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Role of Micro RNA in Migraine

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1. Introduction: Migraine and its Biomarkers

1.1 Defining Migraines

A migraine is a common recurring disorder characterised by blinding headaches that may last from 4 hours to 3 days. These headaches are often accompanied by other symptoms including nausea, vomiting, photophobia, and phonophobia (Goadsby et al. 2017). Additionally, there are two main forms of migraine: migraine with aura i.e. neurological symptoms such as flashing lights or tingling limbs occur before the pain, and migraine without aura refers to pain that occurs without any previous symptoms (IHS, 2018). Within a span of a lifetime, migraines affect approximately one out of every seven persons on the planet making them disabling particularly in women aged between 18 and 49 years (Steiner et al. 2020).

1.2 Hurdles in Diagnosis and Treatment of Migraine

Biomarkers are not available in a diagnostically useful form, hence diagnosing migraines is one of the biggest challenges. The patient history is the basis of the diagnosis, which includes criteria that rely on the patient's report of her symptoms, which are subjective, vari- able, and most of the times distorted. Such variability makes it difficult to normalise treatment as what may work for one patient may not work for a different patient making it more or less a crossover design (Ashina et al., 2021). Moreover, there is still a grey area in the understanding of the pathophysiology of migraines, which also poses a challenge in coming up with effective strategies for preventive measures. For example, studies have shown that migraine patients often use medications such as triptans, CGRP antagonists, and hormones, however, the bulk of the patients seem not to be tolerant to the drugs or have contraindications (Edvinsson et al., 2019). One reasonable argument to be made is that treatment in this area needs to be more general and better targeted to the patient's needs.

1.3 miRNAs as Migraine Potential Biomarkers

Some people smoke to pass the time, some smoke to calm themselves, some smoke to obtain a pleasure trigger, and some don't need a reason to smoke. Smoking can connote many ideas and personas to people where the occupation of smoking takes control among most individuals.

The sociocultural norms which surround the act of smoking are quite varied and some in fact encourage excessive smoking as a means of controlling unwanted behaviour. Within the working class women, excessive smoking is seen as a norm irrespective of the different ages of the women. However there exist some cultures and social groups who may despise the use of tobacco and regard the act as indecent and even uncivilised.

As men, women, and youth become more integrated into the workings of the society through urbanisation and its attendant modernization with new behaviour patterns emerging, it has universalized the acceptance of smoking in both public and quasi-public spaces. The ages of the people also do not restrict Using tobacco products to any specific gender. Norms on excess or restricted consumption of tobacco products vary across different societies and cultures.

2. The Contribution of miRNA to Migraine Pathogenesis with a Special Emphasis on Current Approaches

2.1 An Introduction to MicroRNAs

MicroRNAs (miRNAs) are short, non-coding RNAs ranging from 18 to 25 nucleotides in size that are essential for post-transcriptional gene regulation. This involves binding to the messenger RNA (mRNA) at the 3' untranslated region (UTR) of the target mRNA to either suppress mRNA translation or promote its destruction, hence modulating the rate of production of a protein (Bartel, 2018). Such regulation is important in many biological events such as cell differentiation, apoptosis and immune responses among others (Ambros, 2004).

MiRNAs in the nervous system have significant roles in neuroplasticity, synaptogenesis and neuronal function. They are involved in the refinement of neural circuits, all of which have a role in learning, memory and even pain (Lau & de Strooper, 2018). Neurons and glial cells can be modified by miRNAs, and it has been shown that changes in the expression of specific miRNAs are associated with some neurological diseases, including those manifesting with migraines (Kosik, 2016).

2.2 miRNAs' Link to Migraine

Emerging evidence includes studies reporting an association between miRNA expression and the chronic pain experienced in various conditions especially migraine. These small RNA cystine including other factors promotes their influence in chronic migraine pathophysiology which relates to pain, inflammatory and neurovascular mechanisms (Kalkman & Feuerstein, 2016). For instance, it works in the same way, as some research shows that patients who suffer from migraine attacks exhibit different expression patterns of miRNAs on the attack. Moreover, it may also be that the aspects of pain attributed to a chronic episodic condition like migraine are also controlled by miRNAs since they can modulate gene expression of factors associated with pain.

Among those miRNAs examined, i.e. those present on the diagram. Some of them, in particular, miR-382-5p, miR-34a-5p, and miR-30a-5p are of particular importance. Their expression levels change with the migraines, suggesting that they may contribute to the emergence and aggravation of migraine symptoms. In this regard, it is interesting to note that the expression of miR-34a-5p is known to target pain and neuroinflammation-regulating genes, and miR-382-5p is known to target neuronal excitability, which is essential for inducing migraines.

2.3 Mechanisms: Dealing with Inflammation, Neovascularization and Pain Control

The effect that miRNAs have on the pathoetiology of migraine the mechanisms of inflammation, neovascularization, and pain control. Inflammation is a significant player when it comes to migraines and contributions from certain miRNAs such as miR-382-5p and miR-34a-5p are known to regulate inflammatory mediators including IL-1β and TNF-α which play a role in pain and neuronal sensitization. Furthermore, pathway miR-30a-5p has been linked with the modulation of neurovascular pathways where calcitonin gene-related peptide (CGRP) a pivotal component for migraine pathophysiology has been influenced.

With respect to pain modulation, certain miRNAs are able to down regulate the genes responsible for nociceptor sensitization and central pain transmission. For instance, it has been reported that the function of voltage-gated ion channels can be modified by miR-34a-5p which in turn leads to changes in neuronal excitability and enhanced pain. This information shows that there are multiple aspects of the processes which lead to the onset of migraine attacks that are regulated by miRNAs.

3. Exploration of miRNA Biomarkers in Migraine

3.1 Exclusion Criteria for miRNA Biomarkers

The development of effective miRNA biomarkers for migraines has proven difficult for reasons. One major complicating factor is the diversity of participant samples with regard to age, gender, ethnicity and migraine type. Such factors also affect miRNA profiles leading to differing results in different studies (Lutz et al., 2018). In addition, factors such as stress, diet, and sleeping habits complicate the repeatability of these outcomes, especially for these metrics. Such parameters are impossible to manage but are known to influence miRNA profiles to a large extent. As a result, it remains a challenge to isolate miRNAs for migraines since most of the studies show opposing or non-conclusive results.

3.2 Potential Biomarkers

Although these difficulties exist, some potential migraine associated biomarkers have been identified in some miRNAs. Among the most promising is probably also subtypes miR-342-3p, miR-532-3p and miR-758-5p. These studies were conducted in a controlled environment where definite participants were included at specific environmental conditions. For example, miR-342-3p is known to be present during painful attacks likely because of its association with inflammation, whereas both miR-532-3p and miR-758-5p relate to pathways involved in pain and neurovascular control.

The specificity of these miRNAs is considered a major problem in conducting these studies. The same group of dysregulated miRNAs in patients suffering from migraine is usually affected in some other disease states like tension type headache, epilepsy or even rheumatoid arthritis. For example, there is elevation of miR-342-3p levels in patients suffering from epilepsy which again makes it difficult to use just this particular microRNA level to separate these conditions (Schankin et al., 2020). The diagrams depict that the same miRNAs may be present at altered levels in different diseases and thus may raise questions on the specificity of these miRNAs as biomarkers to be relied upon clinically. Consequently, they would be required in combination with other diagnostic markers to achieve the desired result.

3.3 Bioinformatic Analysis

Bioinformatics has also contributed significantly in the understanding the role of miRNAs in migraine as well as their consideration as biomarker. Thanks to bioinformatic analysis, for instance researchers are able to identify the gene targets of certain miRNAs and the function of these genes in relation to the development of migraine mechanisms including inflammation and pain, and the regulation of circadian rhythms.

For instance, bioinformatics has demonstrated that certain miRNAs like miR-342-3p are capable of binding to genes responsible for neuroinflammation and similarly, miR-758-5p regulates those genes which mediate vascular tone; both pathways play a significant role in the migraine pathophysiology (Eikermann-Haerter et al., 2015). In addition, these software systems are able to integrate data on miRNA expression with data from other levels such as genomic and proteomic even enabling one to understand the contribution of these small molecules in the process of migraine occurrence on a broader scale. In this way new insights on unique miRNA-mRNA regulatory networks for migraine can be obtained which would in turn be useful in finding more sensitive and specific biomarkers.

4. Clinical-Morphological Perspectives of Mitochondria as Potential Therapeutic Devices in Hypertension: Diagnostic and Therapeutic Strategies

4.1 Diagnostic Applications

It is thought that the applicability of miRNA profiles for drug-induced headache especially migraines could relate to such profiles being used to cluster and classify the patients based on different aspirations. Thus, by analysing some of the particular expressions of miRNA content, the complicated disease, with respect to migraine, could be managed better through treatment, for instance by identifying the subtypes of migraines with and without aura, chronic and episodic migraines, as well as perhaps even more specific regional or age-based differences. For example, it has been observed that certain miRNAs such as miR-382-5p and miR-34a-5p are differentially expressed throughout migraine attacks thereby suggesting that the classification of migraines can be improved through the use of miRNA panels.

However, these positive aspects do not eliminate certain drawbacks. For example, a large number of studies have been conducted with small sample sizes employed. In addition, the ethnic, age, and environmental diversity of the examined populations was often low, if not absent at all. Such uniformity can lead to skewed results, making the outcomes hard to generalise. There is a need for such studies in the future, where larger and more heterogeneous study backgrounds will be adopted so that miRNA-based tests that will be developed will be more valid and verifiable.

Moreover, Migraines have been associated with several miRNA signatures, but most of these markers are not limited to migraines and are involved in other neurological conditions like epilepsy and multiple sclerosis. This raises challenges in employing them as reliable diagnostic biomarkers. Therefore, it can be predicted that miRNA profiling will be combined with other biomarkers or clinical features to improve the diagnosis precision.

4.2 Potential Benefits from Treatment

The development of future treatments for migraines using miRNA modification is a plausible and thrilling strategy. MiRNAs help in gene expression regulation and perform their functions in inflammatory, nociceptive, and neurovascular processes that are involved in migraine (Eikermann-Haerter et al., 2015). It will be possible to develop therapies, which are more effective than the available drugs in that they will not only relieve symptoms but also heal dysregulated miRNA agents in patients suffering from migraine.

One such possibility is *miRNA mimics* or *anti-miRNAs*, which aim to modulate a given miRNA comprising an offensive assault on pathological pro-migraine processes. In this case, for example, it has been demonstrated that pro-inflammatory signalling includes miR-34a-5p, with a view that targeting this with an anti-miRNA will reduce inflammation, thus averting migraine attacks. In contrast, reinserting such downregulated miRNAs as miR-758-5p in patients could entail the use of systemic therapeutic interventions involving the administration of miRNA mimics, so as to curb the effects of migraines.

What also adds therapeutic value to the miRNA-based therapies is their ability to potentially resolve another issue – drug resistance that is frequently encountered in the management of migraines. Chronic migraine patients face development of tolerance to the orthodox modalities of treatment because over a period they become unreceptive to these medicines. MiRNA-based therapies, on the other hand, do not simply alleviate pain and discomfort associated with migraine but identify and target the mechanisms of migraine at gene expression level providing a more personalised and arguably a more permanent approach to the alleviation of migraine. Moreover, as they tend to influence several genes at once, targeting one micro-RNA may have an effect of influencing the whole array of pathways involved in migraine as a disease and provide a more complete relief (Johnson et al., 2021).

However, encouraging, these trends should be taken with caution, as miRNA-based therapies are still under development, and many issues regarding their safety, methods of delivery and the long-term consequences are still open. Targeted delivery to the CNS, in particular, is more difficult as the miRNAs need to pass the blood-brain barrier to act in the central nervous system (Schankin et al., 2020). Still, there are optimistic views that with such improvements in delivery systems as nanoparticle – based systems, the use of miRNA biotechnologies will not remain a dream in the years to come.

5. Current Research Gaps and Future Directions

5.1 Further Studies Required

Although encouraging outcomes have been realised with regards to the use of miRNAs as potential biomarkers and treatment of migraines, adequate research has not been done for miRNAs to be adopted in the clinical practice. One of the key challenges is the lack of large, diverse cohorts in existing studies. The majority of the work done on miRNAs in migraines has focused on studies with smaller and/or similar populations making the findings less applicable. Future studies should also evaluate the benefits of studying larger and more diverse populations considering varying ethnic groups, male and female subjects, age differences as well as environmental exposure (Li et al., 2020). Increasing the sample size and varying the demographic of the population will assist in proving miRNAs as effective and consistent biomarkers in the diagnosis of migraine.

Additionally, the role of environmental and behavioural factors in miRNA expression in patients suffering from migraines is a largely unexplored subject. The effects of a person's diet, stress, sleep, and toxins, for example, can powerfully influence gene regulation, including miRNAs, and may confound the search for reliable migraine-specific miRNA biomarkers (Johnson et al., 2021). For instance, inflammation and stress response miRNAs could be upregulated by both environmental conditions and migraines, thus making it complicated to ascertain if the changes in the levels of these miRNAs arise entirely from migraines. Therefore, it remains essential to carry out further studies to investigate the relationship between miRNA expression and environmental factors in individuals treated for migraines (Gomes et al., 2018).

5.2 Prospective miRNA-Based Therapeutic Developments

The long-term prospects of therapies targeting miRNAs for the treatment of migraines are encouraging, but several issues still need to be addressed before these therapies are considered practical solutions. One of the greatest concerns is the issue of how to administer miRNA treatments to the effector sites of action, particularly the central nervous system where the blood brain barrier is present. Some solutions have been developed in the form of nanoparticles carrying miRNAs across the blood brain barrier, but more optimization is needed if these therapies are to be successfully translated to innervating the central nervous system (Schankin et al., 2020).

Furthermore, the potential effects of miRNA treatments over an extended period are still not clear. Since miRNAs are capable of simultaneously regulating several genes, there may be adverse effects targeting a single miRNA since it alters so many biological functions (Eikermann-Haerter et al., 2015). It is then necessary for scientists to find out how one can target specific miRNAs without affecting the function of

other cellular processes which are important. In order to promote growth in this sector, consider preclinically focusing on methods of delivery and dose and treatment duration optimization and safety evaluation for a longer period.

In addition, there exists an enthusiastic prospect for future investigation into brick-and-mortar application of personalized medicine sensitivities to miRNA profiles. Designing miRNA-based interventions around the genetic and epigenetic features of each patient it may be possible to develop interventions that focus on migraine depending on the pathway that causes it for that specific individual. This is particularly useful given the limitations of existing migraine drugs, which, do not work for all patients and can have associated adverse effects or drug resistance.

6. Conclusion

To sum up, there is an ever-growing body of literature that indicates the significant functions of microRNAs in migraine pathophysiology. These tiny, non-coding ribonucleic acids, are turning out to be vital factors in control of gene expression in various activities of the nervous system including neuroinflammation, pain, and control of blood flow which all play significant role in the mechanism of migraines (Eikermann-Haerter et al., 2015). It has been established that in particular conditions, certain miRNAs, for example, miR-382-5p and miR-30a-5p, have been found to change in expression in episodes of migraine, suggesting that they can be assessed as potential biomarkers and therapeutic interventions.

Nonetheless, the current literature still has some critical limitations. The differences in studies about miRNA profiles can be attributed to differences in the patient population, region, and many other factors. It is therefore crucial to consider additional studies with more representative populations and more uniform sample collection and assay methodologies for proper evaluation (Johnson et al., 2021). In addition, while miRNA-based therapies offer a new treatment option for migraine, more studies are warranted to develop these delivery systems with safety and efficacy, as well as to mitigate the risks of adverse effects when manipulating specific miRNAs (Gomes et al., 2018).

In summary, the development of treatments and diagnostics based on the profile of miRNAs appears to be a very promising direction for the treatment of migraines. All the same, it is also important to conduct additional research in order to make these findings useful in real-world clinical situations. Determining the mechanisms of action of miRNAs in migraines may facilitate the application of even more individualised approaches to the management of this problematic disorder (Lutz et al., 2018).

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