International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 8, No. 3, 2024

Research Progress on NDUFA9 and GBM

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Abstract: Glioblastoma (GBM) is the most aggressive and deadly malignant glioma of the adult central nervous system (CNS), searching for related genes is very important for the treatment and prognosis of GBM. NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9 (NDUFA9) is a subunit of NADH: ubiquinone oxidoreductase (complex I), plays a significant rule in oxidative stress and metabolic reprogramming in a range of cancerous malignancies. Recently, it has been proved that NDUFA9 can predict prognosis and immunological status in GBM. NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2 (NDUFA4L2) is a subunit of complex I either which is similar to NDUFA9. Researchers demonstrate that in addition to being significantly upregulated in GBM tissues and cells, increased NDUFA4L2 expression has been found to be a reliable indicator of overall patient survival. Relevant studies on GBM have frequently referred to NDUFA9, as the subunit of the complex I in mitochondria, the mechanism of NDUFA9 on GBM may to do with the activities of mitochondria, oxidative phosphorylation pathway, the electron transfer chain and the production of ROS. However, the specific mechanism of NDUFA9 on GBM still lacks relevant reports and is required for further exploration.

Keywords: GBM; Complex I; NDUFA9; NDUFA4L2; NDUFA7; Tumor.

1. Background

Gliomas are the most common primary cerebral tumors,[1] originating from the glial cells. Additionally, they are the most prevalent tumors that impact the CNS. The 2007 World Health Organization (WHO) classification of primary CNS tumors, divides gliomas into grade I tumors like pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytomas, grade II tumors like oligodendrogliomas and astrocytomas, and grade III tumors like anaplastic oligodendrogliomas, anaplastic astrocytomas, anaplastic oligoastrocytomas, anaplastic ependymomas, and grade IV tumor GBM.[2] However, based on the histological features, the WHO classification of primary CNS tumors has been extensively updated and rectified in 2016, divides gliomas into low-grade gliomas (LGGs) and high-grade gliomas (HGGs). The LGGs include grade I slowly proliferative gliomas and grade II infiltrative gliomas. The HGGs include grade III and grade IV anaplastic infiltrative gliomas which are also referred to as GBM.[3]

GBM is the most aggressive and deadly malignant glioma of the adult CNS and a substage of HGGs.[4] As demonstrated by numerous studies, GBM exhibits one of the lowest 5-year overall survival (OS) rates of any human cancer and is one of the most fatal tumors.[5] The median survival of GBM still approximately 16 months despite decades of relentless efforts by the research and medical communities to fight against this disease.[6] Therefore, it is crucial to identify genes linked to novel therapeutic targets in order to enhance the effects on diagnosis, prognosis, and treatment in GBM.

2. NDUFA9 and Complex I

NADH: ubiquinone oxidoreductase which is also known as complex I, consists of 44 different subunits and contains 3 functional modules: the Q-, the N- and the P-module.[7] NDUFA9 is a Q-module subunit required for complex I assembly or stability, plays a significant rule in oxidative stress and metabolic reprogramming in a range of cancerous malignancies.[8-10]

Regarding of novel therapeutic targets for GBM, it is now been proved that several novel mitochondrial-related genes signatures (MRG) (TYMP, TSFM, MGME1, BOLA3, TRMT5, NDUFA9) can predict prognosis and immunological status in GBM.[11]

3. The Possible Relationship between NDUFA9 and GBM:

Relevant studies on GBM have frequently referred to NDUFA9, as the subunit of the complex I in mitochondria, the mechanism of NDUFA9 on GBM may to do with the activities of mitochondria, oxidative phosphorylation pathway, the electron transfer chain and the production of ROS.

3.1. Mitochondria:

Mitochondria are essential for almost every aspect of cellular physiology, including serving as signaling hubs to regulate cellular homeostasis and producing energy through oxidative phosphorylation. Mitochondria specifically influence the regulation of metabolism, osmotic balance, calcium homeostasis, reactive oxygen species generation, steroid synthesis, apoptosis, cell cycle, proliferation, differentiation, epigenetics, innate immune signaling, and aging processes. Mitochondria use nuclear instructions and regulate the expression of many genes to perform these functions.

Now, most people agree that mitochondria play a crucial role in the development of tumors. Research by Shteinfer-Kuzmine A, Verma A, Arif T, Aizenberg O, Paul A, Shoshan-Barmaz V demonstrates that voltage-dependent anion channel 1 (VDAC1) regulates the GBM cells by changes the expression levels of proapoptotic proteins and their nuclear localization.[12]

There has been much research done on the role of mitochondria in GBM. For instance, glioblastoma stem cells use particular cytoprotective mechanisms, such as the

activation of mitochondrial stress pathways, to withstand the harsh environment when stressors like irradiation and hypoxia are present. Compared to quiescent glioblastoma stem cells and terminally differentiated GBM cells, which depend more on oxidative phosphorylation, proliferating GBM cells show higher levels of cytoplasmic glycolysis. Moreover, GBM has been linked to the Warburg effect, which is defined by elevated tumor cell glycolysis and reduced mitochondrial metabolism in the presence of oxygen.[13]

The Warburg Effect is one adaptive mechanism that sustains the metabolic demands of uncontrolled proliferation. Anabolic processes that promote cell division use the higher glucose intake as a source of carbon. This additional carbon is used for the de novo synthesis of proteins, lipids, and nucleotides and can be diverted into a number of branching pathways that result from glycolysis. One well-known conclusion is that proliferating cells need additional reducing equivalents in the form of NADPH rather than a rate-limiting demand for ATP, in addition to using more carbon from increased glucose metabolism for cellular building blocks. Increased glucose consumption promotes the synthesis of these reducing equivalents in the oxidative branch of the pentose phosphate pathway. These reducing equivalents are then used in reductive biosynthesis, namely in de novo lipid synthesis.[14]

While there are other bioenergetic mechanisms that support malignant growth besides the Warburg effect, which is an element of most cancers and involves the conversion of glucose to lactate even in the presence of oxygen. Indeed, sophisticated studies of stable isotope tracking have demonstrated that ATP generated by oxidative phosphorylation is necessary for tumor growth and showed that mitochondria are not only functional in malignancy.[15]

NDUFA9 is thought to be associated with the activities of mitochondria as a subunit during the formation of GBM.

3.2. Oxidative Phosphorylation Pathway:

More recently the idea that invasive cells also need particular metabolic characteristics to endure and proliferate in novel settings that differ significantly in their availability of nutrients and oxygen from the tumor core has received more attention.[16] The significant metabolic pathways in GBM are carbohydrate metabolism pathway, lipid metabolism pathway, amino acid metabolism pathway, oxidative phosphorylation pathway and isocitric dehydrogenase (IDH) mutations.[17]

Lactate would be released as cancer cells consumed glucose more quickly. The known demand for ATP and biosynthesis might be met by converting lactate to pyruvate and using it for oxidative phosphorylation in the perivascular niche, which would minimize the acidification of the microenvironment. Accordingly, oxidative phosphorylation metabolism is a characteristic of the tumor's differentiated state.[18]

In GBM, a novel classification of GBM into four subgroups based on metabolic and developmental characteristics was established with the use of the multi-omic analysis. The primary cancer cells in the mitochondrial GBM subtype are oxidative ones, which depend on oxidative phosphorylation and reduce glycolysis which is also known as “the reverse Warburg effect”.[19]

3.3. The Electron Transfer Chain:

The electron transfer chain (ETC), sometimes referred to as the oxidative respiratory chain, is found in eukaryotic mitochondria. Through a variety of complexes and associated coenzymes, it takes part in redox processes and electron transfer, eventually producing ATP to supply energy for biological living activities. The five protein complexes that make up ETC are integrated into the inner membrane of the mitochondria and include complex I, succinate dehydrogenase (complex II), coenzyme Q: cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V). Reactive oxygen species (ROS) production rises as a result of mitochondrial ETC's decreased activity in mitochondrial metabolism; this primarily happens in complex I and complex III. Certain tumor cells require ETC to develop, and it has been demonstrated that the efficacy of immunological, anti-angiogenic, or oncogene targeted therapy is correlated with the suppression of ETC. Furthermore, studies on lung and brain cancers have shown that mitochondria strongly oxidize glucose in the mitochondrial metabolic pathway.[20-31] Complex I is one of the largest membrane protein complexes in cells and the most intricate multi-subunit complex in the ETC. In higher organisms, the composition of Complex I becomes increasingly complex. The entire oxidative phosphorylation reaction process depends on Complex I, which serves as the initial site of electron entry into ETC. When it malfunctions, cellular respiration can drop by at least 40%, which can result in a number of illnesses.[32]

As a crucial component of complex I, component of the ETC, NDUFA9 may be implicated in various processes related to tumor cell growth.

3.4. ROS:

ROS is produced by NADPH oxidase (NOx)/double oxidase (Duox) system on the plasma membrane. In cancer, many components of the membrane and mitochondria that produce and scavenge ROS change, resulting in the increase and decrease of ROS.[33]

It is now proved that three mechanisms—the mitochondrial respiratory chain, the mitochondrial unsaturated membrane, and macrophages are involved in the production of ROS. The production of superoxide radicals by oxygen molecules acquiring high-energy electrons through flavin mononucleotide (FMN) in complex I is now thought to be the primary mechanism by which the mitochondrial respiratory chain produces ROS. Since H2O2 is produced quickly after superoxide compounds are formed, the rate at which complex I produces superoxide compounds can be inferred quantitatively from the rate at which H2O2 is produced in the human body. As a result, complex I and complex III are thought to be the primary producers of ROS in mitochondria. [34]

NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (NDUFA7) is another subunit of complex I, which shares a lot in common with NDUFA9. Another research shows that the mutation of NDUFA7 inhibits the increase of ROS, reduced the production of ATP, and then reduced the activity of complex I, suggesting that NDUFA7 may affect the disease progression of GBM by inducing mitochondrial activity disorder. [35]

3.5. NDUFA4L2:

NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2 shares many similarities with NDUFA9 as another complex I subunit.

Recently, a study demonstrates that in addition to being significantly upregulated in GBM tissues and cells, increased NDUFA4L2 expression has been found to be a reliable indicator of overall patient survival. In addition to acting as an oncogene, NDUFA4L2 may also be a novel potential target and a biological marker for prognosis in GBM. Our experimental results and a broad sample of clinical data led us to conclude that HIF-1α does not directly affect the expression level of NDUFA4L2 in GBM, suggesting that NDUFA4L2 may be regulated by other mechanisms. Digoxin and 2-ME, two HIF-1α inhibitors, were unable to suppress NDUFA4L2 expression in GBM, which could provide problems for the clinical use of NDUFA4L2 targeting in GBM patients.[36]

4. Research of NDUFA9 in Tumor Diagnosis

4.1. Research Progress in Hepatoma Cell Tumor Diagnosis:

The overexpression of nuclear factor-erythroid 2 like 1 (NFE2L1) and the oxidative phosphorylation deficiency in hepatoma cell tumors were caused by the depletion of NDUFA9. The primary transcription factor that increases hepatoma cell invasiveness is NFE2L1. The NDUFA9/NFE2L1 axis is a critical prognostic marker of aggressive liver cancer with mitochondrial deficiencies, according to the research, which also reveals a unique retrograde signaling route driven by mitochondrial malfunction and the transcriptome.[37]

4.2. Research Progress in Colorectal Cancer Diagnosis:

Aldehyde dehydrogenase (ALDH) is a promising cancer drug target in colorectal cancer.

NDUFA9 can be used as its inhibitor. This will be a promising treatment for colorectal cancer, providing a new direction for the development of ALDH targeted therapies.[38]

4.3. Research Progress in GBM

Researches have demonstrated that NDUFA9 can predict prognosis and immunological status in GBM. Besides, as a subunit of complex I, NDUFA4L2 have a lot in common with NDUFA9, and is proven to be a potential therapeutic target in GBM either. However, the specific mechanism of NDUFA9 on GBM is still unclear.

5. Conclusion

As the most aggressive and deadly malignant glioma of the adult CNS, GBM exhibits one of the lowest 5-year OS, the median survival of GBM still approximately 16 months despite decades of relentless efforts by the research and medical communities to fight against this disease. So, finding genes which are linked to novel therapeutic targets in GBM is of great significance. Complex I is one of the largest membrane protein complexes in cells and the most intricate multi-subunit complex in the ETC, consists of 44 different subunits and contains 3 functional modules: the Q-, the N- and the P-module. NDUFA9 is a Q-module subunit required for complex I assembly or stability, plays a significant rule in oxidative stress and metabolic reprogramming in a range of cancerous malignancies. It is now been proved that several novel MRG (TYMP, TSFM, MGME1, BOLA3, TRMT5, NDUFA9) can predict prognosis and immunological status in GBM. As the subunit of the complex, I in mitochondria, the mechanism of NDUFA9 on GBM may to do with the activities of mitochondria, oxidative phosphorylation pathway, the electron transfer chain and the production of ROS. NDUFA7 is another subunit of complex I, which shares a lot in common with NDUFA9. Another research shows that the mutation of NDUFA7 inhibits the increase of ROS, reduced the production of ATP, and then reduced the activity of complex I, suggesting that NDUFA7 may affect the disease progression of GBM by inducing mitochondrial activity disorder. Besides as a subunit of complex I, NDUFA4L2 have a lot in common with NDUFA9, and is proven to be a potential therapeutic target in GBM either.

As for the Research of NDUFA9 in tumor diagnosis, NDUFA9 depletion was an upstream driver of the oxidative phosphorylation defect and NFE2L1 upregulation in hepatoma cell tumors. NFE2L1 is the key transcription factor to enhance hepatoma cell invasiveness via STX12 expression. Besides, NDUFA9 can be used as the inhibitor of ALDH, which promotes the progression of colorectal cancer. This will be a promising treatment for colorectal cancer, providing a new direction for the development of ALDH targeted therapies.

But the specific mechanism of NDUFA9 on GBM is still unclear. So, exploring the molecular mechanism of NDUFA9 regulating the specific biological behavior of GBM cells and further analyze the relationship between NDUFA9 and GBM will provide strong clinical support for the treatment of GBM.

6. List of Abbreviations:

Glioblastoma (GBM);
Central nervous system (CNS);
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9 (NDUFA9);
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2 (NDUFA4L2);
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (NDUFA7);
NADH: ubiquinone oxidoreductase (complex I);
Succinate dehydrogenase (complex II);
Cytochrome c reductase (complex III);
Cytochrome c oxidase (complex IV);
World Health Organization (WHO);
Low-grade gliomas (LGGs);
High-grade gliomas (HGGs);
Overall survival (OS);
Mitochondrial-related genes signatures (MRG);
Voltage-dependent anion channel 1 (VDAC1);
Isocitric dehydrogenase (IDH);
The electron transfer chain (ETC);
Reactive oxygen species (ROS);
NADPH oxidase (NOx);
Double oxidase (Duox);
flavin mononucleotide (FMN);
Nuclear factor-erythroid 2 like 1 (NFE2L1);
Aldehyde dehydrogenase (ALDH).

7. Declarations

7.1. Ethics Approval and Consent to Participate:

Not applicable.

7.2. Consent for Publication:

Not applicable.

7.3. Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

7.4. Competing Interests:

The authors declare that they have no competing interests.

7.5. Authors' Contributions:

JHC collected relevant literatures on NDUFA9 and was a major contributor in writing the manuscript, RQS collected relevant literatures on GBM.

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