REVIEW

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Gpnmb/osteoactivin: an indicator and therapeutic target in tumor and non-tumorous lesions

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Non-metastatic melanoma glycoprotein B (Gpnmb), a type I transmembrane glycoprotein, was first cloned and described in low-metastatic human melanoma and xenografts in 1995. Up to now a growing number of studies have confirmed that Gpnmb is expressed not only in numerous normal tissues but also at pathological sites and malignant tissues and often connected with the invasive and metastatic phenotypes, including breast cancer. Nowadays, immunotherapeutic approaches for cancer therapy, by which monoclonal antibodies (Mabs) target tumor specific antigens, have shown great potential. Glembatumumabvedotin, also called CR011-vcMMAE, is a Mab-drug conjugate which was developed for the treatment of Gpnmb-expressing cancers. Several phase I/II studies have confirmed the safety and activity of glembatumumabvedotin in patients with advanced/metastatic breast cancer and unresectable cutaneous melanoma. Moreover, increasing numbers of studies have supported the potential roles of targeting Gpnmb with glembatumumabvedotin in patients with recurrent osteosarcoma, uveal melanoma, ALS, Gaucher disease, pancreatic ductal adenocarcinoma etc. This review will summarize the latest understanding of Gpnmb in the aspects of diagnosis, progression and prognosis of pathological disorders and neoplasms, emphasizing the clinical advances in targeting Gpnmb-expressing malignancies.

1. Introduction

Non-metastatic melanoma glycoprotein B (Gpnmb) is a type I transmembrane glycoprotein that consists of an N-terminal domain with a signal peptide, an integrin-binding (RGD) motif and a polycystic kidney disease domain (PKD) domain in its extracellular domain (ECD), a single pass transmembrane domain and 253 amino acid (AA) cytoplasmic tail (Selim 2009). The Gpnmb gene was originally isolated from a meta- static melanoma cell line (Weterman et al. 1995). In normal tissue, this gene is also known as dendritic cell-associated heparin sulfate proteoglycan-dependent integrin ligand (DC-HIL) (Shikano et al. 2001), osteoactivin (OA), or hematopoietic growth factor inducible neurokinin-1 type (HG-FIN) located on the small arm of chromosome7 (7p15) (Safadi et al. 2001). It is not only expressed in numerous normal tissues and cells including macrophage and dendritic cells in the immune system (Ripoll et al. 2007; Ahn et al. 2002), osteoblasts (Abdelmagid et al. 2008) and osteoclasts (Sheng et al. 2008) in the bone, renal tubular epithelial and renal interstitialintheurinary system, melanocytes and keratinocytes in the skin (Hoashi et al. 2010; Owen et al. 2003), microglia and neuron in the central nervous system, but also abnormally expressed in an increasing number of pathological disorders and malignant tissues, such as colitis, nonalcoholic steatohepatitis, glaucoma, acute liver injury, renal tumor, pancreatic cancer, hepatocellular carcinoma, prostate cancer, glioma, melanoma, breast cancer cells, etc. The properties of being highly expressed at the surface of cancer cells but mainly expressed intracellularly in normal cells (Zhou et al. 2012) and promoting migration, invasion, metastasis of tumor cells and independent prognostic indicator for recurrence (Rose et al. 2010), make Gpnmb attract more and more attention in the fields of diagnosis, targeted therapy and response evaluation of tumors. This review will discuss the latest understanding of Gpnmb in the aspects of diagnosis, progression and prognosis in pathological disorders and neoplasms, especially detailing the clinical advances in targeting Gpnmb-expressing malignancies.

2. Gpnmb and cancer

2.1 Breast cancer

Gpnmb is a transmembrane protein expressed in approximately 40–75% of breast cancers, and the Gpnmb gene is expressed in the tumor epithelium of approximately 10% of human breast cancers and the stromal compartment of nearly 70% of breast tumors. Gpnmb expression is a prognostic indicator of breast cancer recurrence in all breast cancer subtypes, especially in “triple negative” breast cancers (Rose et al. 2007). April et al. signified that primary human breast cancers with high vascular density also displayed increased levels of Gpnmb when compared to those with low vascular density. In addition, Gpnmb expression promotes tumor growth, which is associated with enhanced endothelial recruitment. ADAM10, a kind of sheddase, is able to release the Gpnmb ectodomain from the surface of breast cancer cells, resulting in inducing endothelial cell migration. Therefore, the ectodomain shedding of Gpnmb may explain the mechanism why Gpnmb promotes angiogenesis in breast cancer (Rose et al. 2010). In 2015, Maric et al. identified novel and distinct molecular mediators of GPNMB-induced breast cancer growth and metastasis. They showed that GPNMB engaged distinct functional domains and mechanisms to promote primary tumor growth and metastasis and neuropilin-1 (NRP-1) expression is increased in breast cancer cells that overexpress Gpnmb. They ascribed pro-growth and pro-metastatic functions of Gpnmb to its ability to bind α5β1 integrin and increase downstream signaling in breast cancer cells (Maric et al. 2015).

Breast cancer is the most common malignancy in women all over the world. Although multi-modality treatments exist , the mortality rate of advanced breast cancer is persistently high (Keir and Vahdat 2012). According to gene expression analyses, primary human breast tumors could be classified into distinct molecular subtypes, including normal-like, luminal, human epidermal growth factor receptor 2–positive (HER2+), and basal-like breast cancers, which has implications for disease management (Perou et al. 2000; Sorlie et al. 2003). Breast tumors in different subtypes display distinct

organ-specific patterns of recurrence and treatment, for example, basal-like breast cancers are more aggressive in nature and more inclined to metastasize to the brain and lung (Fadare and Tavassoli 2008). Luminal breast tumors are generally responsive to hormonal therapies (Moulder and Hortobagyi 2008). HER2+ tumors are treated primarily with HER2-targeted therapies such as trastuzumab or lapatinib. However, no targeted therapeutic is currently available for patients with triple-negative breast cancers. CR011-vcMMAE, which is also called glembatumumabvedotin or CDX-011, combines the tumor-targeting specificity of a Mab (CR011) and the cytotoxic activity of a potent antimitotic compound (MMAE). It is a Gpnmb-targeted therapeutic that belongs to a class of drugs known as antibody-drug conjugates (ADCs) (Tse et al. 2006). Several studies have shown that glembatumumabvedotin is safe and active in patients with advanced breast cancer, especially the basal/triple-negative subtype, providing a strong rationale to continue to explore this drug in patients with GPNMB-expressing breast tumors (Keir and Vahdat 2012; Rose et al. 2010; Carter and Senter 2008). Masako Kanematsu et al. thought that Gpnmb may crosstalk with the HER2 signal pathway and act as an important player in anti-HER2 therapy, in which they compared the serum Gpnmb *in vivo* in 162 breast cancer [BC] patients and in 88 controls (50 colorectal cancer [CC] and 38 gastrointestinal cancer [GC] patients). The results showed that the GPNMB level was significantly higher in BC patients than in CC patients and the HER2-rich subtype of BC patients had significantly higher Gpnmb levels than other subtypes. Gpnmb depletion by small interfering RNA (siRNA) increased both HER2 expression and phosphorylation *in vitro*. Therefore GPNMB may emerge as an important player in anti-HER2 therapy (Kanematsu et al. 2015). Johanna Bendell et al also conducted a phase I/II study of glembatumumabvedotin in patients with locally advanced or metastatic breast cancer. Glembatumumabvedotin is a human monoclonal antibody-drug conjugate that targets the extracellular domain of GPNMB. The antibody is conjugated *via* an enzyme-sensitive linker to the antimitotic agent monomethylauristatin E (MMAE), which blocks tubulin polymerization. Upon binding to Gpnmb and internalization of the antibody-drug conjugate, the drug is cleaved, and microtubule inhibition leads to cell cycle arrest and apoptosis (Tse et al. 2006).
Fourty-two patients with advanced/metastatic breast cancer with at least two prior chemotherapy regimens, including taxane, anthracycline, and capecitabine were enrolled. At the phase II dose (1.88 mg/kg), median PFS was 9.1 weeks for all patients, 17.9 weeks for patients with triple-negative breast cancer (TNBC), and 18.0 weeks for patients with Gpnmb-positive tumors. Two patients had confirmed partial responses, both had Gpnmb-positive tumors and one had TNBC, the results of which suggested that glembatumumabvedotin has an acceptable and manageable safety profile, and that activity may be enhanced in patients with TNBC and/or tumor expression of Gpnmb (Bendell et al. 2014). Another phase II study in advanced Gpnmb-overexpressing breast cancer also demonstrated an association between the tumor Gpnmb expression and activity of glembatumumabvedotin, and elevated Gpnmb expression (>25% positive in epithelial cells) was detected in 41% of triple-negative breast cancer tumors (Yardley et al. 2015).

2.2. Prostate cancer

In order to investigate the expression of Gpnmb in prostate cancer, Xiao et al. analyzed 63 prostate cancer and 3 heterosexual hyperplasia prostate tissue and 8 benign prostatic hyperplasia (BPH) samples by immunohistochemical staining, the result of which signified that the expression of Gpnmb in tumor was higher than in non-tumor group, including BPH and atypical hyperplasia (P=0.0001) and Gpnmb expression level was not positively correlated with the degree of malignancy of prostate cancer, which meant that the higher the pathological grading was, the lower the expression of Gpnmb was (Xiao et al. 2011). Then Tsui et al. explored the function or regulation of Gpnmb in human prostate carcinoma cells. They found that the expression of Gpnmb in prostate cells may be related to the extent of neoplasia *in vitro* and ectopic overexpression of Gpnmb greatly attenuated cell proliferation and invasion and exerted antitumorigenic activity on PC-3 cells *in vitro* and *in vivo*, which was depended on the enhancement of Ndrg1 and maspin gene expressions. Therefore the Gpnmb gene should be regarded as an anti-tumor gene for prostate cancer (Tsui et al. 2012). To the contrary, in a recent study Gpnmb was considered as a critical molecular mediator helping to acquire the more aggressive, pro-metastatic phenotype distinctive of human metastatic DU145 and PC3 prostate cancer cells, since small interfering RNA-induced Gpnmb/OA silencing could strongly inhibit the migration capability of both DU145 and PC3 cells as well as the metalloproteinases MMP-2 and MMP-9 activity (Fiorentini et al. 2014). More studies are needed to further explore the role of Gpnmb in human prostate cancer.

2.3. Lung cancer

As for the role of Gpnmb in small cell lung cancer (SCLC), a recent study evaluated the levels of Gpnmb expression in tissues and serum Gpnmb in patients with SCLC and the healthy control. According to the level of Gpnmb expression, the patients with SCLC were divided into weaklypositive and stronglypositive Gpnmb groups. This study revealed that the stronglypositive group showed significantly higher serum Gpnmb levels than the weaklypositive group and healthy controls, moreover the overall survival time in the weaklypositive Gpnmb group was considerably longer than that in the stronglypositive group (27 months *vs* 15 months, $p < 0.01$) (Li et al. 2014).

3. Gpnmb and skin

Gpnmb is expressed in normal cells of the skin, such as melanocytes, keratinocytes and Langerhans cells (Hoashi et al. 2010), in addition to this, it is also aberrantly expressed in inflammatory and malignant skin lesions. Zhao Yan et al. investigated the expression of Gpnmb in benign and malignant skin diseases. The skin tissues were from 102 cases including malignant melanoma (MM, n=15), squamous cell carcinoma (SCC, n=20), basal cell carcinoma (BCC, n=15), and benign dermatosis (n=52) and 20 cases of normal skin and adjacent neoplastic normal skin tissues as controls, which showed that Gpnmb was significant higher expressed in MM (13/15, 87%) and SCC (16/20, 80%) than that in the control and the benign skin tissues, but there was no significant difference in the expression rates between normal control and BCC (Zhao et al. 2012).
Recently, many studies were focused on the role of Gpnmb in the pathogenesis and development of melanoma. Excessive production of melanin in the skin may induce pigment-related diseases such as melanoma. Since endothelin-1 (ET-1) plays an indispensable role in epidermal pigmentation and Gpnmb is a key element in melanosome formation, Ping Zhang et al. supposed that Gpnmb was correlated with ET-1 induced pigmentation. Their study found that melanin synthesis in human melanocytes was significantly upregulated after culturing with ET-1, accompanied by an increased expression of Gpnmb and microphthalmia associated transcription factor (MITF). Total number of melanosomes and melanin synthesis were sharply reduced after Gpnmb-siRNA transfection. Furthermore, MITF-siRNA transfection strikingly inhibited Gpnmb expression and melanogenesis. The results demonstrated that ET-1 can trigger melanogenesis *via* the MITF-regulated Gpnmb pathway (Zhang et al. 2013). Moreover, Tomihari et al. confirmed that Gpnmb knockout significantly reduced the growth of B16F10 melanoma cells *in vivo* following their s.c. injection into syngeneic immunocompetent mice. Gpnmb was able to suppress the activation of T-cells *via* binding to syndecan-4 on the surface of activated T cells and inducing its autophosphorylation, therefore allowing melanoma to evade immunologic recognition and destruction (Chung et al. 2007; Tomihari et al. 2010).
As for treatment, Glembatumumabvedotin has been confirmed to induce complete regression in 100% of Gpnmb expressing SK-Mel-2- and SK-Mel-5-xenografted melanoma tumors (Pollack et al. 2007). And the efficacy of Gpnmb may be increased by combining with other drugs, including imatinib and inhibitors of the Erk pathway, which could improve the cell-surface expression of Gpnmb in cancer cells (Qian et al. 2008). Recently, Patrick A. Ott et al. designed a phase I/II study to assess the safety and activity of glembatumumabvedotin in patients with unresectable stage III or stage IV melanoma, the result of which showed that Glembatumumabvedotin is active in advanced

melanoma. The recommended phase II dose of glembatumumabvedotin (1.88 mg/kg once every 3 weeks) was generally well tolerated, with a promising objective response rate (ORR) and more frequent dosing may be associated with a higher ORR but resulting in increased toxicity, such as rash (Ott et al. 2014).

pigmentary glaucoma involving iris pigment dispersion (IPD) and iris stromal atrophy (ISA) as the study subject to explore the connection between the gene mutations and pigmentary glaucoma. They found that IPD is caused by a premature stop codon mutation in the Gpnmb (GpnmbR150X) gene, as proved by the occurrence of IPD only in D2

Table: Clinical trials related to Gpnmb

Reference	Country	No. of subjects	Phase of clinical trial	Results
Bendell et al. (2014)	USA	42	Phase I/II study	At the phase II dose, median PFS was 9.1 weeks for all patients, 17.9 weeks for patients with TNBC, and 18 weeks for patients with Gpnmb-positive tumors. Glembatumumabvedotin has an acceptable safety profile.
Yardley et al. (2015)	USA	124	Phase II study	Glembatumumabvedotin is well tolerated in heavily pretreated patients with breast cancer.
Zhao et al. (2012)	China	102	/	Over-expression of Gpnmb correlated strongly and might play an important role in the pathogenesis of malignant melanoma (13/15, 87%) and squamous cell carcinoma (16/20, 80%).
Ott et al. (2014)	USA	117	Phase I/II study	Glembatumumabvedotin is active in advanced melanoma. The schedule 1 MTD (1.88 mg/kg once every 3 weeks) was associated with a promising ORR and was generally well tolerated.
Williams et al. (2010)	USA	22	/	Eighteen of 21 tumors were expressed Gpnmb in 10-90% of tumor cells, among which eleven of 18 tumors (61.1%) expressed Gpnmb in >or=50% of cells. Uveal melanoma commonly expresses Gpnmb.
Roth et al. (2016)	USA	67	/	Gpnmb is expressed in osteosarcoma and targeting Gpnmb with the antibody-drug conjugate glembatumumabvedotin demonstrates osteosarcoma cytotoxic activity.
Xiao et al (2011)	China	74	/	The expression of Gpnmb in tumor was higher than in non-tumor group, which included BPH and atypical hyperplasia. The detection of Gpnmb may be useful for the early diagnosis of prostate cancer.
Li et al. (2014)	China	132	/	For patients with SCLC, the overall survival in the weak-positive GPNMB expression group was significantly longer than in the strong-positive group (27 months vs 15 months, $p < 0.01$), suggesting that the expression of GPNMB may be useful as a prognostic indicator in patients with SCLC.

TNBC, triple-negative breast cancer; MTD, maximum-tolerated dose; ORR, objective response rate; BPH, benign prostatic hyperplasia.

4. Gpnmb and eyes

Uveal melanoma, the most common primary intraocular tumor in adults, is similar to cutaneous melanoma in terms of morphological features and immunonophenotypic markers but different from cutaneous melanomas in etiological factors, clinical course and genomic alterations (Triozzi et al. 2008; Singh et al. 1996). Since only few therapeutic agents have an effect against uveal melanoma cells, the prognosis of patients with uveal melanoma is poor (Singh and Topham 2003). Michelle Williams et al. thought that the identification of factors shared in common between cutaneous and uveal melanomas may signify that a certain treatment for cutaneous melanoma, known as CDX-011, may be applicable to uveal melanoma as well, therefore they evaluated the primary uveal melanoma for reactivity to CDX-011. They found that Gpnmb was expressed in the majority (85.7%) of uveal melanomas, similar to that reported earlier in cutaneous melanomas (80%). Based on the natural history of uveal melanoma that a third of the high-risk tumors have metastasized within the first 2 years of follow-up resulting in death, therapeutic agents for the treatment of patients with metastatic disease are needed. CDX-011, a novel targeted therapy which has been confirmed safe and effective in patients with cutaneous melanoma, should also be investigated in patients with metastatic uveal melanoma (Ott et al. 2014; Williams et al. 2010).

Pigmentary glaucoma is an important cause of human blindness, characterized by increased intraocular pressure (IOP) which is induced by abnormally liberating iris pigment and cell debris entering the ocular drainage structures. Anderson et al. chose DBA/2J (D2) with a form of mice that are homozygous with respect to GpnmbR150X and indicated that pigment production and mutant melanosomal protein genes, such as Gpnmb, may contribute to human pigmentary glaucoma (Anderson et al. 2002). Moreover, a previous study also confirmed that Gpnmb as an intracellular, endosomal/melanosomal compartment specific protein was important for melanin biosynthesis and the development of the retinal pigment epithelium and iris (Bachner et al. 2002).

Since genetic studies of TYRP1 and Gpnmb in human pigment dispersion patients have not detected mutations, people are suggesting that other genes in a pathway linked to TYRP1 and Gpnmb may be the next most logical candidates worth to be considered (Lynch et al. 2002; Anderson et al. 2002). Recently, Colleen et al. explored genes that may contribute to ocular diseases including OCA, pigment dispersion syndrome and exfoliation syndrome by analyzing the genoma-wide iris gene expression patterns from mouse (C57BL/6J) models of these diseases. Compared with the wild-type C57BL/6J mice, every disease showed a lot of statistically significant changes in gene expression, for example albino mice with a Tyr mutation, pigment dispersion–prone mice with TYRP1 and Gpnmb mutations, and mice resembling exfoliation syndrome with a Lyst mutation, which represent a useful resource for further mechanistic studies (Trantow et al. 2011).

5. Gpnmb and bone

In 2001, Safadi et al. firstly pointed out that osteoactivin (OA) played an important role in osteoblast differentiation and matrix mineralization, the expression of which in bone was by mature, matrix producing osteoblasts and osteoblast-specific. Inhibition of

OA by neutralizing antibodies or siRNA, in developing osteoblasts inhibited their differentiation and ability to produce bone matrix (Selim et al. 2003; Abdelmagid et al. 2007). Bone regeneration is a coordinated process involving the connection between blood vessels and bone cells. And fibroblast growth factor receptor (FGFR)-mediating signaling is pivotal in bone formation and angiogenesis. Therefore Hu et al. regarded Gpnmb function as a communicating molecule between osteoblasts and angiogenesis, and explored the possible correlation between Gpnmb and FGFR-1 signaling. Recombinant Gpnmb dose-dependently increased the differentiation of human bone marrow stromal cells (hBMSCs) into osteoblasts, as well as the mRNA levels of osteoblast markers alkaline phosphatase (ALP) and osteocalcin (OCN), relying on the activation of FGFR-1 signaling. They concluded that Gpnmb stimulates bone regeneration by inducing osteogenesis and angiogenesis *via* regulating FGFR-1 signaling (Hu et al. 2013). Gpnmb also acts as a matricellular protein that stimulates osteoblast adhesion through binding to αv β1 integrin and cell surface HSPGs, resulting in increased cell spreading, actin reorganization, and osteoblast differentiation, showing a positive role in osteogenesis (Moussa et al. 2014). In addition to that, OA/Gpnmb acts as a negative regulator of osteoclast differentiation and survival but not through inhibiting the ERK/AKT signaling pathways (Abdelmagid et al. 2015). OA was also expressed in muscle and played a role in wound healing and its expression was shown to increase in post fracture calluses, denervation and unloading stress (Nikawa et al. 2004; Abdelmagid et al. 2010; Arosarena et al. 2011). Then the same group made an analysis to figure out the regulatory mechanisms of OA in muscle and bone, which signified that OA is able to induce transdifferentiation of myoblasts into osteoblasts through increasing levels of phosphorylated FAK (Sondag et al. 2014).

In regard to bone tumors, recent studies showed that Gpnmb may be expressed in osteosarcoma (Kubista et al. 2011). Osteosarcoma is the most common malignant primary bone tumor in children. Although chemotherapy in combination with surgery introduced in the 1970s has increased the long-term survival for patients without metastatic disease, the cure rates for these patients have remained 60-70% in the past 3 decades. Treatments for patients with metastatic and relapsed osteosarcoma remain dismal with a poor prognosis, emphasizing the need for novel treatments to improve survival (Gill et al. 2013). In 2014, the Pediatric Preclinical Testing Program (PPTP) demonstrated that targeting Gpnmb with glembatumumabvedotin inhibits tumor cell growth in xenograft models of osteosarcoma (Kolb et al. 2014). Recently, Michael Roth et al. explored the potential utility of glembatumumabvedotin in patients with osteosarcoma. Tumor tissues were obtained from 67 patients with osteosarcoma at the time of initial biopsy, definitive surgery, or at disease recurrence. Gpnmb was expressed in >90% of all osteosarcoma tumor specimens and 100% of recurrent tumor specimens, paired with glembatumumabvedotin *in vitro* and *in vivo* cytotoxicity in osteosarcoma cell lines, supporting the potential development of a prospective clinical trial targeting Gpnmb with glembatumumabvedotin in patients with recurrent osteosarcoma (Roth et al. 2016).

6. Gpnmb and kidney

The expression of Gpnmb in renal cell carcinoma (RCC) (Qin et al. 2013) and its role as independent risk factor for clear-cell renal cell carcinoma (ccRCC) have been confirmed before (Qin et al. 2014). Moreover, Gpnmb was a kind of sensitive indicators for kidney injury after acute cyclosporine A toxicity in SD rats, which were more sensitive than serum creatinine. Gpnmb was mainly expressed in the tubular epithelial cells and renal interstitium (Ye et al. 2011). In addition, the expression of Gpnmb in renal tissues also increased in diabetic nephropathy and the elderly kidney (Rodwell et al. 2004; Schmid et al. 2006). Gpnmb expression was significantly elevated in intact monocytes of dialysis patients (n=21) (8.6-fold), compared to a negligible expression in control subjects (n=22). *In vitro*, the monocyte-to-macrophage transformation resulted in a increased expression of Gpnmb in cells from both dialysis patients and the control group, but much more in dialysis patients (17.5-fold higher). Uremic macrophages exhibit increased Gpnmb expression and heightened expression of pro-inflammatory and a suppressed expression of anti-inflammatory cytokines. Further studies are needed to figure out the role of Gpnmb expressed from intact monocytes in the pathogenesis of ESRD-associated inflammation and vascular calcification (Pahl et al. 2010).

Birt-Hogg-Dubé syndrome (BHD) is an inherited disorder associated with a germline mutation of the folliculin gene (FLCN). Affected families have a high risk for developing multiple renal cell carcinomas (RCC). It is meaningful to distinguish between FLCN-related RCC and sporadic RCC since many patients with undiagnosed BHD fail to receive proper medical care. In consideration that Gpnmb has been identified as a downstream targeting molecule induced by FLCN inactivation (Hong et al. 2010), Furuya (2015) used western blotting and immunohistochemical staining to compare the expression levels of FLCN and Gpnmb between FLCN-related RCCs and sporadic renal tumors (n=62),which revealed that FLCN-related RCCs showed overexpression of Gpnmb and underexpression of FLCN, whereas sporadic tumors showed inverted patterns. The distinctive expression patterns of Gpnmb and FLCN might identify patients with RCCs who need further treatment for BHD.

7. Gpnmb and the nervous system

Malignant glioma, such as glioblastoma multiforme (GBM), are highly aggressive and account for almost 50% of all brain neoplasms. Until now no effective treatment exists, leaving glioma patients an average survival time of about one year after diagnosis, even after surgical tumor resection, radiotherapy or chemotherapy (Wen and Kesari 2008). Glioma-associated microglia/macrophages (GAMs) have been confirmed to actively support glioma growth by the release of factors that stimulate angiogenesis, invasion, or suppression of immunity (Gabrusiewicz et al. 2011; Li and Graeber 2012). Therefore inhibiting the activation of these cells might be useful to inhibit glioma progression. Szulzewsky et al.(2015) chose Gpnmb and SPP1 as the possible new targets and identified GAMs as the main source for the pro-tumorigenic proteins Gpnmb and SPP1 in murine and human malignant glioma, emphasizing the important roles of microglia and macrophages in anti-tumor treatment regimens.

Recently, an increasing number of studies are focused on the role of Gpnmb in non-tumorous neural tissues. Gpnmb is widely expressed by neurons within the central nervous system, including the hippocampus. Murata et al.(2015) investigated the role of Gpnmb in memory and learning by using transgenic (Tg) mice overexpressing Gpnmb (Tg mice on a BDF-1 background) and Gpnmb extracellular fragment (ECF)-treated mice. The results showed that both mice had memory improvement suggesting that Gpnmb may be a novel target for research on advanced brain function. Previous studies have confirmed that inflammation may contribute to many neurodegenerative disorders. Activated microglial cells play an important role in releasing pro-inflammatory factors, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) for inducing inflammation. Since Gpnmb has been confirmed to function as an anti-inflammatory regulator by inhibiting the activation of T lymphoctyes (Chung et al. 2007) or by reducing the secretion of proinflammatory cytokines from macrophages (Ripoll et al. 2007). Moreover, some reports have suggested that Gpnmb is highly expressed in microglia after LPS treatment. Therefore, in order to figure out the role of Gpnmb in activated microglia, Shi et al.(2014) detected the expression of Gpnmb and matrix metalloproteinase-3 (MMP-3) in activated nicroglia-microglial BV2 cells which showed that the levels of Gpnmb and MMP-3 were greatly increased in BV2 cells after LPS treatment and the expression of MMP-3 was dependent on the level of Gpnmb, when inhibiting the Gpnmb or MMP-3 expression, the expressions of pro-inflammatory factors such as TNF-α, IL-1β, iNOS, and NO were dramatically reduced in activated microglia. Jian-Jun Huang also confirmed the important role of Gpnmb in the regulation of immune/inflammatory responses by detecting the number of

Gpnmb-positive cells in the area postrema after intraperitoneal injection of bacterial endotoxin lipopolysaccharide (HuangMa and Yokoyama 2012).

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive loss of motor neurons and subsequent muscular atrophy, only by ameliorating muscular symptoms can patients with ALS have a better quality of life. In 2012, Tanaka et al. suggested that Gpnmb may have the effect of suppressing motor neuron degeneration in ALS . Three years later, the same group further confirmed that the expression of Gpnmb directly affected skeletal muscles and prevented muscular pathology in SOD1 (G93A) mice (the model of ALS) since the weight and cross-sectional area of the gastrocnemius muscle, number and cross-sectional area of myofibers, and denervation of neuromuscular junctions were ameliorated in SOD1 (G93A)/Gpnmb compared to SOD1 (G93A) mice and direct injection of a Gpnmb expression plasmid into the gastrocnemius muscle of SOD1 (G93A) mice could increase the numbers of myofibers and prevent myofiber atrophy. Therefore, Gpnmb may be the efficient therapy for ALS (Nagahara et al. 2015). Gpnmb also served as a novel neuroprotective factor in cerebral ischemia-reperfusion injury (IRI). The expression of Gpnmb was up-regulated after IRI, and the over-expression could greatly decrease infarct volume. Moreover, the phosphor-Akt and phosphor-ERK might be a part of the protective mechanisms, and the neuroprotective effect of Gpnmb was seemingly induced by the extracellular sequence of Gpnmb (Nakano et al. 2014). Zigdon et al.(2015) identified Gpnmb as an authentic marker of brain pathology in neurological forms of Gaucher disease, which is a recessively inherited metabolic disorder caused by defects in the gene encoding glucosylceramidase (GlcCerase), and can be divided into three subtypes according to the appearance of symptoms associated with central nervous system involvement. Their data suggested that Gpnmb can be used to quantify neuropathology in Gaucher disease patients and evaluate the effect of drugs towards the neurological symptoms of Gaucher disease (Zigdon et al. 2015).

8. Gpnmb and digestive system

8.1. Liver

Gpnmb was also overexpressed in hepatocellular carcinoma and increased the invasiveness and metastasis of rat hepatoma cells *in vitro* and *in vivo* (Onaga et al. 2003). As for the regulation of Gpnmb in hepatocellular carcinoma, Tian et al. (2013) supposed that the expression of Gpnmb was regulated by the epithelial cell adhesion molecule (EpCAM) and colony-stimulating factor (CSF-1) partly through their common downstream product c-myc, and Gpnmb may be a potential target for HCC therapy . In addition, Gpnmb is expressed in macrophages infiltrating into injured liver tissues and the Gpnmb-positive macrophages showed increased phagocytic activity and balanced fibrosis and fibrolysis in the repair process of acute liver injury by MMP-13 secretion (Haralanova-Ilievaet al. 2005; Kumagai et al. 2015). Moreover, previous studies confirmed the existence of Gpnmb mRNA in the Kupffer cells and white adipose tissues (WATs) and it was up-regulated in obesity (Haralanova-Ilieva et al. 2005; Gabriel et al. 2014). Gpnmb was also considered as a significant biomarker in nonalcoholic steatohepatitis (NASH), one of the most common causes of chronic liver disease worldwide, since the soluble Gpnmb concentrations in sera were higher compared with the patients with simple steatosis (SS). The overexpression of Gpnmb in hepatic macrophages and stellate cells ameliorated the oxidative stress in liver by binding calnexin in endoplasmic reticulum (ER). Therefore, Gpnmb may be a promising biomarker and therapeutic target for the development and progression of NAFLD in obesity (Katayama et al. 2015).

8.2. Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, with an 85% death rate of 45,220 new cases in the year 2013. Although the proportion of PDCA in all cancers is only 2.68%, it represents the fourth leading cancer-related death worldwide and remains less responsive to conventional chemotherapy (Siegel et al. 2014). Due to the promising role of Gpnmb in cancer and unclear implication in PDAC development and progression, Torres et al. (2015) explored its involvement in PDAC *in vitro* using the both Gpnmb-overexpressed and Gpnmb-silenced transfected pancreatic cancer cell line Panc-1. Gpnmb could induce proliferation, reduce apoptosis and enhance the invasion of pancreatic cancer cells. In view of its main membrane localization in cancer cells, Gpnmb could represent a novel targeted approach for the treatment of PDAC (Torres et al. 2015).

8.3. Colitis

Gpnmb has been confirmed to regulate the inflammatory response of macrophages, while the role of Gpnmb in intestinal macrophages is still unclear, Therefore, Sasaki et al. (2015) analyzed the expression of Gpnmb and its effects on colonic mucosal injuries associated with dextran sulfate sodium (DSS) induced colitis in BALB/c mice, DBA/2J (D2) mice lacking Gpnmb and Gpnmb transgenic DBA/2J mice (D2Gpnmb+). The results indicated that macrophages infiltrating injured mucosa express Gpnmb, and that Gpnmb positive macrophages may ameliorate inflammation in the intestinal mucosa by decreasing proinflammatory cytokine production via the ERK and p38 signaling pathways (Sasaki et al. 2015).

9. Conclusion

Gpnmb was first cloned and described in low-metastatic human melanoma and xenografts, namely as nmb in 1995 (Weterman et al. 1995). Then the following studies confirmed that Gpnmb was widely expressed not only in all kinds of normal tissue and cell types but also in various pathological disorders and human malignant tissues, including breast cancer, melanoma, osteosarcoma and played a vital role diagnosis and prognosis. Moreover, the properties of high Gpnmb expression at the surface of cancer cells but significant expression intracellularly in normal cells, provoked considerable interest in the development of Gpnmb-targeted therapies for cancer. So glembatumumabvedotin, also referred to as CR011-vcMMAE or CDX-011, emerged as a Gpnmb-targeted therapeutic that belongs to a class of drugs known as antibody-drug conjugates (ADCs). Studies have partly confirmed the efficacy of glembatumumabvedotin in several cancers, such as breast cancer, cutaneous melanoma and glioma. Recently, a wide array of studies emphasize the vital role of Gpnmb in many tumors and nonneoplastic disorders, including SCLC, prostate cancer, pancreatic cancer, hepatocellular carcinoma, kidney injury, NASH, colitis, IRI, ALS. As to the aspects of diagnosis, prognosis and treatments, however, most of them were preliminary studies. More and more ongoing studies are intended to further figure out the role of Gpnmb in healthy and unhealthy individuals with great significance.

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