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Study of the Possible Role of MicroRNA 106b in Psoriasis Vulgaris

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Abstract

Objectives: Investigating the role of the serum level of MicroRNA106b in psoriatic patients and its relation to disease severity. **Background:** MicroRNA106b has been shown to play a crucial role in the pathogenesis of several autoimmune diseases but was poorly investigated in patients with psoriasis. **Data Sources:** By searching and reviewing Medline databases (Pub Med and Medscape) and looking for studies that examined the possible role of MicroRNA106b in patients with psoriasis available till 2022. **Study Selection:** All studies were independently assessed for inclusion. They were included if they fulfilled the following criteria: 1.Written and published in English language. 2. Published in peer-reviewed journals. 3.Explain how the level of serum MicroRNA106b may be linked to psoriasis vulgaris. **Data Extraction:** If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment factors included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and well-defined evaluation measures. Data from each eligible study were independently abstracted using a data collection form to capture information related to our concerned study outcomes. **Conclusions:** Serum MicroRNA106b level is lower in patients with psoriasis vulgaris.

Key words: Psoriasis Vulgaris, MicroRNAs.

Introduction

Psoriasis is recognized as the most prevalent immune – mediated inflammatory disease, involving skin and joints and associated with abnormalities of other systems. Psoriasis patients constitute 6-8 % of the patients admitted to dermatology clinics **[1]** MicroRNAs (Mi-RNAs) are members of small RNA family ranging in length of 19-25 nucleotides. Over 2500 mi- RNAs that play a role in the regulation of basic biological processes have be identified to date. **[2].**

MicroRNAs are found to have control on a wide range of genes which control biological activity like cell division, cellular differentiation, and death (apoptosis) **[3].**

MIR-106b circulating expression levels were significantly down regulated in the blood of patients affected by psoriasis vulgaris compared to healthy subjects **[4].**

Materials and methods

Data Sources: The literature on the putative link between serum MIR-106b and Psoriasis Vulgaris and its connection to severity of disease decline up to 2023 was sourced via a search of the Medline databases (Pub Med and Medscape**).**

Study Selection: Studies were chosen after being subjected to a rigorous, objective and transparent selection process. They were included if they fulfilled the following criteria:

1. Written in English language and published. 2. Appearing in publications with a strict peer-review process.3.Explain the relation between serum MIR-106b and psoriasis vulgaris.

Data Extraction: Research studies were not included if they did not meet the inclusion criteria. Ethical permission, eligibility criteria, controls, information and well-defined evaluation measures were all factors in determining the study`s quality. Data from each eligible qualifying study were independently abstracted using a data collection form to capture information relevant to our concerned study outcomes.

Review of literature:

Psoriasis

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits. Psoriasis is characterized by red and scaling skin plaques. Patients with psoriasis are at higher risk of multiple comorbidities, including diabetes, cardiovascular diseases, psoriatic arthritis, Crohn's disease, lymphomas, and depression **[5].** The worldwide prevalence is about 2%, but varies according to regions. It shows a lower prevalence in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations **[6].** Psoriasis skin lesions are characterized by hyper proliferation and aberrant differentiation of keratinocytes and infiltration of inflammatory cells into the dermis and epidermis [**7].**

A higher prevalence in males has been reported with a peak age at onset is in the third and fourth decade of life **[8].** The peak age at onset among boys is in the 6–10 years age group compared to girls in 11–15 years age group **[9].**

It is presented clinically by sharply demarcated erythematous and scaly epidermal lesions that affect

both genders and can occur on any anatomical site, preferentially involving the knees, elbows, scalp and genitals. Psoriasis imposes huge physical and mental burdens on individuals who suffered worldwide **[10].**

Etiopathogenesis of Psoriasis

The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The inflammatory pathways active in plaque psoriasis and the rest of the clinical variants overlap, but also display discrete differences that account for the different phenotype and treatment outcomes **[11].**

The risk factors for psoriasis include mainly infections, stress, drugs, smoking and endocrinal factors **[12].**

The pathogenesis of psoriasis is complex, multifactorial and still not well understood. Psoriasis is a genetically programmed disease of dysregulated inflammation, which is driven and maintained by multiple components of the immune system [**13].**

The activation of the adaptive immune response via the distinct T cell subsets drives the maintenance phase of psoriatic inflammation. Th17 cytokines, namely IL-17, IL-21, and IL-22 activate keratinocyte proliferation in the epidermis **[14].**The inflammatory milieu activates keratinocyte proliferation via TNF-α, IL-17, and IFN-γ. Keratinocytes are also activated by LL37 and DNA, and greatly increase the production of type I IFNs.

Furthermore, they participate actively in the inflammatory cascade through cytokine (IL-1, IL-6, and TNF-α), chemokine, and AMP secretion. The clinically relevant signaling in psoriasis is mediated mostly by IL-17A and IL-17F; both act through the same receptor but have different potencies. IL-17A exerts a stronger effect than IL-17F, and the IL-17A/IL-17F heterodimer has an intermediate effect **[15]**

Clinical Classification of psoriasis

Psoriasis is clinically classified in 2 groups: pustular and non-pustular lesions **[16].**

Psoriasis vulgaris (PV)

The most frequently seen clinical form of psoriasis, Psoriasis vulgaris, constitutes nearly 90% of cases. Clinically it is observed as erythematous plaques with sharp boundaries and covered with pearlescent squamae. Lesions demonstrate symmetric distribution, and they are most frequently localized on knees, elbows, scalp, and sacral region. Predilection for these lesions may be a result of traumatic incident **[17].** If the surface of psoriatic plaque is scraped with a blunt scalpel, squamae fall off as layers of white lamellae that exhibit coherence after removal, much like candle wax. This desquamation is sometimes referred to as "wax spot phenomenon." It is a sign of parakeratotic hyperkeratosis. If psoriatic plaque is scraped further, a wet layer adhered to the lesion can be revealed. This is the last layer of the dermal papillae of the epidermis, and it is a pathognomonic sign of psoriasis, known as "last membrane phenomenon." Further scraping of the plaque reveals erythematous background and bleeding foci with appearance of small red pinpoints known as "Auspitz sign,'' signifying papillomatosis on tips of dermal papillae **[17].**

Guttate psoriasis

This type of psoriasis is frequently seen in children and young adults. Lesions onset suddenly with an appearance like small droplets, and less frequently as squamous psoriatic papules, generally manifesting after streptococcal infections. This form of psoriasis is most frequently associated with HLA-Cw6 gene. Often antistreptolysin titers are elevated. With regression of the infection, lesions generally disappear spontaneously. Lesions are generally seen on the trunk, proximal part of extremities, face, and scalp. They generally regress within 3–4 months. Sometimes lesions enlarge and take the shape of psoriatic plaque **[19].**

Inverse (Flexural) psoriasis

Psoriasis that is localized in skin folds**.** Fissured plaques with sharp contours are diagnostic for this form of psoriasis. It is more frequently seen in obese individuals, and there is tendency to develop seborrheic lesions. This form is generally more resistant to classical treatments. Squamous lesions do not form due to friction and moisture in skin folds. Lesions manifest as bright red, symmetric, infiltrative, fissured plaques with distinct contours **[20].**

Erythrodermic psoriasis

Psoriatic lesions affect nearly 80% of the body surface in this generalized form of psoriasis. Predominantly erythematous lesions are seen, typical papules and plaques lose their characteristic features. In patients with erythrodermic psoriasis, hypothermia due to widespread vasodilatation can be seen. Desquamation may also lead to protein loss and related systemic problems, such as edema of the lower extremities, and cardiac, hepatic, and renal failure can occur **[21].**

Palmoplantar psoriasis

Psoriasis symmetrically involves palms of the hands and soles of the feet, and thenar regions are more frequently affected than hypothenar regions.

Erythema is not always found, but when it exists it appears as a pinkish-yellow lesion. Squamae are the predominant lesions. Thick squamae may give appearance of keratoderma **[22].**

Generalized pustular psoriasis

This is a rarely seen form of psoriasis that progresses with pustules. Pustules dry within a few days, followed by eruption of new pustules. Peripustular erythema has tendency to disseminate, and thus it can result in erythroderma. It should be promptly treated. If disseminated form is not treated, acute phase may lead to a fatal course **[23].**

Palmoplantar pustular psoriasis

It is a chronic, recurrent form more frequently seen in women and those with a family history of palmoplantar pustulosis. Clinically, it is observed as 2–4 mm-sized pustules localized on palmoplantar region, and especially erythematous thenar and hypothenar regions. While its etiology is not precisely known, underlying contact sensitivity is remarkable. Smoking, tonsillitis, humidity, and high temperature may activate the disease **[24].**

Psoriatic Arthritis

Psoriatic arthriris can be seen in different clinical forms. Most often used are the classification criteria developed by Moll and Wright describing 5 subgroups 1) Classical PsA: It affects distal interphalangeal joints of the hands and feet and has an incidence of nearly 10%. Nail involveme nt is usually seen 2) Asymmetric oligoarticular arthritis: It is the most characteristic form of joint involvement. In addition to major joints, such as knee joints, distal and proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints are asymmetrically affected. It is seen in 11% of cases. 3) Symmetric polyarticular form: It resembles rheumatoid arthritis (RA). When compared to RA, distal interphalangeal joints are more frequently involved, and a tendency to bone ankylosis is observed in joints. In various studies, incidence has been demonstrated to range between 15–61%. 4) Arthritis mutilans: It is characterized by progressive osteolysis of phalangeal and metacarpal bones. It is frequently associated with sacroiliitis. This definition is generally used for hands; however, feet can also see similar involvement. 5) Spondylitic form: Isolated spondylitis is rarely seen (2–4%). Generally, it is associated with peripheral arthritis. This form resembles ankylosing spondylitis, and symmetric or asymmetric sacroiliac joint involvement is seen. Due to less severe joint ankylosis, it has a better prognosis than ankylosing spondylitis **(25).**

MicroRNAs origin and biogenesis:

MicroRNAs are small (approximately 22 nucleotides) noncoding RNAs derived from larger primary RNA transcripts in the human genome. Individual miRNA genes are transcribed by polymerase II or III into primary miRNA (pri-miRNA) transcripts **(27).**

Subsequently, they are processed into a precursor miRNA (pre-miRNA) by Drosha (RNASEN) and DGCR8 (DiGeorge syndrome critical region 8) enzymes. After nuclear processing, a pre-miRNA is exported into the cytoplasm by XPO5 (Exportin 5) for final processing by Dicer and loading into the RNA-induced silencing complex **[28].**

Mechanism of action of miRNAs:

MiRNAs have regulatory roles in development, differentiation, organogenesis, stem cell and germline proliferation, growth control and apoptosis. Deregulation of miRNA expression may contribute to human diseases, they are often aberrantly expressed or mutated in cancer and represent important targets for potential therapeutic and diagnostic agents. However, neither their expression nor roles have been characterized in skin diseases **[29].**

MiRNAs can regulate differentiation, proliferation, and cytokine responses of keratinocytes, activation, and survival of T cells, as well as the crosstalk between immunocytes and keratinocytes **[30].**

Role of miRNAs in Inflammatory Response and Immune Dysfunction:

In disorders of inflammatory responses, immune cells of the innate and/or adaptive immune system are activated and recruited to the site of inflammation. Attraction and activation of immune cells is regulated by a variety of different cytokines and chemokines, which can affect or be affected by miRNAs in autoimmune diseases like psoriasis **[31].**

MicroRNAs in Psoriasis

Psoriasis has a strong genetic background, and it has become apparent that genetic polymorphisms in miRNA genes and/or in miRNA binding sites of target genes can affect miRNA activity and contribute to disease susceptibility. Which can be supported by the following studies addressed. For instance, in a genome-wide interaction analysis, it has been identified 4 single nucleotide polymorphisms (SNPs) in miRNA (miR-324-3p, miR-433, and miR-382) target sites which interact with 5 SNPs to contribute to psoriasis **[32].** The immune dysfunction in patients with psoriasis vulgaris is found to be induced by overexpression of miR-210, whose target gene is forkhead box P3 (FOXP3). It is reported that overexpression of miR-210 inhibited FOXP3

expression and impaired immunosuppressive functions of Treg cells in CD4 (+) T cells from healthy controls, while on the other hand, inhibition of miR-210 increased FOXP3 expression and reversed immune dysfunction in CD4(+) T cells from patients with psoriasis vulgaris**[34].**

MiR-125b is one of the most downregulated miRNAs in psoriatic skin. In situ hybridisation detection identified that decreased miR-125b staining mainly took place in keratinocytes. Overexpression of miR-125b in primary human keratinocytes hampered cell proliferation and promoted cell differentiation. Conversely, inhibition of endogenous miR-125b promoted cell proliferation and delayed differentiation. Moreover, miR-125b was found to specially target FGFR2, an important cell proliferation regulator **[35].**

Yan et al. revealed that miR-145-5p was downregulated in psoriatic lesions and is a key player in suppressing epidermal keratinocyte proliferation and IL-17A-induced secretion of chemokines, including CCL2, CCL7, CCL20, CXCL1, CXCL2, CXCL5, CXCL8 and CXCL10. MiR-145-5p targets mixed lineage kinase 3 (MLK3) and positively regulates NF-κB and STAT-3 signaling. This study revealed that the downregulation of miR-145-5p both promoted epidermal thickening and exacerbated skin inflammation in psoriasis **[36].**

MicroRNA 106b:

MicroRNA106b, located at Chromosome 7, is one member of miR-106b-25 cluster. Several genes have been evidenced to be the targets of miR-106b, such as p21/CDKN1A and TGF-β type II receptor (TβR II). It has reported that miR-106b gain of function promotes cell cycle progression, whereas loss of function reverses this phenotype. And p21/CDKN1A is a direct target of miR-106b and that its silencing plays a key role in miR-106b-induced cell cycle phenotypes **[37].**The miR-106b gene expression had been investigated in many cancer as hepatocellular cancer, chronic lymhocytic leukemia (CLL), breast cancer, ovarian cancer, prostate cancer, gastric cancers and renal cell carcinoma **[33]**. **Ivanovska et al.** have shown that overexpression of miR-106b in cancer cells promotes cell cycle progression while downregulation inhibits it. In addition, up-regulation of miR-106b was also related to enhancing the proliferation, migration and invasion of tumor cells in human cancers **[37].**

Conclusion:

From the results of present study, it is concluded that the level of mir-106b expression is significantly lower in the psoriasis patients. And that this drop is connected to psoriasis severity

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