OnLine Journal of Biological Sciences

Review

Unveiling the Impact of Endogenous Sialidases on Human Non-Infectious Disease Pathogenesis

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Article history
Received: 18-09-2023
Revised: 07-11-2023
Accepted: 17-11-2023

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Abstract: In our review, we have compiled existing information regarding the role of endogenous sialidases (neuraminidases) in the initiation and development of various non-infectious processes in humans. Precisely, pathologies of the cardiovascular system, tumor formations, neurological and metabolic disorders, and hereditary diseases. Sialidases appeared to be widely involved in a variety of human pathologies. An increase or decrease in the enzymatic activity of sialidase can be a triggering factor in the pathogenesis of these disorders. This led us to the conclusion that enzymes of this family are essential for the normal functioning of human organisms. Therefore, with a detailed study of the characteristics and functions of sialidase, it is possible to develop new and effective diagnostic methods, treatment strategies, and prevention of many important human diseases. In this review, we are linking all sialidase-related features of different diseases, which can set a direction for further studies.

Keywords: Sialidase, Neuraminidase, LDL, Cardiovascular Disease, Cancer

Introduction

Sialidases, the other name of which is Neuraminidases, (Neu) (EC 3.2.1.18), are enzymes playing a significant role in hydrolyzing α-glycosidic bonds in the interaction of sialic acid residues with carbohydrate groups found in glycoproteins and glycolipids (Minami *et al*. 2021a; Keil *et al*., 2022; Feng *et al*., 2017). They have a wide distribution in vertebrates, as well as in various viruses, bacteria, and parasites. The mammalian sialidases consist of four types: Neu1-4 (Yuan *et al*., 2020; White *et al*., 2018; Kijimoto-Ochiai *et al*., 2019; Minami *et al*., 2021b). These sialidases are encoded by distinct genes and exhibit variations in the localization within cells, enzymatic characteristics, and the specific substances they target (Karhadkar *et al*., 2021; Hata *et al*., 2015; Maurice *et al*., 2016; Smutova *et al*., 2014).

Neu1 demonstrates high activity in body cells and has the ability to hydrolyze various glycoproteins oligosaccharides and gangliosides under acidic pH conditions (Schauer and Kamerling, 2018; Zhou *et al*., 2020; Pearce and Läubli, 2016). Conversely, Neu2 and Neu4 exhibit minimal expression and function in neutral and weakly acidic pH environments to cleave sialic acid from gangliosides and glycoproteins (Rahman *et al*., 2015; Nath *et al*., 2020). On the other hand, Neu3, the second most active enzyme after Neu1, plays a crucial role in ganglioside hydrolysis (Rodriguez-Walker and Daniotti, 2017a; Pilling *et al*., 2022).

In terms of the localization within the cell, Neu1 is found in lysosomes and the plasma membrane, Neu2 is located in the cytosol, Neu3 is associated with the plasma membrane and can be present in endosomes, while Neu4 functions within the endoplasmic reticulum, mitochondria and lysosomes (Cirillo *et al*., 2016; Volkhina and Butolin, 2022; van der Wal *et al*., 2020; Rodriguez-Walker and Daniotti, 2017b; Oliveira *et al*., 2018). Refer to Fig. 1 for an illustration of the functions of sialidases. Notably, Neu3 demonstrates activity towards gangliosides present in the plasma membrane of neighboring cells. The modifications in ganglioside composition are reversible and reliant on transient Neu3 expression, emphasizing its role in facilitating cell-to-cell interactions (Papini *et al*., 2004).

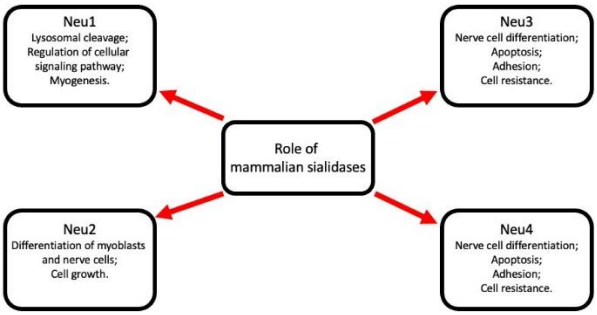

Fig. 1: Functions of sialidases in mammals

The exploration of sialidases in the context of non-infectious diseases has gained significant attention due to their involvement in diverse biological processes and their potential as therapeutic targets. By removing sialic acid residues from glycolipids and glycoproteins, sialidases are able to modulate cellular interactions, signaling pathways, and immune responses. This literature review aims to provide comprehensive research of the current knowledge on sialidases in diseases of non-infectious etiology. By examining their enzymatic activities, subcellular localizations, and their implications in disease pathogenesis, we hope to contribute to the growing body of knowledge in this field and pave the way for future research and therapeutic advancements targeting sialidases.

The process of cleavage of sialic acid from glycolipids, glycoproteins, or gangliosides is called desialylation. The subsequent results of desialylation are largely determined through the characteristics of sialic acid, which is a sugar with high electronegativity (Lillehoj *et al*., 2022). Cleavage of sialic acids influences the electrical charge of targeted molecules and can also impact the cell surface with significant sialylation. On a molecular scale, this process leads to the discovery or masking of glycoprotein binding sites for their molecular patterns. Desialylation also affects the interactions within molecules and the resulting folding of the protein, thereby modulating the functions of targeted glycoproteins as receptors, enzymes, or through signaling. Thus, sialidases are involved in the metabolism of various biomolecules, including lipids, carbohydrates, and proteins. Therefore, they can regulate essential biological functions and mediate the development of various diseases (Heimerl *et al*., 2020).

Sialidases in the Cardiovascular Diseases

In the cardiac tissue, there is a significant presence of sialylated cardiomyocytes and endothelial cells. The inclusion of terminal sialic acid in glycoconjugates is crucial for maintaining proper cellular function and cardiovascular physiology (Ghosh, 2020; Tian *et al*., 2017). Clinical studies have revealed that high serum total sialic acid concentration contributes to a heightened likelihood of experiencing cardiovascular complications in the future, regardless of Body Mass Index (BMI), cholesterol levels, and socioeconomic status (Li *et al*., 2020; Hou *et al*., 2019). Sialic acid is also associated with several risk factors for Coronary Heart Disease (CHD), namely dyslipidemia and insulin resistance.

Sialidases, regulating the exchange of sialic acids, are involved in the development of such diseases as atherosclerosis, CHD, cardiomyopathy, and congenital heart defects (Zhang *et al*., 2018a; Guo *et al*., 2018a-b).

Thus, the development of atherosclerosis is based on the formation of modified Low-Density Lipoproteins (LDL), which are deposited on the vessel wall. Several modifications occur to LDL particles, increasing their atherogenic properties. However, desialylation is the most significant and crucial atherogenic modification of LDL. Neu1 and Neu3 are responsible for this process and their activity is a of atherogenesis (Summerhill *et al*., 2019; Zhang *et al*., 2019; Yang *et al*., 2012). A study by Demina *et al*. (2021) indicated that the disabling of Neu1 and Neu3 genes through genetic means or inhibiting them pharmacologically in mice lacking the apolipoprotein E gene or LDL receptor had a substantial effect on the delay of fatty streak formation within the aortic intima, all while having no impact on plasma cholesterol and low-density lipoprotein levels. In addition, Neu1 is abnormally active in the hearts of patients with CHD, especially those with myocardial infarction. Knockdown of Neu1 reduces plasma sialic acid levels and prevents ischemic myocardial injury *in vitro* and *in vivo*, which is proved by a cardiac function improvement, as well as a reduction in inflammatory cell number (Li *et al*., 2021).

With cardiomyopathy, the heart, which has undergone pathological processes, cannot cope with the increased load. Cardiomyocyte hypertrophy develops, which further leads to altered inotropy, redundant oxygen consumption, and the development of heart failure (Nakamura and Sadoshima, 2018; Lee *et al*., 2017). At the same time, high levels of Neu1 are noted. González *et al*. (2018) suggest Neu1 facilitates cardiac hypertrophy through its interaction with transcription factor GATA4, thereby stimulating cardiomyocyte hypertrophy.

Neu3 is involved in cellular stress response. The division and differentiation of cardiac progenitor cells during fetal development are regulated by the level of oxygen that enters the cells. During oxygen starvation, the Neu3 enzyme is activated. Neu3 desialylates gangliosides GM3, which in turn stimulates the Epidermal Growth Receptor (EGFR). EGFR activates anti-apoptotic and proliferative signaling pathways and stimulates the synthesis of Hypoxia-Induced Factor α (HIF-1α) (Fig. 2). HIF-1α increases the resistance of cells to hypoxic stress and counteracts their apoptosis (Piccoli *et al*., 2017;

2022). Neu3 appeared to have a protective effect against cardiac fibrosis. Ghiroldi *et al*. (2020) showed that by inhibiting the TGF-β signaling pathway, Neu3 up-regulation has a notable impact on reducing cardiac fibrosis in primary cultures of human cardiac fibroblasts, leading to a decrease in collagen I deposition.

Thus, endogenous sialidases are essential for the pathogenesis of cardiovascular diseases and are promising markers for diagnosing these diseases.

Sialidases in Tumors

Different effects on carcinogenesis have been observed among the four identified types of mammalian sialidases. Some sialidases prevent the formation of tumors, while others promote the progression of cancer (Haxho *et al*., 2016; Hugonnet *et al*., 2021; Verheijen, 2008).

Neu1 has emerged as a significant contributor to neoplasm development in recent years (Munkley, 2022). For example, Neu1 overexpression is observed in mouse and human colon adenocarcinoma cells with different metastatic potentials. The enzyme inhibits cell migration and invasion. Also, a decrease in metastasis and the development of increased sensitivity of tumor cells to apoptosis is observed when Neu1 is introduced into B16 melanoma cells (Peng *et al*., 2022). Activation of Neu1 expression was observed in several tumor types. Thus (Kong *et al*., 2020) reported the role of the Neu1 enzyme in the development of hepatocarcinoma. The core protein of the hepatitis B virus enhances the expression of sialidase, thereby promoting the migration and proliferation of tumor cells. This increase is mediated through the NF-κB pathway, which also stimulates the downstream signaling pathways. The investigators also highlight the potential use of Neu1 as a therapeutic target (Wu *et al*., 2021). Also, Neu1 can promote metastasis of pancreatic cancer. Gilmour *et al*. (2013) showed the potential of Neu1 as a cancer-targeting enzyme. They demonstrated the efficacy of the neuraminidase inhibitor Tamiflu against Neu1 influences multiple glycosylated receptors (such as toll-like receptors, EGFR, TrkA) utilizing a receptor signaling pathway located on the cell surface. The comprehension of Neu1's involvement in cancer development stems from the discovery that Neu1 and MMP-9 are already associated with inactive EGFRs and are swiftly induced when exposed to EGF stimulation.

When studying the activity of Neu2 against tumors, it was shown that when the human Neu2 gene is introduced into K562 leukemic cells, there is a notable reduction in the levels of antiapoptotic factors Bcl-XL and Bcl-2. As a result, the cells become more susceptible to apoptotic triggers (Vajaria *et al*., 2016). Neu2 inhibition has also been documented in cases of pancreatic ductal adenocarcinoma. Overexpression of Neu2 in pancreatic carcinoma has shown an enhanced cell number at the late stage of apoptosis and a decrease in metastasis, invasiveness, and cell proliferation (Nath *et al*., 2018).

Neu3 activation is observed in various tumors. Thus (Bovio *et al*., 2020) proved that increased expression of Neu3 stimulates EGFR, contributing to its dimerization and activation of downstream effectors, which leads to colorectal cancerogenesis (Forcella *et al*., 2017). In addition, Neu3 is involved in the formation of a prostate malignancy through the stimulation of androgen receptors (Forcella *et al*., 2018). Additional studies have established that knockdown of Neu3 in PC-3 cells (cell line of human prostate adenocarcinoma) decreased the motility of cancer cells, suppressed their invasiveness and bone metastasis *in vivo* due to a reduction in the levels of matrix metalloproteinase MMP-2 and MMP-9 (Zhang *et al*., 2018b).

Glioblastoma multiforme is known as a highly aggressive tumor of the human Central Nervous System (CNS), displaying significant tissue invasiveness (Khabibov *et al*., 2022; Kim and Lee, 2022). With the development of this tumor, the expression of Neu3 is suppressed. An increase in Neu3 expression in human glioblastoma cell lines U251, A172, and T98G leads to a decrease in invasiveness and migration and promotes the assembly of focal adhesions due to a decrease in calpain-dependent proteolysis, while the suppression of Neu3 activity leads to an acceleration of cell invasion through the disassembly of focal adhesions (Sasaki *et al*., 2021).

The role of Neu4, which functions in the endoplasmic reticulum and outer mitochondrial membranes, in tumor transformation has been found in the development of colon cancer. The suppression of Neu4 expression in a tumor causes a noticeable suppression of apoptosis and an increase in cell invasiveness and motility (Cai *et al*., 2019).

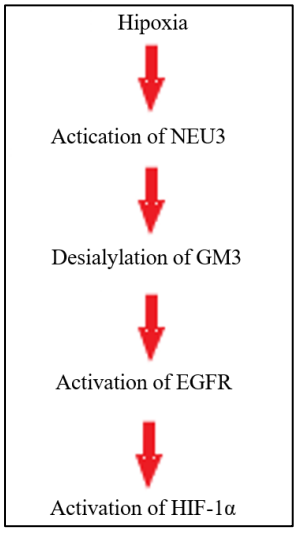

Fig. 2: Neu3 stimulates synthesis of HIF-1α (Piccoli *et al*., 2017; 2022)

Sialidases in Hereditary Diseases

There are several hereditary diseases associated with mutations in the sialidase genes. Mutations in the Neu1 gene result in sialidosis, a neurodegenerative lysosomal storage disease (Glanz *et al*., 2019; Ikeda *et al*., 2022; Seol *et al*., 2021).

Sialidosis arises from genomic DNA defects, which encompass frameshift insertions and missense mutations in the Neu1 gene located at 6p21.33 and is an autosomal recessive disease (Fan *et al*., 2020; Flores-Contreras *et al*., 2021). A deficiency in enzyme activity disrupts the degradation process of sialoglycoproteins, leading to the accumulation of excessively sialylated metabolites (Khan and Sergi, 2018).

Sialidosis exhibits heterogeneity, presenting a wide array of symptoms. It is classified into two types based on the varying onset and severity of clinical manifestations: I and II (Mosca *et al*., 2020; Gultekin *et al*., 2018).

Type I sialidosis, also referred to as cherry-red spot myoclonus syndrome, is a milder variant of the condition that tends to manifest later in life. Common indications of type I sialidosis comprise gradual vision impairment, bilateral cherry-red spots, and myoclonus, typically emerging during adolescence (Lv *et al*., 2020; Cao *et al*., 2021; Riboldi *et al*., 2021).

Type II sialidosis, on the other hand, is a more severe form and is categorized into three subtypes: Congenital, infantile, and juvenile. Congenital sialidosis type II is formed in utero following the second trimester of pregnancy and is accompanied by non-immunological dropsy or isolated fetal ascites (Ahn *et al*., 2019; Pérez-Cabeza *et al*., 2019). Patients are stillborn, or the disease is diagnosed at birth. The clinical symptoms of type II sialidosis are facial dysmorphism, skeletal dysplasia, mental retardation, hepatomegaly, and splenomegaly cases of infantile and juvenile types, individuals are typically born in good health (Rodriguez Criado *et al*., 2003; Tazi *et al*., 2022; Odaka *et al*., 2021). Nevertheless, soon after being born, these patients experience a gradual enlargement of their internal organs (visceromegaly) and the development of multiple skeletal abnormalities (dysostosis). Moderate to severe mental retardation has been seen as well (Han *et al*., 2020; Arora *et al*., 2020).

Galactosialidosis refers to a condition characterized by a simultaneous deficiency in sialidase and β-galactosidase activity (Annunziata and d'Azzo, 2017). This condition is caused by a malfunction in the lysosomal serine carboxypeptidase enzyme, also known as the Protective Protein Cathepsin A (PPCA). PPCA plays a vital role in safeguarding sialidase and β-galactosidase against lysosomal proteases (Mitsiakos *et al*., 2019; Cadaoas *et al*., 2021). When the enzyme complex is disrupted, leading to decreased sialidase activity, conditions such as sialidosis and galactosialidosis show no significant variation in the chemical composition of the glycoprotein-derived sialooligosaccharides excreted in the urine. This indicates that the disease phenotype is determined by the deficiency in sialidase rather than β-galactosidase (Hassan *et al*., 2021). Galactosialidosis presents in early infantile, late infantile, and juvenile-adult forms. The symptoms and characteristics of galactosialidosis closely resemble those observed in sialidosis (Hu *et al*., 2021; Alsahlawi *et al*., 2022). Galactosialidosis is classified as a rare disease with a low prevalence, often referred to as an orphan disease. Currently, there is no known treatment available for this condition (Nakajima *et al*., 2019).

Sialidases in Neurological and Metabolic Disorders

The behavior of neurons and glial cells is influenced by the sialylated carbohydrates present on the cell surface of central nervous system tissues (Rosa *et al*., 2022). Sialylation levels are not static but rather undergo dynamic changes throughout brain development. Likewise, alterations in sialylation patterns have been observed in both neurological disorders and the microglia's inflammatory response (Minami *et al*., 2017; Annunziata *et al*., 2013).

Khan *et al*. (2021) found that Neu1 deficiency can cause an amyloidogenic process similar to Alzheimer's Disease (AD) in mice (Khan *et al*., 2021; Khan and Sergi, 2022). In this disease, Neu1 desialylates macrophage and dendritic cell surface receptors and activates phagocytosis. Differentiated macrophages phagocytize amyloid plaques. Therefore, it can be concluded that Neu1 has therapeutic potential in AD (Lipničanová *et al*., 2020).

Moreover, Zhang *et al*. (2022) presented findings indicating a noteworthy upregulation of Neu1 mRNA expression in children diagnosed with Autism Spectrum Disorder (ASD). They also observed a correlation between heightened Neu1 expression and impaired social functioning in ASD children. However, the precise mechanisms underlying this correlation remain unclear and warrant further investigation (Pshezhetsky and Ashmarina, 2018). Employing sialidases to elevate brain gangliosides GM1 levels via the breakdown of polysialogangliosides emerges as a promising therapeutic avenue for Parkinson's disease (Miyagi *et al*., 2018; Schneider *et al*., 2015).

Thus, stimulation of the production of sialidases or their introduction into cells can be a promising strategy for treating neurodegenerative diseases or achieving a neuroprotective effect (Zhang *et al*., 2022).

The extent of sialylation is recognized as a significant factor governing energy metabolism and the absorption of glucose (Minami *et al*., 2020). Based on the existing experimental evidence, it has been observed that insulin attaches to the Insulin Receptor (IR) kinase on the cell surface, triggering a prompt association of this receptor with Neu1. Sialidase 1 acts by breaking down sialic acid residues present in the glycan chains of IR kinase, leading

to the activation of the IR dimer's active conformation (Fig. 3 In individuals with sialidosis, a genetic deficiency of the Neu1 enzyme is observed in their cells, which results in impaired insulin-induced phosphorylation of downstream protein kinases. However, the administration of purified Neu1 enzyme to these cells restores normal enzymatic processes (Fougerat *et al*., 2018). The interaction between Neu1 and matrix metalloproteinase-9 is vital for the activation of insulin receptors and cellular signaling in response to insulin. Consequently, targeting the Neu1 enzyme holds promise as a therapeutic approach for addressing insulin resistance (Alghamdi *et al*., 2014).

Limitations

The studies in the field of sialidases and their involvement in human non-infectious diseases may have several limitations that should be taken into account. Here are some common limitations.

Some studies may have a small sample size, which may reduce statistical power and limit the generalizability of the findings. Moreover, many studies rely on animal models or cell cultures to explore the impact of sialidases on disease pathogenesis. While these models are useful for initial investigations, they may not fully reflect the complexity of human diseases.

Also, some studies may establish correlations between sialidase levels or activities and disease outcomes. However, establishing a causal relationship requires additional experimental designs, such as intervention studies or genetic manipulation. Another limitation is confounding factors: Non-infectious diseases often have multifactorial causes and the contribution of sialidases may be influenced by various confounding factors, such as genetic predispositions, environmental factors, or lifestyle choices. It can be challenging to disentangle the specific impact of sialidases from these other factors.

The lack of longitudinal studies influences the data interpretation, too. Many studies focus on cross-sectional data, providing a snapshot of sialidase involvement in diseases at a specific time point. Longitudinal studies following individuals over time would provide a more dynamic understanding of the association.

Also, non-infectious diseases encompass a wide range of conditions with distinct pathophysiological mechanisms. Sialidase involvement may vary across different diseases, making it difficult to draw overarching conclusions.

It's important to consider these limitations when interpreting the results of studies in the field and to seek further evidence from a variety of sources to gain a more comprehensive understanding.

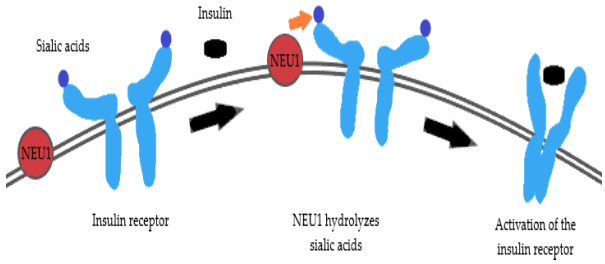

Fig. 3: Neu1 hydrolyzes sialic acid residues within the chain consisting of glycans of IR kinase and stimulates the active conformation of IR dimer (Zhang *et al*., 2019)

Conclusion

Endogenous sialidases are essential for managing numerous important processes in the human body. Changes in sialidase activity directly impact sialylation levels, leading to various effects, both positive and negative. Increased sialidase activity can positively regulate metabolic reactions and suppress the development and metastasis of tumor diseases. On the other hand, sialidase-mediated modifications of LDL can confer atherogenic properties, highlighting a negative consequence.

Manipulating sialylation levels by modulating sialidase expression or inhibiting their action presents promising therapeutic opportunities for managing and preventing a range of illnesses. Neu1, for instance, shows potential as a target for combating insulin resistance, whereas inhibiting Neu1 could be beneficial in managing Coronary Heart Disease (CHD). Additionally, Neu2, along with Neu4 and other sialidases, has shown promise as targets in various cancer types.

The broad participation of sialidases in such a diverse array of conditions showcases their significance in the field of medicine. Furthermore, this diverse set of actions aligns with the principles of personalized medicine, driving the development of tailored treatment approaches.

Recent research has shed light on the diverse and significant roles of endogenous sialidases in regulating important processes in the human body. The direct impact of sialidase activity on sialylation levels and subsequently, on various physiological effects, underscores the potential for developing novel therapeutic strategies targeting these enzymes. Moreover, the identification of specific sialidases, such as Neu1 and Neu2, as promising targets for addressing insulin resistance, coronary heart disease, and various types of cancer, highlights the innovative possibilities for tailored treatments and the advancement of personalized medicine. Specific mechanisms and strategies for targeting Neu1 and Neu2 involve sophisticated

approaches aimed at modulating their activity for therapeutic benefits. One strategy is the design and development of small molecular inhibitors that selectively bind to the active sites of these sialidases, effectively blocking their enzymatic function. This inhibition can impede the pathological processes associated with insulin resistance and coronary heart disease, offering potential therapeutic benefits. Additionally, targeted gene therapies using specific nucleic acid sequences or gene editing techniques like CRISPR-Cas9 hold promise for regulating the expression levels of Neu1 and Neu2, thereby influencing sialylation patterns. These precise interventions offer exciting avenues for personalized medicine by tailoring the modulation of sialidase activity to individual patient needs and disease conditions. The ongoing research in this area aims to unlock the full therapeutic potential of Neu1 and Neu2, paving the way for innovative treatments and improved patient outcomes.

In summary, understanding and harnessing the potential of sialidases offer exciting avenues for therapeutic intervention across multiple diseases. By targeting sialylation levels through sialidase modulation, researchers can pave the way for more effective treatments and contribute to the advancement of personalized medicine paradigms.

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which have enabled us to share our findings with a wider audience. We appreciate the efforts of the editorial team in reviewing and editing our work, and we are thankful for the opportunity to contribute to the field of research through this publication.

Funding Information

This research was funded by the Russian Science Foundation, grant number 23-65-10014.

Author's Contributions

Raisa Sergeevna Surkova: Drafted the manuscript.

Anastasia Vladimirovna Poznyak, Dmitry Alexandrovich Kashirskikh, Vasily Nikolaevich Sukhorukov, Alexandra Alexandrovna Melnichenko and Alexander Nikolaevich Orekhov: Revised and polished the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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