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Micrornas As Regulators of Oxidative Stress and Neuroinflammation in Parkinson's Disease: Consequences for Treatment and Management of The Illness

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative illness marked by intracellular protein clumps called Lewy bodies and the death of dopaminergic neurons in the substantia nigra. MicroRNAs (miRNAs) are important regulators of oxidative stress and neuroinflammation pathways linked to Parkinson's disease (PD) progression, according to recent studies. By targeting genes involved in antioxidant defense systems, mitochondrial activity, and alpha-synuclein aggregation, miRNAs influence oxidative stress and affect the vulnerability of neurons to oxidative damage. MicroRNAs (miRNAs) control the activation states of astrocytes and microglia in neuroinflammation. This regulates the release of pro-inflammatory cytokines and increases the damage to neurons. This review highlights the potential of miRNAs as therapeutic targets while examining their functions in Parkinson's disease. MiRNA-based therapies present a viable avenue for the development of innovative therapeutics with the goals of maintaining dopaminergic neurons, lowering neuroinflammation, and attenuating oxidative stress. Moreover, miRNA biomarkers linked to the development of a disease may help with early diagnosis and individualized treatment plans. There are still many obstacles to overcome, including the effective delivery of miRNA therapies to the brain and guaranteeing their safety and specificity in clinical settings. However, more investigation into miRNA-mediated pathways in Parkinson's disease (PD) offers significant potential to advance our knowledge of the biology of the illness and enhance patient outcomes.

Keywords: Parkinson's disease, microRNAs, oxidative stress, neuroinflammation, therapeutic targets, biomarkers.

1. INTRODUCTION

In Parkinson's disease (PD), neuroinflammation and oxidative stress are not separate physiological processes; rather, they are entwined and commonly build up each other.

The connection among irritation and oxidative stress is a significant calculate the development of Parkinson's disease (PD), which is described as a neurodegenerative disorder. Actuated microglia are responsible for the release of favorable to fiery cytokines, which drive the arrangement of reactive oxygen species (ROS) in neurons and glial cells. This pathway is associated with irritation actuated oxidative stress. One model is the actuation of the NADPH oxidase chemical complex by growth necrosis factor-alpha (TNF-α), which results in an increase in the development of reactive oxygen species (ROS). The oxidative stress that is caused by fiery mediators is a supporter of the harm that is finished to cells and makes neuronal weakness worse in Parkinson's disease.

Oxidative stress, on the other hand, may also be responsible for initiating and exacerbating inflammation via a variety of processes. Within the cells, reactive oxygen species (ROS) have the ability to activate inflammatory signaling pathways, one example of which is the NF-κB pathway. When NF-κB is activated, it triggers the production of cytokines and chemokines that promote inflammation, which in turn further enhances the inflammatory reactions that occur in the brain. What's more, harm to cell components that is caused by oxidative stress might result in the creation of harm associated atomic patterns (DAMPs), which thusly enact microglia and proceed with the provocative cascade. Continuous neuroinflammation is the result of this pattern of oxidative stress-prompted irritation, which also plays an essential job in the progressive neurodegeneration that is characteristic of Parkinson's disease (PD).

In order to develop tailored therapy options for Parkinson's disease (PD), it is essential to

have a solid understanding of the reciprocal interaction that exists between inflammation and oxidative stress. Researchers are attempting to lower neuroinflammation, lessen the amount of damage caused by oxidative stress, and maybe halt the course of the illness by concurrently targeting both pathways. For the purpose of achieving neuroprotection and improving outcomes for those who are afflicted with Parkinson's disease, potential future medicines may concentrate on modifying these interrelated physiological pathways.

Aggravation of the nervous system and oxidative stress are two of the most significant factors that add to the turn of events and progression of Parkinson's disease. By gaining an understanding of these processes, one might get information about prospective treatment targets. Strategies that attempt to reduce neuroinflammation and oxidative stress, such as the use of anti-inflammatory medications, antioxidants, and medicines that boost mitochondrial function, show promise for delaying the course of Parkinson's disease (PD) and enhancing the quality of life for those who have the condition.

2. LITERATURE REVIEW

Cai, L. J., et.al., (2020). Through the process of down-directing transcription factor specificity protein 1 (SP1), the purpose of this research is to assess the defensive impact that increased microRNA-375 (miR-375) plays in dopaminergic neurons in Parkinson's disease. Collected neurobehavioral changes, increased neuroinflammatory response and oxidative stress, and decreased dopamine content were seen in the rats that were actually imitated with Parkinson's disease. Overexpressed miR-375 in Parkinson's disease mice resulted in upgraded neurobehavioral change, decreased neuroinflammatory response and oxidative stress, increased dopamine content, and diminished neuronal demise. These effects were accomplished by the down-guideline of SP1. Increasing the expression of SP1 had the opposite effect of the defensive impact that increased miR-375 had on Parkinson's disease illness. The substantia nigra striatum was harmed to make a Parkinson's disease rodent model. This was accomplished by the administration of 6-hydroxydopamine in concentrated doses. To actually repeat Parkinson's illness in rats, intracerebroventricular injections of miR-375 mimics or pcDNA3.1-SP1 were administered. In the substantia nigra of Parkinson's disease rats, the roles of microRNAs miR-375 and SP1 were investigated. These functions included neurobehavioral change, neuroinflammatory response, oxidative stress, dopamine content, and creation of proteins associated to apoptosis. Using bioinformatics analysis and a double luciferase columnist quality trial, affirmation of the objective connection between miR-375 and SP1 was accomplished.

Khish, N. S., et.al.,(2023). The neurodegenerative illness known as Parkinson's disease (PD) is a pervasive condition that is characterized by the development of α-synuclein and the destruction of dopaminergic neurons in the substantia nigra. Despite the way that the sub-atomic grounds for the improvement of Parkinson's disease are not totally understood, a substantial collection of information suggests that neuroinflammation is closely related with the advancement of Parkinson's disease. Despite the fact that neuroinflammation may not be a significant cause in that frame of mind with Parkinson's disease (PD), it seems to be a main thrust for the headway of the illness. As a result, it is of utmost significance to investigate the job that pathways engaged with neuroinflammation play in the development of the disease progression. What's more, the significance of non-coding RNAs (ncRNAs), which incorporate microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and contending endogenous RNAs (ceRNAs), has been extensively researched, with a specific emphasis on the pathophysiology of Parkinson's disease (PD specifically). Be that as it may, there is no comprehensive audit with respect to the job of neuroinflammation-related non-coding RNAs (ncRNAs) as prospective biomarkers and helpful targets engaged with the pathogenesis of Parkinson's disease (PD). This is despite the way that the quantity of studies interfacing ncRNAs to neuroinflammatory pathways and oxidative stress has significantly increased throughout recent years. As a result, the purpose of this story survey was to give a description

of the connection between administrative non-coding RNAs and neuroinflammatory targets comparable to Parkinson's disease (PD) to distinguish and suggest potential mix biomarkers or treatment targets in clinical settings.

Singh, G., & Khatri, D. K. (2023). It is estimated that 10 million individuals all through the globe are impacted with Parkinson's disease (PD), which is the second most common neurological illness. In the advancement of Parkinson's disease (PD), neuroinflammation is quite possibly of the most significant pathologic process. One of the mechanisms that contributes to neuroinflammation is the enactment of TLRs that are tracked down on safe cells in the brain. Besides, microRNA is responsible for controlling the expression of TLR in neurodegenerative disorders. Nevertheless, there is an absence of information about the microRNA that controls the TLR signaling genes in Parkinson's disease. GO, which is a bioinformatics device that uses the representations for genes in an organism; PPI, which shows the physical cooperation between proteins in an organism; and miRNet, which is an instrument to explore the complex relationships among miRNAs and their targets to acquire a more profound understanding of the natural processes engaged with this study. The purpose of this study is to recognize the possible TLR genes and administrative miRNAs that work in neuroinflammation-induced Parkinson's disease (PD). The quality expression profile, which was recognized as GSE26927, was acquired from the GEO Omnibus. The crease improvement score for every pathway was approved using DAVID bioinformatics and SHINY GO software. This was finished to direct GO analysis of differentially expressed genes (DEGs). To distinguish essential or center point genes, the TLR signaling pathways that had the most liberated genes (upregulated: log FC $\geq$ 2.0, downregulated: log FC $\leq$ - 2.0) were selected for network analysis. Following that, a miRNA-quality organization was worked with the assistance of the miRNet program. The most significant TLR signaling quality that differentiates between samples of Parkinson's disease and control samples has been recognized. Inside the Protein Collaboration (PPI) organization, we discovered genes that showed increased connectedness. One of these genes was TLR4, which had the greatest level of betweenness (degree = 22) in the TLR signaling pathway. Moreover, in the organization of miRNA genes, we discovered the five most significant miRNAs: hsa-miR-21-5p, hsa-miR-17-5p, hsa-miR-93-5p, hsa-miR-7-5p, and hsa-mir-92b-3p. These miRNAs were shown to connect with the TLR signaling quality. The 10 most noticeable TLR genes can possibly serve as helpful targets for novel drugs. Moreover, the possible microRNAs that have been found can substantially impact the expression of TLR genes in Parkinson's disease and may go about as remedial targets.

Wang, X., et.al., (2020). The presence of oxidative stress is much of the time seen in neurodegenerative illnesses, and it is associated with neuronal harm and the progression of pathogenic conditions. It has been demonstrated that exosomes, which are classified as extracellular vesicles, are responsible for transporting microRNAs (miRNAs) and establishing a correspondence network between neurons. It has been shown by means of late study that exosomal microRNAs are responsible for managing the action of numerous physiological processes, one of which is the response to oxidative stress, in neurodegenerative disorders. Inside the setting of neurodegenerative illnesses, we will analyze the capability of exosomal microRNAs as well as oxidative stress. In the first spot, we investigate the association between oxidative stress and neurodegenerative disorders. The second piece of this article discusses the properties of exosomes as well as the functions that exosome-related microRNAs play. In the third step of our analysis, we gave a synopsis of the cooperation between exosomal microRNAs and oxidative stress in neurodegenerative disorders. We then happen to the fourth subject, which is the possibility that exosomes could serve as a biomarker in neurodegenerative illnesses. In conclusion, we give a synopsis of the benefits associated with exosome-based conveyance as well as the present status of progress in studies concerning exosome-based conveyance of helpful miRNA. The purpose of our

study is to investigate and strengthen the recognizable proof of the pathomechanism of neurodegenerative disorders, as well as to give the establishment to creative approaches to clinical diagnosis and treatment.

Rasheed, M., et.al., (2021). Neuroinflammation is perhaps of the most significant variable that plays a job in the early phases of Parkinson's disease as well as its turn of events. Parkinson's disease (PD) is a neurodegenerative condition consisting of a development impedance that is associated with an extensive variety of confounded and diverse risk factors. Numerous cell and sub-atomic processes are set off as a result of these variables. Some of these processes incorporate the misfolding of flawed proteins, oxidative stress, mitochondrial dysfunction, and neurotoxic chemicals that advance selective neurodegeneration of dopamine neurons. The brain resistant system, which includes glial cells and provocative cytokines, is initiated as a result of this neuronal injury, which will eventually prompt neuroinflammation. A vicious cycle that leads to the improvement of Parkinson's disease (PD) is shaped when a person experiences a shift from intense to persistent neuroinflammation. This change increases the weakness to irritation induced dopaminergic neuron destruction. Epigenetic pathways have recently arisen in the front of the control of neuroinflammatory variables in Parkinson's disease (PD), suggesting another first light for breaking this vicious cycle. In the present audit, the basic epigenetic processes that are engaged with the actuation and phenotypic alteration of glial cells that are responsible for neuroinflammation in Parkinson's disease were investigated. Despite the way that epigenetic processes must be facilitated with each other to enact neuroinflammatory pathways, we discovered that these mechanisms don't work autonomously. In this respect, we tried to discover the synergistic association and commitment of these epigenetic alterations with an assortment of neuroinflammatory pathways to give a more comprehensive image of the basic pathogenic processes that are ensnared in the improvement of Parkinson's disease. Moreover, this research shed light on the double properties (neuroprotective and neurotoxic) of these epigenetic markers, which can repress the progression of Parkinson's disease (PD) and make them prospective candidates for the improvement of future PD diagnostic and treatment measures.

3. MICRORNAS AND OXIDATIVE STRESS IN PARKINSON'S DISEASE

Small non-coding RNA molecules known as microRNAs (miRNAs) are essential for post-transcriptional gene control. It has been determined that miRNAs are important regulators of oxidative stress pathways in the context of Parkinson's disease (PD). An imbalance between the generation of reactive oxygen species (ROS) and the capacity of cells to eliminate them or repair the harm they cause is known as oxidative stress. Oxidative stress plays a significant role in the gradual degradation of dopaminergic neurons in Parkinson's disease (PD).

MiRNAs control oxidative stress in a number of methods:

1. **Regulation of Antioxidant Defense:**MiRNAs have the ability to target genes that encode antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase (SOD). For instance, it has been discovered that miR-7 controls SOD2 expression, which has an impact on mitochondrial activity and neuronal oxidative stress levels.
2. **Mitochondrial Function:**The dynamics and function of the mitochondria, which are essential for preserving the cellular energy balance and reducing ROS generation, are regulated by miRNAs. Oxidative stress in Parkinson's disease (PD) may worsen due to dysregulation of miRNAs involved in mitochondrial biogenesis or function.
3. **Alpha-Synuclein Regulation:**The expression of a protein linked to Parkinson's disease pathology, alpha-synuclein, can be affected by miRNAs. Aggregation of alpha-synuclein can cause mitochondrial malfunction and oxidative stress, which can harm neurons. Thus, miRNAs that target alpha-synuclein mRNA may indirectly affect the levels of oxidative stress.

4. **Neuronal Survival:** Neuronal survival and death mechanisms in Parkinson's disease are also impacted by miRNAs that control oxidative stress pathways. miRNAs can affect how susceptible dopaminergic neurons are to oxidative stress-induced cell death by regulating the expression of genes involved in apoptotic pathways or cellular responses to oxidative damage.

Overall, through modifying antioxidant defense mechanisms, mitochondrial activity, and cellular responses to oxidative damage, miRNAs play a major role in the regulation of oxidative stress in Parkinson's disease. Comprehending the distinct miRNA regulatory networks implicated in oxidative stress pathways may offer perspectives on innovative therapeutic approaches targeted at ameliorating neuronal degeneration and delaying the advancement of Parkinson's disease (PD).

4. ROLE OF MICRORNAS IN NEUROINFLAMMATION AND THERAPEUTIC IMPLICATIONS

MicroRNAs (miRNAs) have a major role in neuroinflammation in Parkinson's disease (PD), which influences the disease's course as well as possible treatment approaches. In Parkinson's disease (PD), neuroinflammation is caused by the activation of microglia and astrocytes, which releases pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS) that injure neurons. MiRNAs target genes involved in immune responses and glial cell activation to control this inflammatory cascade. For example, miR-155 has been shown to increase the expression of pro-inflammatory cytokines such as TNF-α and IL-1β in activated microglia, which in turn exacerbates neuroinflammation in Parkinson's disease models. On the other hand, miRNAs that target signaling molecules involved in the activation of microglia and astrocytes, such miR-146a, work to decrease inflammation.

Deeply rooted therapeutic implications arise from miRNA participation in neuroinflammation. MiRNAs associated with neuroinflammatory pathway regulation may be targets for new treatment approaches intended to reduce neuroinflammation and protect dopaminergic neurons in Parkinson's disease (PD). One tactic might be the creation of miRNA-based treatments, which would specifically alter the expression of miRNAs that are either pro- or anti-inflammatory, reducing the detrimental effects of inflammation. Additionally, finding particular miRNA patterns linked to neuroinflammation in individuals with Parkinson's disease (PD) has promise for diagnostic applications, possibly allowing for early diagnosis and intervention during the disease process. For clinical translation, there are still important obstacles to overcome, such as establishing the safety and specificity of miRNA therapies and their transport to the brain. Sustained investigation into miRNA-mediated pathways of neuroinflammation in Parkinson's disease (PD) is imperative in order to unveil novel therapeutic approaches and develop tailored treatment approaches for this intricate neurodegenerative condition.

5. CONCLUSION

The study of microRNAs (miRNAs) in Parkinson's disease (PD) reveals their role in regulating oxidative stress and neuroinflammation. MiRNAs regulate antioxidant defense mechanisms, mitochondrial function, and the expression of proteins like alpha-synuclein, which are crucial in PD pathogenesis. They also contribute to neuroinflammation by influencing microglial and astrocytic activation states and the secretion of pro-inflammatory mediators. Targeting miRNAs that modulate these inflammatory responses holds promise for developing therapies aimed at reducing neuroinflammation and its detrimental effects on dopaminergic neurons. MiRNA-based interventions present novel opportunities for therapeutic interventions, such as enhancing neuroprotective miRNA expression or suppressing pro-inflammatory miRNAs. However, the translation of miRNA research into clinical applications faces challenges, including effective delivery methods and ensuring safety and efficacy in human trials.

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