Glycoprotein Non-Metastatic Protein B (GPNMB): The Missing Link Between Lysosomes and Obesity

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ABSTRACT

As a result of an unhealthy diet and limited physical activity, obesity has become a widespread pandemic worldwide and is an important predictor for the development of cardiovascular disease. Obesity is often characterized by a pro-inflammatory environment in white adipose tissue (WAT), mainly due to increased macrophage infiltration. These immune cells boost their lipid concentrations by accumulating the content of dying adipocytes. As the lysosome is highly involved in lipid handling, the progressive lipid accumulation may result in lysosomal stress and a metabolic shift. Recent studies have identified glycoprotein non-metastatic melanoma protein B (GPNMB) as a novel marker of inflammatory diseases. GPNMB is a type I transmembrane protein on the cell surface of various cell types, such as macrophages, dendritic cells, osteoblasts, and microglia, from which it can be proteolytically cleaved into a soluble molecule. It is induced by lysosomal stress via microphthalmia-associated transcription factor and thus has been found to be upregulated in many lysosomal storage disorders. In addition, a clear connection between GPNMB and obesity was recently established. GPNMB was shown to have protective and anti-inflammatory effects in most cases, preventing the progression of obesity-related metabolic disorders. In contrast, soluble GPNMB likely has the opposite effect and promotes lipogenesis in WAT. This review aims to summarize and clarify the role of GPNMB in the progression of obesity and to highlight its potential use as a biomarker for lipid-associated disorders.

Introduction

Obesity can be described as a disproportionate accumulation or organization of body fat and has become an increasingly important health problem worldwide, referred to as the obesity pandemic [1]. Obesity is usually assessed by measuring height and weight to calculate the body mass index (BMI, kg/m^2). Recently, however, it has emerged that this parameter is not an efficient predictor of mortality risk and should be replaced by the estimation of percent body fat despite the complexity and high financial cost of assessment [2].

Obesity contributes to chronic diseases, including type 2 diabetes (T2D), hepatic steatosis and steatohepatitis, cardiovascular disease, stroke, dyslipidemia, hypertension, and different types of cancers [3, 4]. Moreover, progressive caloric pressure on white adipose tissue (WAT) results in low-grade but persistent inflammation, called "metaflammation", associated with increased macrophage infiltration responsible for the clearance of dysfunctional and dying adipocytes [5, 6]. Adipocytes and infiltrating immune cells can produce and release a plethora of chemokines and cytokines that mediate systemic inflammation in obese patients [7]. This continuous inflammatory status in WAT also leads to a metabolic switch from a storage to an inflammatory phenotype, causing ectopic lipid deposition in secondary tissues such as the liver or muscle, which in turn results in deregulated systemic insulin signaling [8].

Adipose tissue macrophages (ATMs) play a central role in the development and progression of inflammation in WAT. In fact, inhibition or silencing of various mediators produced by these immune cells was shown to be sufficient to ameliorate the multiple pathological consequences of obesity [9, 10]. By investigating the molecular mechanism of this polarization switch in macrophages, inositol-requiring enzyme 1a and peroxisome proliferator-activated receptor gamma were identified as important regulators in this process, as they create an inflammatory environment [11, 12]. To reduce WAT inflammation and adipocyte hypertrophy, caloric restriction is widely used as a treatment strategy. However, this therapy paradoxically increases the number of ATMs and the expression of related cytokines in humans and mice [13–16]. In addition, various pharmacological approaches have been used in an attempt to reduce obesity. For instance, melatonin, a powerful antioxidant, has been demonstrated to reduce obesity-related problems by lowering inflammatory adipokines such as interleukin-6 (IL-6), monocyte chemoattractant protein-1, leptin, and tumor necrosis factor-α [17]. The numerous beneficial effects of glucagon-like peptide-1 (GLP-1) render this hormone an interesting candidate for the development of pharmacotherapies to treat obesity, diabetes, and neurodegenerative disorders [18]. In fact, a weekly dose of the GLP-1R agonist semaglutide was associated with a sustained reduction in body weight [19]. In mice, semaglutide reduced adipocyte hypertrophy and macrophage infiltration and activated adipocyte browning and mitochondrial biogenesis to promote weight loss [20].

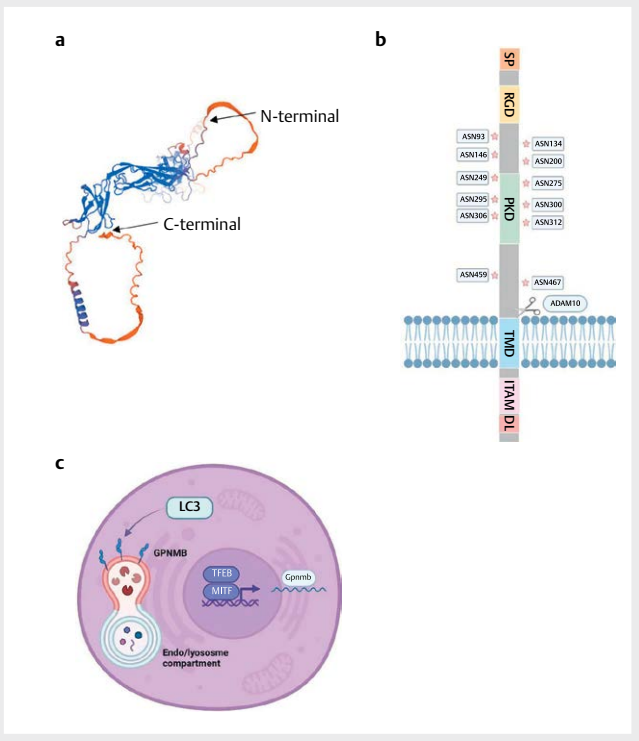
Other studies focused on discovering the non-inflammatory role of immune cells induced in obesity. Under conditions of increased adiposity, secreted factors from WAT trigger a program of lysosome biogenesis in ATMs to buffer the huge amount of lipids from adipocytes [21]. Unexpectedly, ATMs from obese mice do not polarize toward one of the classical M1 or M2 phenotypes. The authors, therefore, hypothesized that these are not qualitative changes in the expression profile of ATMs, but that these cells increase in number and, thus, no clear polarization was observed [21]. Obesity reprograms ATMs into a pro-inflammatory metabolically activated state that is transcriptionally, mechanistically, and functionally distinct from M1- or M2-like phenotypes [22]. A unique pleiotropic phenotype in WAT health has been attributed to these macrophages, which varies between beneficial (removal of dead adipocytes) and deleterious (release of pro-inflammatory cytokines) determined by the duration of high-fat diet feeding, at least in mice [23]. Single-cell RNAseq studies have recently identified a new macrophage subset induced during obesity, termed lipid-associated macrophages, characterized by the expression of triggering receptors expressed on myeloid cells 2 [24]. These cells appear to activate an expression profile that involves phagocytosis, lipid catabolism, and lysosomal pathways, which is a common phenotype of macrophages in different inflamed tissues such as the liver, brain, and atherosclerotic plaques [24–27].

In the last 10 years, the search for new genes that are differentially regulated in the WAT of obese mice has substantially increased. The discovery that glycoprotein non-metastatic melanoma protein B (GPNMB) is highly expressed in the WAT of obese animals [28], opened the way for many studies on this protein. This review aims to emphasize the importance of GPNMB in the context of ATMs, lysosomal function, and obesity.

Structure, function, and regulation of glycoprotein non-metastatic melanoma protein B

GPNMB was first identified in 1995 in a screen using high and low metastatic human melanoma cell lines [29]. It is a type I transmembrane glycoprotein, also known as osteoactivin or dendritic cell heparan sulfate proteoglycan integrin-dependent ligand [30, 31]. GPNMB was detected in a range of cell types, including osteoblasts and osteoclasts in bone, melanocytes, keratinocytes, microglia in the central nervous system, as well as macrophages and dendritic cells [31]. It was found to be increased in a variety of inflammatory diseases such as colitis, renal diseases, different types of cancers, and neurodegenerative disorders [32, 33]. In addition, GPNMB was associated with other disorders, such as senescence [34], vitiligo [35], glaucoma [35], myocardial infarction [37], and atherosclerosis [38]. Mutations in *Gpnmb* cause hypopigmented lesions and pigmentary glaucoma in mouse models [39–41] and recessive and semi-dominant amyloidosis cutis dyschromica in humans [42, 43].

The human *Gpnmb* gene, located at chromosome 7p15, encodes for 2 alternative splicing isoforms of 572 and 260 amino acids [44]. Mouse *Gpnmb* codes for a protein of 574 amino acids and shares 70.16 % sequence identity with the human protein [45, 46]. In its extracellular domain, GPNMB contains an N-terminal signal peptide (SP), an integrin-binding RGD motif and a polycystic kidney disease domain, a single-pass transmembrane domain, as well as an immunoreceptor tyrosine-based activation-like motif and a lysosomal targeting di-leucine motif in the cytoplasmic tail (▶ **Fig. 1a, b**) [47, 48]. The protein has 12 potential N-glycosylation sites, described in numerous cell types [49–51]. It is predominantly located in endosomal/lysosomal compartments, where it promotes the recruitment of light chain 3 (LC3/Atg8) to the phagosome for lysosomal fusion (▶ **Fig. 1c**) [52–55]. In addition to phagocytosis, GPNMB was also associated with efferocytosis, the clearance of apoptotic and necrotic cells primarily by macrophages [56]. IL-6, under the control of the phosphorylated-signal transducer and activator of transcription 3 (pSTAT3), was shown to be a positive regulator of this progress [57]. Although *Gpnmb*-deficient bone marrow-derived macrophages can initiate phagocytosis, they are unable to digest the cargo content, as pSTAT3 activation is not sustained over time. Moreover, this impairment does not allow macrophages to correctly switch from an inflammatory to a restorative phenotype, underscoring the link between GPNMB, phagocytosis, and tissue repair [57].



▶ **Fig. 1** GPNMB structure and localization. (**a**) Model of human GPNMB. The structure of the protein was predicted using the BIOZENTRUM SWISS-MODEL tool [62]. (**b**) Schematic model of the GPNMB structure, including N-glycosylation sites and cleavage site for AD-AM10. SP, signal peptide; RGD, RGD motif; PKD, polycystic kidney disease domain; TMD, transmembrane domain; ITAM, immunoreceptor tyrosine-based activation-like motif; DL, di-leucin motif. (**c**) Gpnmb expression is regulated by melanogenesis associated transcription factor (MITF) and transcription factor EB (TFEB). It localizes to the endo/lysosomal com-partment, where it recruits LC3/Atg8 for phagosome fusion. This image was created with Biorender.com (accessed on September 22nd 2023). [rerif]

Although the precise mechanisms driving this process are unknown, a disintegrin and metalloproteinase 10, a proteolytic enzyme belonging to the matrix metalloproteinase (MMP) family, contributes to GPNMB extracellular domain shedding [58]. This soluble form (sGPNMB) can bind to a variety of receptors, including Na^+/K^+-ATPase, CD44, epidermal growth factor receptor, vascular endothelial growth factor receptor, and other molecules such as integrins, heparin, and syndecan-4 [31, 59]. In addition, GPNMB signaling increases extracellular signal-regulated kinase and protein kinase B phosphorylation in many disease models [60–63]. GPNMB is tightly transcriptionally regulated, with melanogenesis-associated transcription factor (MITF) as one of the major players. MITF overexpression increased GPNMB expression by binding and activating its promoter in both human and animal cells [55, 64, 65]. In addition, transcription factor EB was identified as a regulator of GPNMB expression [34].

Endo/lysosomal localization of glycoprotein non-metastatic melanoma protein B and its role in lysosomal storage diseases

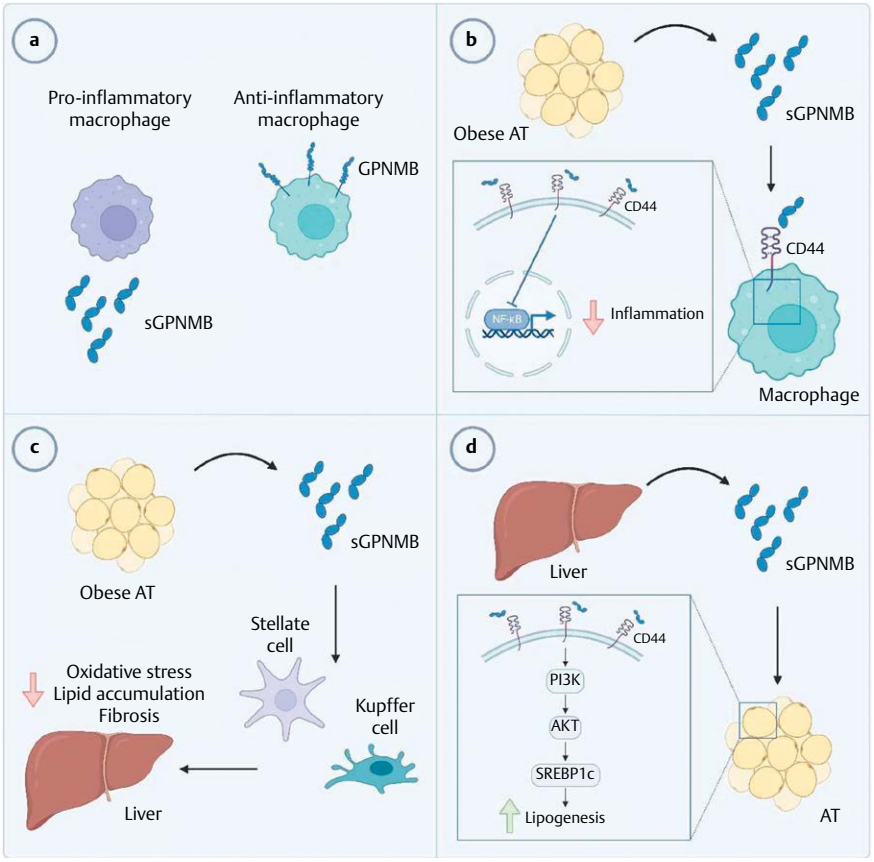
Since GPNMB is localized to endo/lysosomes, studies focused on understanding its role in the biology of these organelles and its link to macrophages, one of the cell types that primarily utilize lysosomal degradation to generate energy in response to the nutritional status of the cell. The link between GPNMB and lysosomal function is supported by many *in vitro* studies. Numerous inducers of lysosomal stress, such as HEPES, sucrose, chloroquine, bafilomycin, concanamycin A, or palmitate, increase GPNMB expression in macrophage cell lines [28, 66]. Moreover, the lysosomal/endocytic marker lysosomal associated membrane protein 2 was reported to co-localize with GPNMB in osteoclasts [55]. GPNMB is essential for the recruitment of the autophagy protein LC3/Atg8 to the surface of autophagosomes and subsequent acidification and fusion with lysosomes [54], highlighting its close association with this organelle.

The accumulation of lysosomal macromolecules and the resulting stress condition may be due to a genetic deficiency of lysosomal enzymes, leading to lysosomal storage disorders (LSDs). Tissue macrophages are among the primary storage cells involved in LSDs because they contribute to the cleavage of various substrates. Biomarkers such as chitotriosidase (CHIT1) and chemokine (C-C motif) ligand 18 (CCL18) have been identified in patients with LSD but cannot be used in mouse models because CHIT1 is not expressed in phagocytes [67] and a CCL18 homolog is absent in rodents [68]. The urgent need to find a new marker for this group of diseases led to the discovery of GPNMB. Van Ejik and colleagues were among the first to demonstrate an increase in GPNMB in Gaucher disease spleen and, in particular, in Gaucher cells, the lipid-laden macrophages characteristic of this pathology, accompanied by several hundred-fold increase in circulating sGPNMB concentrations [69]. These discoveries paved the way for many other studies that underscored the importance of GPNMB in Gaucher disease [70–73] and other LSDs [74–76] and, like CHIT1 and CCL18, confirmed its strong association with LSDs and lipid-laden macrophages.

Further findings provided important insights into the possible molecular mechanisms underlying the increase in GPNMB in LSDs. Another important player during lysosomal stress is the mammalian target of rapamycin complex 1 (mTORC1), a protein localized to the surface of lysosomes and implicated in the control of autophagy [77, 78]. In several models of impaired lysosomal function, mTORC1 was downregulated, and *Mitf*, the main transcription factor regulating *Gpnmb* expression, was upregulated [28, 79]. Moreover, lysosomal Ca^{2+} release, as a consequence of organelle stress, was shown to induce nuclear translocation and activation of transcription factor EB, another important transcription factor for *Gpnmb* [80].

Glycoprotein non-metastatic melanoma protein B and obesity

Across several models of obesity, expansion of WAT induces a program of lysosome biogenesis in ATMs associated with lipid catabolism but not a classic inflammatory phenotype [21], arguing that the increase in the inflammatory profile of WAT associated with obesity derives primarily from quantitative increases in immune cell populations. Thus, in addition to genetic defects, lysosomal



▶ **Fig. 2** Overview of the role of GPNMB in macrophage function and obesity. (**a**) Membrane bound GPNMB is retained on the surface of anti-inflammatory macrophages, whereas soluble (s)GPNMB is released by pro-inflammatory cells. (**b**) Obesity induces the production of sGPNMB by adipocytes, which lowers the inflammatory capacity of macrophages by interacting with CD44 on the cell surface and inhibiting the function of NF-kB. (**c**) To reduce oxidative stress, lipid accumulation, and fibrosis in the liver, obese adipocytes release sGPNMB, which interacts with calnexin on Kupffer and stellate cells. (**d**) In obese WAT, the hepatokine sGPNMB activates SREBP1c to promote lipogenesis by binding to CD44 on adipocytes. This image was created with Biorender.com (accessed on September 24th 2023). [rerif]

lipid accumulation is also triggered when the amount of fat exceeds the storage capacity of the adipocytes, which eventually undergo apoptosis and recruit macrophages. When the WAT is no longer able to process lipids properly, they may accumulate in ectopic tissues, such as the liver or skeletal muscle.

Since the reports that GPNMB is drastically induced in WAT of several obese animal models [28, 81, 82], many studies have focused on describing the role of this protein in obesity and associated metabolic disorders (▶ **Fig. 2**). GPNMB was identified as a negative regulator of macrophage inflammatory responses and only reparative, anti-inflammatory M2-like macrophages activated by TGFβ retain full-length GPNMB on their surface [83]. Pro-inflammatory macrophages activated by interferon γ and lipopolysaccharide secrete sGPNMB [83]. sGPNMB, which is abundantly produced by hypertrophied adipocytes, was also suggested to reduce the inflammatory capacity of macrophages by inhibiting nuclear factor-κB signaling mainly through binding to CD44. Thus, chronic WAT inflammation was severely exacerbated in high-fat diet-fed *Gpnmb*-deficient mice, accompanied by a pronounced increase in crown-like structures [84]. These data emphasize the critical function of GPNMB in macrophage activation and the subsequent inflammatory response in obese WAT.

The phenomenon that GPNMB plays an essential role in decreasing WAT inflammation during obesity by reducing the number of ATMs was absent when GPNMB was over-expressed in adipocytes and macrophages of mutant mice [81]. Whether the discrepancy in the observed phenotype is due to the different high-fat diet (coconut oil [81] versus lard [83]) remains elusive.

In fact, only palmitic acid present in lard is able to trigger insulin resistance [85] and GPNMB expression [28], leading to a stronger effect on WAT of obese mice. However, both diets were very effective in inducing liver steatosis. Furthermore, both studies showed that sGPNMB secreted by adipocytes from obese mice was responsible for decreased oxidative stress, fat deposition, and fibrosis in the liver by interacting with calnexin on Kupffer and stellate cells. However, sGPNMB was also described as a hepatokine that activates SREBP1c and thus lipogenesis in obese WAT by binding CD44 on adipocytes, resulting in a positive correlation between

sGPNMB and BMI [86]. These findings indicate that GPNMB is a strong risk factor for obesity.

GPNMB was also linked to T2D, one of the diseases potentially associated with obesity. Numerous sequelae, such as acute renal injury, cardiovascular disease, muscle failure, ocular pathologies, and cognitive dysfunction, frequently accompany the development of T2D. Indeed, GPNMB was found to be increased in many of these T2D-associated disorders [87–89], once more emphasizing the important role of this protein as a biomarker in obesity and its related conditions.

Conclusions

This review highlights GPNMB as a key player in lysosomal dysfunction and obesity and its potential as a biomarker for the identification and progression of these diseases. In particular, the studies described underscore the binomial role of the two forms of GPNMB in preventing or aggravating obesity and its related disorders. However, the exact mechanism by which GPNMB modulates obesity and obesity-associated metabolic disorders remains controversial and requires further investigation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] The Lancet Gastroenterology & Hepatology. Obesity: Another ongoing pandemic. Lancet Gastroenterol Hepatol 2021; 6: 411. DOI: 10.1016/S2468-1253(21)00143-6

[2] Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. Circ Res 2016; 118: 1752–1770. DOI: 10.1161/CIRCRESAHA.115.306883

[3] Safaei M, Sundararajan EA, Driss M et al. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med 2021; 136: 104754. DOI: 10.1016/j.compbiomed.2021.104754

[4] Haslam DW, James WPT. Obesity. The Lancet 2005; 366: 1197–1209. DOI: 10.1016/S0140-6736(05)67483-1

[5] Xu H, Barnes GT, Yang Q et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112: 1821–1830. DOI: 10.1172/JCI19451

[6] Weisberg SP, McCann D, Desai M et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1796–1808. DOI: 10.1172/JCI19246

[7] Oliveros E, Somers VK, Sochor O et al. The concept of normal weight obesity. Prog Cardiovasc Dis 2014; 56: 426–433. DOI: 10.1016/j.pcad.2013.10.003

[8] Poulain-Godefroy O, Lecoeur C, Pattou F et al. Inflammation is associated with a decrease of lipogenic factors in omental fat in women. Am J Physiol-Regul Integr Comp Physiol 2008; 295: R1–R7. DOI: 10.1152/ajpregu.00926.2007

[9] Zhang T, Fang Z, Linghu K-G et al. Small molecule-driven SIRT3-autophagy-mediated NLRP3 inflammasome inhibition ameliorates inflammatory crosstalk between macrophages and adipocytes. Br J Pharmacol 2020; 177: 4645–4665. DOI: 10.1111/bph.15215

[10] Aouadi M, Tencerova M, Vangala P et al. Gene silencing in adipose tissue macrophages regulates whole-body metabolism in obese mice. Proc Natl Acad Sci 2013; 110: 8278–8283. DOI: 10.1073/pnas.1300492110

[11] Shan B, Wang X, Wu Y et al. The metabolic ER stress sensor IRE1α suppresses alternative activation of macrophages and impairs energy expenditure in obesity. Nat Immunol 2017; 18: 519–529. DOI: 10.1038/ni.3709

[12] Odegaard JI, Ricardo-Gonzalez RR, Goforth MH et al. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. Nature 2007; 447: 1116–1120. DOI: 10.1038/nature05894

[13] Kratz M, Hagman DK, Kuzma JN et al. Improvements in glycemic control after gastric bypass occur despite persistent adipose tissue inflammation. Obesity 2016; 24: 1438–1445. DOI: 10.1002/oby.21524

[14] Capel F, Klimčáková E, Viguerie N et al. Macrophages and adipocytes in human obesity: Adipose tissue gene expression and insulin sensitivity during calorie restriction and weight stabilization. Diabetes 2009; 58: 1558–1567. DOI: 10.2337/db09-0033

[15] Zamarron BF, Mergian TA, Cho KW et al. Macrophage proliferation sustains adipose tissue inflammation in formerly obese mice. Diabetes 2016; 66: 392–406. DOI: 10.2337/db16-0500

[16] Kosteli A, Sugaru E, Haemmerle G et al. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. J Clin Invest 2010; 120: 3466–3479. DOI: 10.1172/JCI42845

[17] Farias TDSM, Paixao RID, Cruz MM et al. Melatonin supplementation attenuates the pro-inflammatory adipokines expression in visceral fat from obese mice induced by a high-fat diet. Cells 2019; 8: 1041. DOI: 10.3390/cells8091041

[18] de Farias TDSM, Cruz MM, de Sa RCDC et al. Melatonin supplementation decreases hypertrophic obesity and inflammation induced by high-fat diet in mice. Front Endocrinol 2019; 10: 750. DOI: 10.3389/fendo.2019.00750

[19] Wilding JPH, Batterham RL, Calanna S et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021; 384: 989–1002. DOI: 10.1056/NEJMoa2032183

[20] Martins FF, Marinho TS, Cardoso LEM et al. Semaglutide (GLP-1 receptor agonist) stimulates browning on subcutaneous fat adipocytes and mitigates inflammation and endoplasmic reticulum stress in visceral fat adipocytes of obese mice. Cell Biochem Funct 2022; 40: 903–913. DOI: 10.1002/cbf.3751

[21] Xu X, Grijalva A, Skowronski A et al. Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. Cell Metab 2013; 18: 816–830. DOI: 10.1016/j.cmet.2013.11.001

[22] Kratz M, Coats BR, Hisert KB et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab 2014; 20: 614–625. DOI: 10.1016/j.cmet.2014.08.010

[23] Coats BR, Schoenfelt KQ, Barbosa-Lorenzi VC et al. Metabolically activated adipose tissue macrophages perform detrimental and beneficial functions during diet-induced obesity. Cell Rep 2017; 20: 3149–3161. DOI: 10.1016/j.celrep.2017.08.096

[24] Jaitin DA, Adlung L, Thaiss CA et al. Lipid-associated macrophages control metabolic homeostasis in a trem2-dependent manner. Cell 2019; 178: 686–698.e14. DOI: 10.1016/j.cell.2019.05.054

[25] Ulland TK, Song WM, Huang SC-C et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell 2017; 170: 649–663.e13. DOI: 10.1016/j.cell.2017.07.023

[26] Ulland TK, Colonna M. TREM2 — a key player in microglial biology and Alzheimer disease. Nat Rev Neurol 2018; 14: 667–675. DOI: 10.1038/s41582-018-0072-1

[27] Patterson MT, Firulyova M, Xu Y et al. Trem2 promotes foamy macrophage lipid uptake and survival in atherosclerosis. 2022; 2022.11.28.518255

[28] Gabriel TL, Tol MJ, Ottenhof R et al. Lysosomal stress in obese adipose tissue macrophages contributes to MITF-dependent Gpnmb Induction. Diabetes 2014; 63: 3310–3323. DOI: 10.2337/db13-1720

[29] Weterman MA, Ajubi N, van Dinter IM et al. nmb, a novel gene, is expressed in low-metastatic human melanoma cell lines and xenografts. Int J Cancer 1995; 60: 73–81. DOI: 10.1002/ijc.2910600111

[30] Lazaratos A-M, Annis MG, Siegel PM. GPNMB: A potent inducer of immunosuppression in cancer. Oncogene 2022; 41: 4573–4590. DOI: 10.1038/s41388-022-02443-2

[31] Maric G, Rose AA, Annis MG et al. Glycoprotein non-metastatic b (GPNMB): A metastatic mediator and emerging therapeutic target in cancer. OncoTargets Ther 2013; 6: 839–852. DOI: 10.2147/OTT.S44906

[32] Saade M, Araujo de Souza G, Scavone C et al. The Role of GPNMB in Inflammation. Front Immunol 2021; 12: 674739. DOI: 10.3389/fimmu.2021.674739

[33] Chung J-S, Ramani V, Kobayashi M et al. DC-HIL/Gpnmb is a negative regulator of tumor response to immune checkpoint inhibitors. Clin Cancer Res 2020; 26: 1449–1459. DOI: 10.1158/1078-0432.CCR-19-2360

[34] Suda M, Shimizu I, Katsuumi G et al. Glycoprotein nonmetastatic melanoma protein B regulates lysosomal integrity and lifespan of senescent cells. Sci Rep 2022; 12: 6522. DOI: 10.1038/s41598-022-10522-3

[35] Biswas KB, Takahashi A, Mizutani Y et al. GPNMB is expressed in human epidermal keratinocytes but disappears in the vitiligo lesional skin. Sci Rep 2020; 10: 4930. DOI: 10.1038/s41598-020-61931-1

[36] Howell GR, Libby RT, Marchant JK et al. Absence of glaucoma in DBA/2J mice homozygous for wild-type versions of Gpnmb and Tyrp1. BMC Genet 2007; 8: 45. DOI: 10.1186/1471-2156-8-45

[37] Järve A, Mühlstedt S, Qadri F et al. Adverse left ventricular remodeling by glycoprotein nonmetastatic melanoma protein B in myocardial infarction. FASEB J 2017; 31: 556–568. DOI: 10.1096/fj.201600613R

[38] Nickl B, Qadri F, Bader M. Role of Gpnmb in atherosclerosis of female mice. Biochem Biophys Res Commun 2022; 621: 20–24. DOI: 10.1016/j.bbrc.2022.06.082

[39] Anderson MG, Smith RS, Hawes NL et al. Mutations in genes encoding melanosomal proteins cause pigmentary glaucoma in DBA/2J mice. Nat Genet 2002; 30: 81–85. DOI: 10.1038/ng794

[40] Mo J-S, Anderson MG, Gregory M et al. By altering ocular immune privilege, bone marrow–derived cells pathogenically contribute to DBA/2J pigmentary glaucoma. J Exp Med 2003; 197: 1335–1344. DOI: 10.1084/jem.20022041

[41] John SW, Smith RS, Savinova OV et al. Essential iris atrophy, pigment dispersion, and glaucoma in DBA/2J mice. Invest Ophthalmol Vis Sci 1998; 39: 951–962

[42] Rahman OU, Kim J, Mahon C et al. Two missense mutations in GPNMB cause autosomal recessive amyloidosis cutis dyschromica in the consanguineous pakistani families. Genes Genomics 2021; 43: 471–478. DOI: 10.1007/s13258-021-01071-6

[43] Onoufriadis A, Hsu C-K, Eide CR et al. Semidominant GPNMB mutations in amyloidosis cutis dyschromica. J Invest Dermatol 2019; 139: 2550–2554.e9. DOI: 10.1016/j.jid.2019.05.021

[44] GPNMB - Transmembrane glycoprotein NMB - *Homo sapiens* (Human) | UniProtKB | UniProt. Im Internet: https://www.uniprot.org/uniprotkb/Q14956/entry Stand: 04.07.2023

[45] Gpnmb - Transmembrane glycoprotein NMB - *Mus musculus* (Mouse) | UniProtKB | UniProt. . Im Internet: https://www.uniprot.org/uniprotkb/Q99P91/entry Stand: 04.07.2023

[46] Shikano S, Bonkobara M, Zukas PK et al. Molecular cloning of a dendritic cell-associated transmembrane protein, DC-HIL, that promotes RGD-dependent adhesion of endothelial cells through recognition of heparan sulfate proteoglycans. J Biol Chem 2001; 276: 8125–8134. DOI: 10.1074/jbc.M008539200

[47] Selim AA. Osteoactivin bioinformatic analysis: Prediction of novel functions, structural features, and modes of action. Med Sci Monit 2009; 15: MT19–MT33

[48] Singh M, Del Carpio-Cano F, Belcher JY et al. Functional roles of osteoactivin in normal and disease processes. Crit Rev Eukaryot Gene Expr 2010; 20: 341–357. DOI: 10.1615/critreveukargeneexpr.v20.i4.50

[49] Hoashi T, Sato S, Yamaguchi Y et al. Glycoprotein nonmetastatic melanoma protein b, a melanocytic cell marker, is a melanosome-specific and proteolytically released protein. FASEB J 2010; 24: 1616–1629. DOI: 10.1096/fj.09-151019

[50] Abdelmagid S, Barbe M, Rico M et al. Osteoactivin, an anabolic factor that regulates osteoblast differentiation and function. Exp Cell Res 2008; 314: 2334–2351. DOI: 10.1016/j.yexcr.2008.02.006

[51] Kuan C-T, Wakiya K, Dowell JM et al. Glycoprotein nonmetastatic melanoma protein B, a potential molecular therapeutic target in patients with glioblastoma multiforme. Clin Cancer Res 2006; 12: 1970–1982. DOI: 10.1158/1078-0432.CCR-05-2797

[52] Ripoll VM, Irvine KM, Ravasi T et al. Gpnmb is induced in macrophages by IFN-γ and lipopolysaccharide and acts as a feedback regulator of proinflammatory responses. J Immunol 2007; 178: 6557–6566. DOI: 10.4049/jimmunol.178.10.6557

[53] Zhou LT, Liu FY, Li Y et al. Gpnmb/osteoactivin, an attractive target in cancer immunotherapy. Neoplasma 2012; 59: 1–5. DOI: 10.4149/neo_2012_001

[54] Li B, Castano AP, Hudson TE et al. The melanoma-associated transmembrane glycoprotein Gpnmb controls trafficking of cellular debris for degradation and is essential for tissue repair. FASEB J 2010; 24: 4767–4781. DOI: 10.1096/fj.10-154757

[55] Ripoll VM, Meadows NA, Raggatt L-J et al. Microphthalmia transcription factor regulates the expression of the novel osteoclast factor GPNMB. Gene 2008; 413: 32–41. DOI: 10.1016/j.gene.2008.01.014

[56] Boada-Romero E, Martinez J, Heckmann BL et al. The clearance of dead cells by efferocytosis. Nat Rev Mol Cell Biol 2020; 21: 398–414. DOI: 10.1038/s41580-020-0232-1

[57] Campana L, Starkey Lewis PJ, Pellicoro A et al. The STAT3–IL-10–IL-6 pathway Is a novel regulator of macrophage efferocytosis and phenotypic conversion in sterile liver injury. J Immunol 2018; 200: 1169–1187. DOI: 10.4049/jimmunol.1701247

[58] Rose AAN, Annis MG, Dong Z et al. ADAM10 releases a soluble form of the GPNMB/Osteoactivin extracellular domain with angiogenic properties. PloS One 2010; 5: e12093. DOI: 10.1371/journal.pone.0012093

[59] Taya M, Hammes SR. Glycoprotein non-metastatic melanoma protein B (GPNMB) and cancer: A novel potential therapeutic target. Steroids 2018; 133: 102–107. DOI: 10.1016/j.steroids.2017.10.013

[60] Tanaka H, Shimazawa M, Kimura M et al. The potential of GPNMB as novel neuroprotective factor in amyotrophic lateral sclerosis. Sci Rep 2012; 2: 573. DOI: 10.1038/srep00573

[61] Yu B, Sondag GR, Malcuit C et al. Macrophage-associated osteoactivin/GPNMB mediates mesenchymal stem cell survival, proliferation, and migration via a CD44-dependent mechanism. J Cell Biochem 2016; 117: 1511–1521. DOI: 10.1002/jcb.25394

[62] Nakano Y, Suzuki Y, Takagi T et al. Glycoprotein nonmetastatic melanoma protein B (GPNMB) as a novel neuroprotective factor in cerebral ischemia–reperfusion injury. Neuroscience 2014; 277: 123–131. DOI: 10.1016/j.neuroscience.2014.06.065

[63] Ono Y, Tsuruma K, Takata M et al. Glycoprotein nonmetastatic melanoma protein B extracellular fragment shows neuroprotective effects and activates the PI3K/Akt and MEK/ERK pathways via the Na + /K + -ATPase. Sci Rep 2016; 6: 23241. DOI: 10.1038/srep23241

[64] Gutknecht M, Geiger J, Joas S et al. The transcription factor MITF is a critical regulator of GPNMB expression in dendritic cells. Cell Commun Signal CCS 2015; 13: 19. DOI: 10.1186/s12964-015-0099-5

[65] Loftus SK, Antonellis A, Matera I et al. Gpnmb is a melanoblast-expressed, MITF-dependent gene. Pigment Cell Melanoma Res 2009; 22: 99–110. DOI: 10.1111/j.1755-148X.2008.00518.x

[66] Tol MJ, van der Lienden MJC, Gabriel TL et al. HEPES activates a MiT/TFE-dependent lysosomal-autophagic gene network in cultured cells: A call for caution. Autophagy 2018; 14: 437–449. DOI: 10.1080/15548627.2017.1419118

[67] Boot RG, Bussink AP, Verhoek M et al. Marked differences in tissue-specific expression of chitinases in mouse and man. J Histochem Cytochem 2005; 53: 1283–1292. DOI: 10.1369/jhc.4A6547.2005

[68] Schutyser E, Richmond A, Van Damme J. Involvement of CC chemokine ligand 18 (CCL18) in normal and pathological processes. J Leukoc Biol 2005; 78: 14–26. DOI: 10.1189/jlb.1204712

[69] Kramer G, Wegdam W, Donker-Koopman W et al. Elevation of glycoprotein nonmetastatic melanoma protein B in type 1 Gaucher disease patients and mouse models. FEBS Open Bio 2016; 6: 902–913. DOI: 10.1002/2211-5463.12078

[70] Zigdon H, Savidor A, Levin Y et al. Identification of a biomarker in cerebrospinal fluid for neuronopathic forms of Gaucher disease. PLoS One 2015; 10: e0120194. DOI: 10.1371/journal.pone.0120194

[71] Xu Y-H, Jia L, Quinn B et al. Global gene expression profile progression in Gaucher disease mouse models. BMC Genomics 2011; 12: 20. DOI: 10.1186/1471-2164-12-20

[72] Murugesan V, Liu J, Yang R et al. Validating glycoprotein non-metastatic melanoma B (gpNMB, osteoactivin), a new biomarker of Gaucher disease. Blood Cells Mol Dis 2018; 68: 47–53. DOI: 10.1016/j.bcmd.2016.12.002

[73] van der Lienden MJC, Gaspar P, Boot R et al. Glycoprotein non-metastatic protein B: An emerging biomarker for lysosomal dysfunction in macrophages. Int J Mol Sci 2018; 20: 66. DOI: 10.3390/ijms20010066

[74] Marques ARA, Gabriel TL, Aten J et al. Gpnmb Is a potential marker for the visceral pathology in Niemann-Pick type C disease. PLoS One 2016; 11: e0147208. DOI: 10.1371/journal.pone.0147208

[75] Rodriguez-Gil JL, Baxter LL, Watkins-Chow DE et al. Transcriptome of HPβCD-treated Niemann-Pick disease type C1 cells highlights GPNMB as a biomarker for therapeutics. Hum Mol Genet 2021; 30: 2456–2468. DOI: 10.1093/hmg/ddab194

[76] Eskes ECB, van der Lienden MJC, Sjouke B et al. Glycoprotein non-metastatic protein B (GPNMB) plasma values in patients with chronic visceral acid sphingomyelinase deficiency. Mol Genet Metab 2023; 139: 107631. DOI: 10.1016/j.ymgme.2023.107631

[77] Yu L, McPhee CK, Zheng L et al. Termination of autophagy and reformation of lysosomes regulated by mTOR. Nature 2010; 465: 942–946. DOI: 10.1038/nature09076

[78] Betz C, Hall MN. Where is mTOR and what is it doing there? J Cell Biol 2013; 203: 563–574. DOI: 10.1083/jcb.201306041

[79] Kinghorn KJ, Grönke S, Castillo-Quan JI et al. A drosophila model of neuronopathic Gaucher disease demonstrates lysosomal-autophagic defects and altered mTOR signalling and is functionally rescued by rapamycin. J Neurosci 2016; 36: 11654–11670. DOI: 10.1523/JNEUROSCI.4527-15.2016

[80] Kim J, Kim SH, Kang H et al. TFEB–GDF15 axis protects against obesity and insulin resistance as a lysosomal stress response. Nat Metab 2021; 3: 410–427. DOI: 10.1038/s42255-021-00368-w

[81] Katayama A, Nakatsuka A, Eguchi J et al. Beneficial impact of Gpnmb and its significance as a biomarker in nonalcoholic steatohepatitis. Sci Rep 2015; 5: 16920. DOI: 10.1038/srep16920

[82] Zambonelli P, Gaffo E, Zappaterra M et al. Transcriptional profiling of subcutaneous adipose tissue in Italian large white pigs divergent for backfat thickness. Anim Genet 2016; 47: 306–323. DOI: 10.1111/age.12413

[83] Nickl B, Qadri F, Bader M. Anti-inflammatory role of Gpnmb in adipose tissue of mice. Sci Rep 2021; 11: 19614. DOI: 10.1038/s41598-021-99090-6

[84] Prabata A, Ikeda K, Rahardini EP et al. GPNMB plays a protective role against obesity-related metabolic disorders by reducing macrophage inflammatory capacity. J Biol Chem 2021; 297: 101232. DOI: 10.1016/j.jbc.2021.101232

[85] Buettner R, Parhofer KG, Woenckhaus M et al. Defining high-fat-diet rat models: Metabolic and molecular effects of different fat types. J Mol Endocrinol 36: 485–501. DOI: 10.1677/jme.1.01909

[86] Gong X-M, Li Y-F, Luo J et al. Gpnmb secreted from liver promotes lipogenesis in white adipose tissue and aggravates obesity and insulin resistance. Nat Metab 2019; 1: 570–583. DOI: 10.1038/s42255-019-0065-4

[87] Li W, Guo J, Chen J et al. Identification of immune infiltration and the potential biomarkers in diabetic peripheral neuropathy through bioinformatics and machine learning methods. Biomolecules 2023; 13: 39. DOI: 10.3390/biom13010039

[88] Qin T, Xi X, Wu Z. Downregulation of glycoprotein non-metastatic melanoma protein B prevents high glucose-induced angiogenesis in diabetic retinopathy. Mol Cell Biochem 2023; 478: 697–706. DOI: 10.1007/s11010-022-04537-7

[89] Huo D, Liu Y-Y, Zhang C et al. Serum glycoprotein non-metastatic melanoma protein B (GPNMB) level as a potential biomarker for diabetes mellitus-related cataract: A cross-sectional study. Front Endocrinol 2023; 14: 1110337. DOI: 10.3389/fendo.2023.1110337