatin have also been reported by another group, which showed that the effect could be abolished by inhibition of visfatin enzymatic activity.[29] In endometrial cancer, visfatin increased the proliferation of both Ishikawa and KLE cells via promoting G1/S phase progression through the PI3K/Akt and MAPK/ERK1/2 signaling pathways. The regulation of endometrial carcinoma tumor growth was also revealed in a BALB/c-nu mice model.[30] Furthermore, the NAD biosynthetic pathway is essential for RCC growth. The visfatin inhibitor KPT-9274 was shown to interfere with the signaling pathway and resulted in a reduction of G2/M transit as well as an induction of apoptosis in several human RCC cell lines.[31] In addition, NAMPT gene silencing by specific siRNA decreased cell proliferation and increased apoptosis in multiple myeloma RPMI 8226 cells.[32] The pharmacological inhibition of visfatin by its specific inhibitor FK866 together with gemcitabine revealed the antitumor activity in PDAC cells, and in orthotopic xenograft mouse models.[7] A similar inhibitory effect of FK866 was reported in a study of CRC progression. FK866 addition blocked the NAMPT-mediated upregulation of the NAD(H) pool which protected cancer cells against detrimental oxidative stress.[4]

Visfatin and angiogenesis

Visfatin appears to be involved in the regulation of cancer cell angiogenesis. In breast cancer, visfatin increased the expression of the matrix metalloproteinase (MMP)-2, MMP-9 and vascular endothelial growth factor genes, which demonstrates its potential function in angiogenesis.[33] Visfatin induced thromboxane synthase-dependent IL-8 production leading to the activation of angiogenesis in

Table 2 The correlation of visfatin receptor (*INSR*) with cancer patient survival

Symbol	Cancer type	Prognosis	Endpoint	*p*-value	Cases	Dataset/cohort	Method	Probe ID
INSR	Bladder urothelial carcinoma	–	Overall survival	N.S.	390	TCGA	RNA sequencing	
INSR	Glioblastoma multiforme	–	Overall survival	N.S.	538	TCGA	RNA sequencing	
INSR	Breast invasive carcinoma	–	Overall survival	N.S.	962	TCGA	RNA sequencing	
INSR	Cervical squamous cell carcinoma	–	Overall survival	N.S.	191	TCGA	RNA sequencing	
INSR	Colon and rectum adenocarcinoma	–	Overall survival	N.S.	467	TCGA	RNA sequencing	
INSR	Esophageal carcinoma	–	Overall survival	N.S.	184	TCGA	RNA sequencing	
INSR	Uveal melanoma	Good	Overall survival	0.0015	80	TCGA	RNA sequencing	
INSR	Head and neck squamous cell carcinoma	Poor	Overall survival	0.0558	502	TCGA	RNA sequencing	
INSR	Acute myeloid leukemia	Good	Overall survival	0.0039	168	TCGA	RNA sequencing	
INSR	Kidney PAN cancer	–	Overall survival	N.S.	792	TCGA	RNA sequencing	
INSR	Liver hepatocellular carcinoma	–	Overall survival	N.S.	361	TCGA	RNA sequencing	
INSR	Lung adenocarcinoma	–	Overall survival	N.S.	475	TCGA	RNA sequencing	
INSR	Ovarian serous cystadenocarcinoma	–	Overall survival	N.S.	578	TCGA	RNA sequencing	
INSR	Pancreatic adenocarcinoma	–	Overall survival	N.S.	176	TCGA	RNA sequencing	
INSR	Prostate adenocarcinoma	–	Overall survival	N.S.	497	TCGA	RNA sequencing	
INSR	Skin cutaneous melanoma	–	Overall survival	N.S.	336	TCGA	RNA sequencing	
INSR	Stomach adenocarcinoma	Poor	Overall survival	0.0404	352	TCGA	RNA sequencing	
INSR	Testicular germ cell tumors	–	Overall survival	N.S.	133	TCGA	RNA sequencing	
INSR	Thymoma	–	Overall survival	N.S.	118	TCGA	RNA sequencing	
INSR	Thyroid carcinoma	–	Overall survival	N.S.	489	TCGA	RNA sequencing	
INSR	Uterine corpus endometrioid carcinoma	–	Overall survival	N.S.	332	TCGA	RNA sequencing	
INSR *INSR*	Breast cancer	Good	Relapse-free survival	<0.0001	1764	E-MTAB-365, E-TABM-43, GSE: 11,121, 12,093, 12,276, 1,456, 16,391, 16,446, 16,716, 17,705, 17,907,	Array	226450_at

(*Continued*)

Table 2 (Continued).

Symbol	Cancer type	Prognosis	Endpoint	*p*-value	Cases	Dataset/cohort	Method	Probe ID
INSR						18,728, 19,615, 20,194, 20,271, 2,034, 20,685, 20,711,		
INSR						21,653, 2,603, 26,971, 2,990, 31,448, 31,519, 32,646,		
INSR						3,494, 37,946, 41,998, 42,568, 45,255, 4,611, 5,327,		
INSR						6,532, 7,390, 9,195		
INSR	Ovarian cancer	–	Post progression survival	N.S.	382	GSE: 14,764, 15,622, 18,520, 19,829, 23,554, 26,193,	Array	226450_at
INSR						26,712, 27,651, 30,161, 3,149, 51,373, 63,885, 65,986,	RNA sequencing	
INSR						9,891, TCGA (N=565)		
INSR	Lung cancer	Poor	Post progression survival	0.053	138	CAARRAY, GSE: 14,814, 19,188, 29,013, 30,219,	Array	226450_at
INSR						31,210, 3,141, 31,908, 37,745, 43,580, 4,573, 50,081,	RNA sequencing	
INSR						8,894, TCGA (N=133)		
INSR	Gastric cancer	Poor	Post progression survival	0.0025	499	GSE: 14,210, 15,459, 22,377, 29,272, 51,105, 62,254	Array	226450_at

Note: Survival data were collected from SurvExpress, The Cancer Genome Atlas (TCGA) and Kaplan–Meier plotter database.
Abbreviations: INSR, insulin receptor; N.S., no significance; GSE, Gene Expression Omnibus (GEO) Series.

endothelial cells.[34] Visfatin exerted an angiogenic effect through activation of the mTOR pathway, thereby increasing the expression of vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1α in human endothelial cells.[35] Furthermore, visfatin stimulated fibroblast growth factor 2 gene expression in a Notch1-dependent manner, which triggered tube formation of endothelial cells.[36] Visfatin promoted endothelial cell angiogenesis via IL-6, and its functions demonstrated by the tube formation, the rat aortic ring assay, and the mouse Matrigel plug assay were further eliminated by the inactivation of STAT3 signaling or the neutralization of IL-6 activity.[37] In addition, visfatin showed the dosage and time-dependent effects in terms of the increase in tube formation capacity via the PI3K/DDAH2/VEGF pathway in human umbilical vein endothelial cells, whereas the angiogenic effect was inhibited by dimethylarginine dimethylaminohydrolase 2 (DDAH2) siRNA and PI3K inhibitors.[38] The results from another group further indicated that 24-h treatment with visfatin (400 ng/mL) significantly increased capillary tube formation, the mechanism of which was shown to be via activation of the MCP-1/CCR2 receptor axis in endothelial cells.[39] Another group also suggested that visfatin increased gene expression and protein production of VEGF and MMP-2/9, and suppressed expression of tissue inhibitors of MMPs (TIMP-1 and TIMP-2) in a dose-dependent manner, which led to capillary-like tube formation.[40] Importantly, visfatin significantly triggered in vivo neovascularization in chick chorioallantoic membrane and mouse Matrigel plug assays.[41] The combination of GMX1777, which inhibits visfatin activity, with radiotherapy has been explored in head and neck cancer in vivo. Tumor microvessel density was estimated using the CD31 expression level, which was significantly reduced to 18% after GMX1777 treatment alone ($p<0.01$) and 4% when combined with radiotherapy ($p<0.01$) in FaDu tumors.[42]

Visfatin and metastasis

The visfatin level is clinically correlated with cancer metastasis in different cancer types. Patients with endometrial cancer have significantly higher visfatin levels than controls (p=0.011), and the association of visfatin with deep myometrial invasion (p=0.019) was also observed.[43] In addition, elevated levels of visfatin in the serum of small cell lung cancer (SCLC) patients correlated with brain metastasis.[44] Furthermore, the positive correlation of plasma visfatin with cancer invasion depth, lymph node metastasis, distant metastasis and tumor node metastasis stage was observed in gastric cancer patients.[18] Visfatin also plays critical roles in the modulation of cancer cell metastasis. In non-SCLC, the visfatin plasma level was found to be associated with lymph node metastasis (p=0.015) and distant metastasis (p=0.003). Visfatin (100 ng/ml) triggered wound closure, migration and invasion as well as the upregulation of MMP-2 and MMP-9 in A549 and H358 cells, whereas those effects were blocked by BAY 11-7082 (NF- B inhibitor).[45] Similar associations between serum visfatin and clinical pathologic variables were observed in breast cancer patients along with regulation of MDA-MB-231 cell migration and invasion capabilities via c-Abl and STAT3 activation.[16] The induction of the epithelial–mesenchymal transition process by visfatin was investigated in CRC, and the results indicated that visfatin could upregulate Snail in CRC cells by activating Akt/GSK-3β/β-catenin signaling.[15] Furthermore, visfatin was found to significantly increase the in vitro migration and invasion capability of osteosarcoma MG-63 and HOS cells, and to upregulate MMP-2 and fibronectin expression through the NF- B/IL-6 signaling axis.[46] In addition, ascites-derived visfatin was investigated for its potential biological impact during ovarian cancer progression. Ascites-derived visfatin was found to augment migration of ovarian cancer cells via the Rho/ROCK axis, which triggered actin polymerization, actin stress fiber aggregation and formation of lamellipodia and filopodia.[47] Importantly, visfatin appeared to promote CC chemokine ligand 2-dependent SCLC NCI-H446 cell migration through human brain microvascular endothelial cells using an in vitro blood–brain barrier model.[44] On the contrary, visfatin knockdown in breast cancer cells revealed significant increase in metastatic activity as compared with the control shRNA-transduced cells. It was proposed that the reduction in NAD^+ synthesis led to aggressiveness of MDA-MB-231 breast cancer cells.[48]

Visfatin and drug resistance

Emerging studies have suggested the involvement of visfatin in cancer drug resistance. In CRC, plasma visfatin might serve as a prognostic indicator for poor response upon 5-fluorouracil chemotherapy because a higher visfatin level was observed in patients who experienced disease progression compared with those in partial response and the stable disease group.[4949] In addition, visfatin appeared to decrease doxorubicin sensitivity in NSCLC A549 and H1793 cells via activation of the Akt/ABCC1 signaling axis. The visfatin protein and mRNA expression levels were found to be significantly increased in doxorubicin-resistant NSCLC cells, and visfatin appeared to increase the binding of Akt toward the ABCC1 promoter region, leading to its upregulation.[50] Furthermore, the visfatin level was increased in established doxorubicin-resistant CRC HCT-116 and SW480 cells. Visfatin silencing resulted in the elevation of drug sensitivity in CRC-resistant cells through transcriptional activation of multidrug resistance 1 (MDR1) via p65 activation and nuclear localization.[51] The visfatin inhibitor GMX1778 further showed an enhancement in the efficacy of 177Lu-DOTATATE treatment for neuroendocrine tumors.[5252] Moreover, pharmacological suppression of visfatin by the inhibitor FK866 decreased the NAD level and glycolytic activity, which led to an elevated antitumor capability of gemcitabine in orthotopic xenograft animal models and PDAC cells.[7] Another study indicated that suppression of vistatin signaling by the inhibitors FK866 and CHS828 could sensitize glioblastoma to temozolomide treatment via activation of the ROS/JNK axis.[53] In myeloma, the combination of NAD^+ depletion by FK866 and bortezomib activated caspase 8, caspase 9, caspase 3 and poly(ADP-ribose) polymerase, leading to synergistic effects in triggering cell death and increasing bortezomib sensitivity. The results of that study also suggested the impact of visfatin in myeloma drug resistance.[22]

Discussion and conclusions

The results from publications and in silico analysis revealed the expression of visfatin and its potential receptor in various types of cancer. Moreover, the critical roles of visfatin in regulating processes relevant to cancer progression, including cancer cell proliferation, angiogenesis, metastasis and drug resistance, have also been illustrated. In this review, we demonstrate the relative levels of visfatin and potential visfatin receptor on a pan-cancer scale which indicates the consensus upregulation of the axis in stomach adenocarcinoma, liver hepatocellular carcinoma, kidney clear cell carcinoma and prostate adenocarcinoma. This points out the potentially critical role of this axis

in tumor progression. In addition, the differential expression of visfatin and its potential receptor at the RNA level in specific cancer types suggests that the alterations in transcriptional activity and RNA stability might be of value for further studies on the mechanism of tumorigenesis and cancer progression. As regards exploration of the prognostic value of visfatin and its potential receptor, the signaling axis concurrently serves as a poor prognostic indicator in head and neck squamous cell carcinoma. On the contrary, the prognostic trend of this axis reveals a discrepancy in several types of cancers. Therefore, the impact of this axis in those tumor types remains to be determined based on additional evidence. Moreover, the differences raised by analytic platforms and endpoint designs of studies are also a concern. The differences in the number of cases enrolled in each cohort also limit the prognostic power. In addition to the variations caused by experimental design, another possibility is that the visfatin-dependent effects are alternatively induced by other receptors. It is noticed that the receptors mediating visfatin's downstream signaling are still under debate.[25,54,55]

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Author contributions

The author contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The author reports no conflict of interest in this work.

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