https://doi.org/10.48047/AFJBS.6.2.2024.1908-1911

AfricanJournalofBiological Sciences

ResearchPaper OpenAccess

Role of miRNA-221 in psoriasis and other diseases: review article

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Article History

Volume 6, Issue 2, April-July

Received: 10July2024

Accepted: 29 July 2024

Published: 29July 2024

doi:

10.48047/AFJBS.6.2.2024.1908-1911

Abstract: Psoriasis is a common chronic inflammatory skin disease that affects skin, nails, and joints. It affects about 0.5–1% of children and 2–3% of the world's population. MicroRNAs (miRNAs) are small noncoding RNAs with 22 nucleotides in length. These miRNAs can regulate the proliferation, differentiation, apoptosis, and cytokine production of keratinocytes, as well as the activation of T cell subsets. Aberrant miRNAs expression is associated with many human diseases and have been reported as potential biomarkers for a variety of diseases.

Keywords: Psoriasis, MicroRNAs, MiRNA-221, Auto immune diseases

Introduction

MiRNAs are small non-coding RNAs, with an average 22 nucleotides in length. Most miRNAs are transcribed from DNA sequences into primary miRNAs (pri-miRNAs) and processed into precursor miRNAs (pre-miRNAs) and mature miRNAs. In most cases, miRNAs interact with the 3′UTR of target mRNAs to suppress gene expression. Interaction of miRNAs with other regions, such as the 5′ UTR, coding sequence, and gene promoters, has also been reported. Moreover, miRNAs have been shown to activate gene expression under certain conditions(1).

MiRNAs are important for normal animal development and are involved in different biological processes. Aberrant miRNAs expression is associated with many human diseases (2). Furthermore, miRNAs are secreted into extracellular fluids and these extracellular miRNAs have been reported as potential biomarkers for a variety of diseases and they also serve as signaling molecules to mediate cell-cell communications(3).

Psoriasis is induced by keratinocytes proliferation and dysfunction of the interplay between T-cell and keratinocytes. MiRNAs that supervise these functions became the prime center of study for researchers. Several studies revealed the different levels of miRNA expressions in psoriasis patients when compared with the normal subjects.Different types of miRNAs were found to be downregulated and several to be upregulated in the diseased conditions. Therefore, miRNA became an important target for psoriasis treatment.MiRNAs that were found to be upregulated in psoriasis include miR-146a, miR-203, miR-21, miR-31, miR155, miR-221, and miR-222 and those that were found to be downregulated included miR-99a, miR-217, and miR-125b (4).

1. Biogenesis of miR-221

When different miRNAs transcribed as a unique long transcript, they are called "clusters" belonging to the same family (5). MiR-221/222 is an example of a gene cluster located on chromosome Xp11.3. The promoter region of miR-221/222 includes two canonical TATA boxes on 550 and 190 base pairs upstream from pre-miR-222 and 3 poly-A sequences downstream from pre-miR-221 (6).

It has been reported that the expression of this gene cluster is regulated by angiotensin II as well as by a repressive complex including estrogen receptor α and the nuclear receptors co-repressor (NCOR1and NCOR2). MiR-221 is encoded and transcribed together with miR-222 as pri-miR, in which the two paralogous miRs are separated by 726 bp and share the same seed nucleotide sequence. The pri-miR transcription is followed by the nuclear processing mediated by Drosha and RNA-binding protein DGCR8, leading to the generation of 110-nucleotide pre-miR-221 and pre-miR-222 (7).

The pre-miR-221 is then subjected to nuclear-cytoplasm translocation by exportin 5-RanGTP-shuttle system and is cleaved by Dicer into the miR-221 mature form. The 5′ strand of pre-miR-221 produces miR-221-5p, while the 3′ strand gives rise to miR-221-3p (7).

2. Role of miR-221 in cancer, cardiovascular and cerebrovascular diseases

Regarding miR-221, the relationship between this miRNA and epigenetic changes has been reported in cancer (8) as well as in other conditions, such as cardiovascular (9) and cerebrovascular diseases (10).

The investigation of epigenetic influences by selected miRNAs in Parkinson's disease was investigated by Tatura et al. who focused their work on miRNAs expression profiling in gyri cinguli. MiR-221 was one of the five miRNAs whose upregulation was correlated to the decrease of the transcript level of genes, which are normally involved in the physiological cellular function (11).

A series of studies conducted by Hromadnikova et al. provided post-partum epigenetic profiling of miRNAs previously associated with cardio- or cerebrovascular pathologies, including miR-221. This analysis, performed in women with pregnancy-related complications, highlighted the association between miR-221 upregulation and gestational hypertension (GH). The aberrant expression profiles of seven miRNAs, including miR-221, in patients with GH only, provided a list of biomarkers for the identification of patients with a higher risk of later development of cardio-cerebrovascular diseases (12). On the other hand, the studies conducted on umbilical cord blood in GH, preeclampsia (PE), and fetal growth restriction (FGR) highlighted the down regulation of miR-221-3p in severe PE and FGR by demonstrating the importance of evaluating the epigenetic changes that characterize each pregnancy-related complication and that may be indicative of subsequent diseases (13).

El-Daly et al. investigated the involvement of miRNAs in the epigenetic switch causing colorectal cancer (CRC) cells transformation via NF-κB and STAT3 signaling pathways. Among the miRNAs included in the study, they found that miR-221 upregulation induces NF-κB/STAT3 constitutive activation through the inhibition of PDZ and LIM domain protein 2 (PDLIM2), which is normally implicated in intra-nuclear degradation of a subunit of NF-κB and proteasome degradation of STAT3 (14).

In their vision of miRNA-mediated epigenetic regulation, Ravegnini et al. investigated the role of miR-221/222 in gastrointestinal stromal tumor (GIST) susceptibility. They identified the variant rs17084733, located in the 3′ UTR of the proto-oncogene, receptor tyrosine kinase (KIT) and clarified that this variant acts

as a sponge that competes with miR-221/222 binding. This polymorphism, together with the rs75246947 (T>A) variant on pri-miR-222, was associated with GIST susceptibility (15).

To investigate the epigenetic mechanisms underlying the lineage homeostasis in breast epithelium, Ke et al. reported the ability of miR-221 to sustain breast cancer (BC) hierarchy in normal and malignant cells. They found that overexpression of miR-221 in normal BC cells induces stem-like cells to differentiate in luminal cancer cells and epithelial-mesenchymal transition via Antioxidant Protein 1 (ATX1) targeting (16).

Coarfa et al. pointed out the epigenetic regulation of miR-221/222 in prostate cancer (PCa) cells. They reported that miR-221 is involved in the control of the androgen receptor axis and it is suppressed in metastatic PCa. The evidence that miR-221 expression level could be restored by treatment with the pan-histone deacetylase (HDAC) inhibitor (vorinostat) and the DNA methyltransferase inhibitor (5-azacytidine) highlighted the importance of the combination between conventional therapies and epigenetic therapies for PCa treatment (17).

3. Role of miR-221 in inflammatory and autoimmune diseases

MiR-221-3p has recently been reported in various inflammatory conditions**.** To date, there are multiple descriptions of aberrant miR-221-3p expression predominantly in pathological conditions so silencing miR-221 could represent a promising approach for therapeutic studies (18).

Rheumatoid arthritis (RA) and psoriasis are autoimmune diseases, and RA has something in common with the development of psoriasis. The miR-221 has been found to be overexpressed in rheumatoid arthritis synovial fibroblasts, serum, and synovial tissues of patients with rheumatoid arthritis. Furthermore, downregulation of miR-221 in fibroblast-like synoviocytes could significantly inhibit the expression of pro-inflammatory cytokines and chemokine, inhibit cell migration and invasion, and induce cell apoptosis via inhibiting vascular endothelial growth factor (VEGF), matrix metalloproteinase-3 (MMP-3), and matrix metalloproteinase-9 (MMP-9). Meanwhile, previous studies have shown a significant increase in miR-221-3p expression in psoriatic arthritis (PsA) (19)**.** The first study to assess the ability of baseline microRNA expression to stratify patient outcomes to treatment was conducted by Wade and colleagues. Six microRNAs (miR-221-3p, miR-130a-3p, miR-146a-5p, miR-151-5p, miR-26a-5p, and miR-21-5p) were identified significantly higher in PsA compared to healthy controls. By analyzing responders versus non-responders, the authors demonstrated that higher baseline levels of miR-221-3p, miR-130a-3p, miR-146a-5p, miR-151-5p, and miR-26a-5p were associated with therapeutic response(20).

MiRNA-221 and miRNA-222 show significant upregulation in psoriasis conditions. Notably, increased miR-221 and miR-222 also target Tissue inhibitor of metalloproteinases 3 (TIMP3) in psoriatic skin lesions, thus underscoring the potential importance of TIMP-3 and matrix metalloproteases in the immunopathogenesis of psoriasis. Deli et al. found that 17 microRNAs increased in the lesional skin of psoriasis patients, including miR-221-3p(21). Whereas Kara and Dogan found that miR-221-3p to be down regulated in psoriasis (22).

Meng et al. reported that miR-221-3p was significantly increased in the serum of patients with psoriasis. The area under the curve was 0.861, the sensitivity was 80.4%, and the specificity was 85.7%. Serum miR-221-3p was positively correlated with the expression levels of tumor necrosis factor-α, IL-17A, and IL-22. Cell experiments showed that reducing the expression of miR-221-3p could significantly inhibit cell proliferation. Additionally, miR-221-3p downregulation also inhibited the release of some inflammatory factors in the Human Keratinocyte Cell Line (HaCaT) cells. Therefore, these results supported that the expression level of miR-221-3p could have a role in the pathogenesis of psoriasis (23).

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