The role of glycoproteins in nasopharyngeal carcinoma pathogenesis

Liudmila Matskova[1,2], Elvira Grigorieva[1]

(1. Institute of Molecular Biology and Biophysics of Federal Research Center of Fundamental and Translational Medicine, Novosibirsk 630117, Russia; 2. Microbiology and Tumor Biology Center, Karolinska Institutet, Stockholm 17165, Sweden)

Dr. Liudmila Matskova is a leading researcher at the Institute of Molecular Biology and Biophysics of the Federal Research Center for Basic and Translational Medicine in Russia. Her research interests focus on the molecular mechanisms underlying the pathologic transformation of human cells in various malignancies. In 2004, she completed her PhD at Karolinska Institutet in Sweden under the guidance of Prof. Ingemar Ernberg. Since then, Dr. Matskova has sustained a collaborative relationship with Prof. Ernberg, as well as with various research groups across Sweden, the German Research Center for Environmental Health, the German Centre for Infection Research in Germany, the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital, the Department of Biology in Canada, the Massachusetts Institute of Technology in the USA, Baltic Federal University, and Kemerovo State University in Russia. Their joint research spans a diverse array of topics, from Epstein-Barr virus (EBV) biology to the human microbiome.

Abstract Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the nasopharyngeal epithelium. It consists of undifferentiated squamous cells in the nasopharynx. This type of epithelial cell neoplasm is globally distributed, with the highest prevalence observed in certain regions of the world. It has been known since ancient times. The incidence of NPC is steadily decreasing as data on the molecular factors involved in the pathogenesis of NPC accumulate. Glycoproteins are characterized by polymers of saccharides attached to the amino acid sequences of proteins during the process of glycosylation. They are present in all animal cells and are especially abundant on the surface of tumor cells. Alterations in expression of cellular glycoproteins have recently attracted attention as a key component of neoplastic progression. Tumor-associated glycoproteins may serve as a hallmark of cancer cells and thus represent novel diagnostic and even therapeutic targets. Interest in the role of glycoproteins in cancer in general and specifically in NPC pathology has steadily increased over the past fifty years, reaching over thousands and two hundred publications in the last five years, respectively. Here, data on a specific class of proteins, glycoproteins, involved in tumorigenesis of NPCs are summarized, with a focus on a few of the best-studied ones. Relevant studies performed mainly in the last five years were retrieved and collected through the PubMed system.

Keywords nasopharyngeal carcinoma; glycoprotein; pathogenesis

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[通信作者] Liudmila Matskova，E-mail：liudmila.matskova@ki.se

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糖蛋白在鼻咽癌发病机制中的作用

Liudmila Matskova[1,2], Elvira Grigorieva[1]

(1.俄罗斯联邦基础与转化医学研究中心分子生物学与生物物理学研究所,新西伯利亚　630117;2.瑞典卡罗林斯卡医学院微生物学与肿瘤生物学中心,斯德哥尔摩　17165)

Liudmila Matskova博士是俄罗斯联邦基础和转化医学研究中心分子生物学和生物物理学研究所的首席研究员。主要研究专注于揭示人类细胞恶变成肿瘤的分子机制。2004年博士毕业于瑞典卡罗林斯卡学院,其导师为Ingemar Ernberg教授。并多年来与瑞典的多个研究团队、德国环境健康研究中心、德国感染研究中心、西奈山医院的Lunenfeld Tanenbaum研究所、加拿大生物系、美国麻省理工学院、波罗的海联邦大学以及俄罗斯克麦罗沃州立大学在EB病毒生物学和人类微生物组研究领域保持着紧密的合作与交流。

摘要　鼻咽癌(NPC)是一种源自鼻咽上皮细胞的恶性肿瘤,主要由未分化的鳞状细胞构成。这种上皮细胞肿瘤在全球范围内均有分布,尤其在一些地区发病率极高。NPC自古以来便为人类所认识,随着对NPC发病机制中分子因素的了解不断深入,其发病率正逐渐下降。糖蛋白是一类在糖基化过程中附着于蛋白质氨基酸序列上的糖聚合物,存在于所有动物细胞中,尤其是在肿瘤细胞表面更为丰富。近年来,细胞表面糖蛋白表达的变化作为肿瘤进展的关键因素,引起了广泛关注。肿瘤相关糖蛋白可能作为癌细胞的标志,因此成为新的诊断和治疗靶点。在过去50年中,人们对糖蛋白在癌症中的作用,特别是在NPC病理学中的作用的兴趣持续增长,近5年来在这两个领域中分别发表了数千篇和两百多篇相关论文。本文旨在总结参与NPC肿瘤发生的一类特殊蛋白质—糖蛋白的相关数据,特别关注其中研究最为深入的几种。我们通过PubMed系统检索并收集了主要在近　5年中进行的相关研究。

关键词　鼻咽癌;糖蛋白;发病机制

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1 Introduction

Nasopharyngeal carcinoma (NPC) is a disease with high incidence in East and Southeast Asia[1].

Many factors, both genetic and environmental, contribute to the occurrence of this disease. Epstein-Barr virus (EBV) is recognized as one of the major factors contributing to the oncogenic transformation of epithelial cells in the nasopharynx leading to NPC. EBV contributes to the oncogenesis mainly by inducing chronic inflammation in the nasopharyngeal environment[2, 3]. Radiotherapy, combined with chemotherapy is the most successful treatment modality against the primary NPC tumor[4]. Late detection and metastasis pose the greatest challenges in NPC treatment.

The development of an anti-tumor vaccine based on targeting strategies against EBV[5, 6] or cancer cell markers[7] is currently a highly demanded task that requires detailed studies of tumor antigens of all types. Glycoproteins are characterized as inflammation-related DNA damage and cancer stem cell markers in NPC[8]. Glycoproteins are formed by the enzymatic attachment of an assortment of carbohydrate structures, all derivable from glucose, to the backbone of a protein. Therefore, the increased consumption of sugar and highly processed foods that characterizes the modern Western diet should also be of concern in terms of NPC pathology[9]. Glycoproteins function as membrane receptors, transporters, hormones, and signaling molecules. Carbohydrates, mono- or polysaccharides/glycans, could be attached to the protein backbone at the serine or threonine amino acids (O-

glycosylation) or at the asparagine amino acid (N-glycosylation) [10]. Glycosylation is a type of post-translational modification. It is not an exaggeration to say that it is this post-translational modification that determines the tumorigenic potential of glycoproteins. For example, these proteins are involved in tumor cell dissemination, as many of the glycoproteins (both structural and secreted) form the extracellular matrix (ECM) or cleave ECM factors[10] and thus serve as diagnostic markers of metastasis[11-25]. The glycoproteins are involved in the shaping of the NPC tumor microenvironment (TME)[26-28] and immune responsiveness[26].

EBV infection largely contributes to the immunosuppressive TME observed in NPC[29]. Investigation of the molecular mechanisms has revealed that glycoproteins are involved in chronic unresolving inflammatory signaling through the PI3K/AKT, NF-κB[30, 31], MAPK[32], and Ras[33] pathways in NPC tumor cells. Alterations in the NF-κB signaling pathway play a central role in NPC development. Abnormally activated NF-κB signaling results in an increased production of glycosylated cytokines IL-6 and leukemia inhibitory factor (LIF) together with IL-8 cytokine. This facilitates the recruitment of immune cells to establish a chronic and non-specific inflammation niche. Such inflammation is mainly characterized by the prevalence of macrophages and granulocytes rather than dendritic cells (DCs), resulting in a reduced tumor antigen presentation environment and a decreased activation of T lymphocytes and NK cells [34, 35], abundance of Treg cells, and activity of suppressive type II macrophages[36], allowing immune escape of EBV infected NPC cells[37]. Another cytokine, TNF-α, which is an O-glycosylated, membrane bound, and soluble extracellular protein, activates EBV lytic replication, contributes to EBV load, modulates the immune response[36] and drives cell invasion[24]. Recent findings suggesting that diabetes may increase the prevalence of EBV infection and worsen the prognosis of NPC confirm the complex relationship between viral infection, blood sugar levels, and NPC pathology[29, 38]. In addition, glycoproteins, both viral and host, play a role in NPC cancer cell initiation[26, 39-47] and behavior[12, 13, 19, 27, 48-54], as well as determine therapy sensitivity and disease progression[6, 23, 55].

EBV viral glycoproteins gB/gL, gH, gp42, gp110, gp350/gp220 determine the efficiency of EBV entry into epithelial cells, and viral load subsequently determines the degree of oncogenic transformation[56]. These glycoproteins and antibodies to them serve as unfavorable diagnostic markers in NPC, both locally, as indicators of the tumor mass and systemically, as indicators of hematogenic spread.

Glycosylation of macromolecules with linear or branched oligosaccharides attached to the protein backbone, and their modification by sulfate groups determines the accessibility of glycoproteins to binding partners, oligomerization, turnover, conformation, and ultimately their function. Sugars as building blocks of carbohydrates are delivered via dietary supply. Consequently, the degree of glycosylation depends on diet and the proper functioning of glycosylating enzymes, altered expression of which has been reported in varying cancers[57]. There is an increasing interest in the use of diet interventions during the treatment of many tumors, including NPC. Low-fat diets (LFDs) or very low carbohydrate diets (VLCDs) have the potential to reduce food intake and alter the level of tumorigenic hormones when compared to standard diets[38].

To date, more than a hundred glycosylated proteins are known, the altered expression of which indicates a poor prognosis in patients with NPC. The specificity of their expression for NPC pathology is emphasized by their association with the level of EBV viral load in NPC and association with other EBV-loaded tumors. Here, information on glycoproteins involved in the tumorigenesis of NPCs is summarized, with a focus on the best-studied ones to date. In the following, information is summarized on a few of the best-studied glycosylated proteins involved in tumorigen-

esis of NPC, the altered expression of which indicates a poor prognosis.

2 Glycoproteins in NPCs

2.1 CD44

CD44, as a cell-surface receptor, engages extracellular matrix components such as hyaluronan/HA, collagen, growth factors, cytokines, and proteases through its ectodomain, and it serves as a platform for signal transduction by assembling, via its cytoplasmic domain, protein complexes containing receptor kinases and membrane proteases. Having varying interacting partners, CD44 plays an important role in cell-cell interactions, cell adhesion, and migration, helping cells to sense and respond to changes in the tissue microenvironment[58]. CD44 is N- and O-glycosylated. The extent of these modifications determines the access of proteases to CD44 and ultimately the extent of its detachment from the cell membrane. CD44 is over-expressed in NPC cells. Moreover, CD44 expression is a hallmark of NPC cancer stem cells (CSC), and resistance to chemoradiotherapy[59].

A molecular mechanism associated with the accumulation of a specific splice form of CD44V in CSC and radiotherapy-resistant cells has been identified. The lncRNA HOTAIRM1 promotes acetylation and stabilization of demethylase FTO; it demethylates the CD44 transcript at position m6A, rendering it unrecognizable to the splicing factor YTHDC1, leading to accumulation of the CD44V protein isoform[60]. The transcription factor Bmi-1[59] and miR-150[61] have been shown to be involved in the control of CD44 expression. In particular, polymorphisms of the 3′UTR region of CD44 mRNA reduce their binding efficiency which contributes to stabilization of CD44 levels in NPC[61]. This focus on regulating the expression of CD44 emphasizes its importance in NPC pathology. The significance of CD44 glycoprotein expression in NPC pathology is also emphasized by the positive association between EBV and CD44 genes [8]. High EBV load is positively correlated with high CD44 expression[62]. Another proteoglycan, serglycin, has been shown to bind and upregulate CD44 expression in an autocrine mode in NPC cells by reciprocally activating the MAPK/β -catenin axis[63]. CD44 has also been reported to activate Ras signaling in NPC cells and to be controlled by redox regulation [64]. Increased expression of CD44 in NPC cells explains epithelial-mesenchymal transition (EMT) of epithelial cells and metastasis[64, 65]. CD44 cooperates with another glycoprotein CD24 to reprogram NPC cells to CSC[66]. Even $CD44^+$ lymphocytes in NPC patients treated with radiochemotherapy indicate an unfavorable clinical outcome[67]. A CD44-targeted therapy has been suggested, either using siCD44 adenovirus[68] or shRNA against Bmi-1[69].

2.2 E-cadherin and β-catenin

E-cadherin is a cell surface protein, and facilitates intercellular connection via homophilic interactions. β -catenin is an intracellular protein with multiple functions, and it acts as transcriptional factor if detached from the complex with E-cadherin and not targeted for degradation. The E-cadherin/β-catenin complex resides on the plasma membrane, forming an adherence junction complex, one of three structures involved in intercellular connections. Without a stimulatory signal (one of which is the Wnt factor), β-catenin is permanently phosphorylated by GSK3b kinase and directed for proteasomal degradation. Appropriate environmental signals induce alternative phosphorylation of β -catenin, which then moves to the nucleus to serve as a transcription factor[70]. Thus, the E-cadherin/β -catenin complex plays an important role in maintaining epithelial integrity, and disruption of this complex affects not only the cell adhesive capacity but also the Wnt-signaling pathway, abnormally activated in many tumors. Aberrant expression of this complex is associated with a wide range of human malignancies and diseases[71].

Expression of E-cadherin is decreased and β-catenin is increased in NPC. Altered expression of these two

proteins has been well studied in NPC cells and is associated with late-stage disease and metastasis to lymph nodes. E-cadherin expression is decreased in NPC cells, which is associated with the invasive and metastatic potential of NPC cells[38]. E-cadherin is modified by the N- and O-glycosylations. N-glycosylation at Asn-637 is essential for expression, folding, and trafficking of E-cadherin. Beta-catenin is O-glycosylated at Ser-23, which decreases its nuclear localization and transcriptional activity but increases its localization to the plasma membrane and its interaction with E-cadherin[72]. Beta-catenin is reported to be upregulated in NPC cells due to mutations disabling its proper degradation[73]. The EBV-encoded microRNA miR-BART9 facilitates switching from E-cadherin to oncogenic N-cadherin[74]. E-cadherin expression is controlled at several levels. At the level of gene expression, it is silenced due to methylation of the E-cadherin promoter induced by IL-8 signaling [75]. MicroRNA 23b targets E-cadherin mRNA for degradation[76]. LncRNA HOTAIR regulates the expression of E-cadherin by recruiting histone methylase EZH2 to mediate H3K27 trimethylation, resulting in silencing of the E-cadherin promoter. O-glycosylation of EZH2 increases the stability of EZH2, enhancing its function[77]. EZH2 forms a co-repressor complex with HDAC1/HDAC2 and Snail to inhibit E-cadherin expression. Snail is also a glycoprotein, its O-GlcNAcylation stabilizes the protein and thus results in decreased expression of E-cadherin[77]. The lncRNA transcribed from the metastasis-specific super-enhancer region of the genome LOC100506178 (seRNA LOC100506178) existing only in metastatic NPC cells and powerfully aggravating NPC metastasis is capable of down-regulating E-cadherin expression[78]. The oncogenic variant of the transcription factor KLF6-SV1 is associated with the lack of E-cadherin expression[79].

Downregulation of E-cadherin in NPCs may be caused by activation of another glycosylated protein, the cell surface receptor NgR3[80]. Stimulation of NPC cells with epidermal growth factor (EGF) activates PI3K/AKT signaling resulting in the downregulated membranous E-cadherin and β-catenin expression[81]. The increased expression level of the cytoskeletal proteins CKAP4 and Ezrin in NPC results in decreased membrane expression of E-cadherin in NPC cells. Demethylation of the E-cadherin gene in NPC could serve as a potential therapeutic strategy[82].

2.3 Osteopontin

Osteopontin (OPN) is up-regulated in NPC. Osteopontin is an extracellular O-glycosylated protein, the elevated expression of which in NPC cells promotes cell proliferation and migration, predicts bone metastasis, and reduces the survival of NPC patients[82]. Osteopontin is upregulated in NPC. Expression of osteopontin is controlled by a polymorphism of its gene [83] and the hypoxic condition in the NPC tumor[84]. The plasma osteopontin level defines the response to radiotherapy in nasopharyngeal cancer[85]. Osteopontin promotes EZH2 expression and facilitates repression of E-cadherin expression via methylation of its promoter[86]. Coordinated CD44-osteopontin signaling during disease progression in NPC has also been reported[87]. A recent review describes many aspects of the effects of deregulated osteopontin expression on tumorigenesis. OPN plays a role in cancer progression and OPN-mediated tumor-stromal interaction, EMT, CSC amplification, immunomodulation, metastasis, chemoresistance, and metabolic reprogramming[88].

2.4 Lactoferrin

Lactoferrin/lactotransferrin is down-regulated in NPC. Lactoferrin/lactotransferrin is a major iron-binding, secreted multifunctional protein, both O-and N-glycosylated[89]. Lactotransferrin is down-regulated in NPC[90]. MiR-214 targets lactotransferrin mRNA[91]. Lactotransferrin acts as a tumor suppressor in NPC by repressing AKT through multiple mechanisms[89]. Lactoferrin deficiency induces a pro-metastatic tumor microenvironment by recruiting im-

mune suppressor cells[26]. Lactotransferrin can be a novel independent molecular prognosticator of NPC [92]. Lactoferrin can inhibit EBV infection of epithelial cells[93]. Lactoferrin suppresses the EBV-induced inflammatory response by interfering with pattern recognition of TLR2 and TLR9[93]. Bactericidal/Permeability-Increasing (BPI) protein family members BPIFA1/SPLUNC1 and BPIFB1/LPLUNC1 are two other secreted glycoproteins like lactoferrin which establish the innate immune protection barrier and are also significantly down-regulated in NPC. The BPI proteins have bactericidal function and possess the capacity for endotoxin neutralization. In addition, BPIFA1 is involved in cancer stem cell homeostasis in EBV-infected NPC cells[94].

2.5 Fibronectin 1

Fibronectin 1 is highly expressed in NPC and serves as a prognostic marker of NPC progression and dissemination of cancer cells[8]. Either one or both of the amino acids Thr-2155 and Thr-2156 of fibronectin 1 is/are N-glycosylated. It is secreted and is an essential component of the extracellular matrix in NPC, which promotes motility and proliferation of NPC cells and suppresses apoptosis of cancer cells[16, 95].

2.6 Serglycin

Serglycin is a small, O-glycosylated extracellular glycoprotein associated with vesicles, the expression of which is elevated in NPC[8]. Serglycin binds CD44 activating the MAPK- β -catenin signaling axis[96] and promoting self-renewal of CSCs and metastasis in NPC, representing an independent marker of distant metastases in NPC[63, 69].

2.7 Other glycoproteins

The role of glycoproteins in NPC is also indicated by the altered expression of several proteins of the same class. For example, secreted glycoproteins of the Wnt family, which are N-glycosylated and serve as activators of the Wnt signaling pathway, can lead to tumor cell proliferation when their expression is unregulated in NPC[97]. Metalloproteinases of the ADAM family, which are N-glycosylated, transform TME facilitating dissemination and metastasis of tumor cells. These glycoproteins with metalloprotease activity are involved in the cleavage of cell surface receptors and/or degradation of extracellular factors such as collagen [12, 13, 31].

CD38, a cell surface protein, undergoes N-glycosylated. CD38 may serve a carcinogenic role in NPC by regulating metabolic-associated signaling pathways. CD38 inhibits cell senescence and promotes metastasis and proliferation of NPC cells. It also regulates metabolic-associated signaling pathways controlled by tumor protein p53, hypoxia-inducible factor-1α, and sirtuin 1[98].

Podoplanin, a cell surface protein, is O-glycosylated. Knocking down PDPN leads to suppression of NPC cell proliferation, migration, and invasion. PDPN may serve as a potential chemotherapeutic target for NPC treatment in the future[99].

3 Conclusion

In conclusion, most of the glycoproteins involved in NPC pathology function around the plasma membrane either as cell surface receptors or as extracellular, secreted proteins and mainly as oncogenic factors (figure 1). The significance of the glycoproteins discussed above, namely in EBV-associated NPC pathology is underscored by an intimate link of these cellular factors with other EBV-associated tumors like B cell lymphomas or gastric carcinoma[8, 100-102]. The role of metabolic reprogramming in tumorigenesis towards glycolysis is currently of increasing interest in the scientific community[103]. Taken together, these data underline the important structural and functional role of glycoproteins in the development of NPC. As discussed above, glycoproteins often act in an autocrine mode (e.g., in the CD44-serglycine pair, osteopontin promotes E-cadherin silencing and cooperates with CD44 signaling), supporting a vicious cycle of cell transformation. The observed changes in the expression of tumor-associated glycoproteins re-

flect the metabolic changes normally occurring in NPC cells, which increase interest in dietary interventions as a promising treatment for NPC[38]. Identification of novel glycoproteins associated with NPCs, and understanding the variations, mechanisms, and consequences of glycosylation processes in NPCs will provide important insights into the tumorigenesis of NPCs.

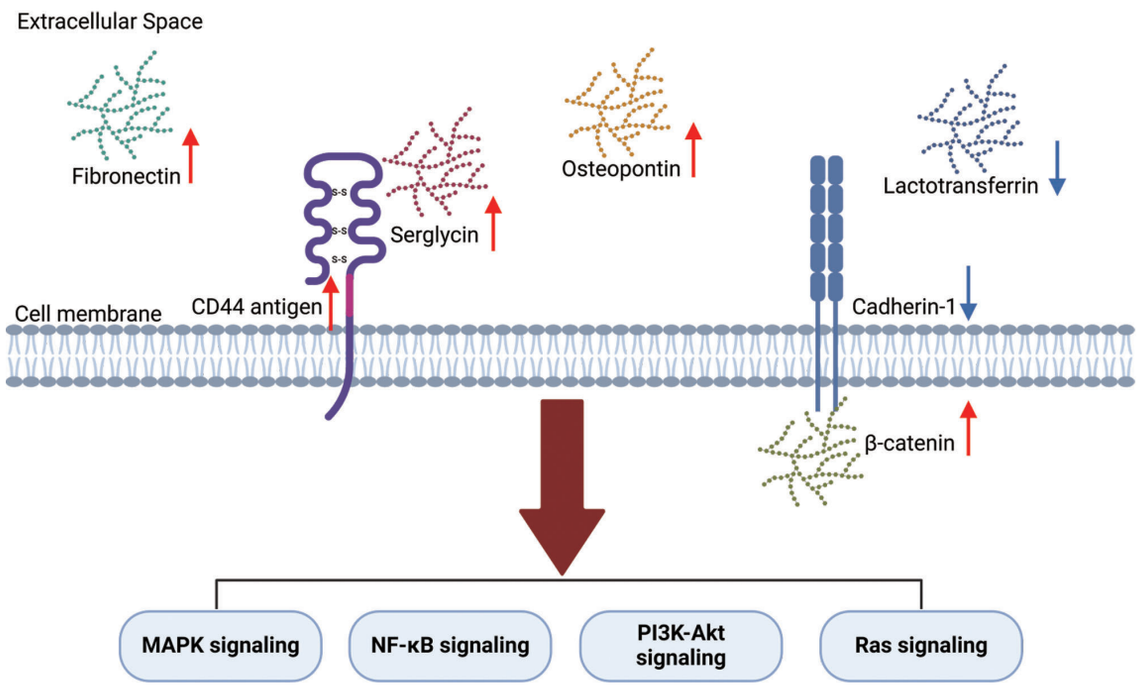

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Figure1. Altered glycoprotein expression in NPC pathology and impact on cell signaling

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