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MicroRNAs as biological regulators in skin disorders

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ABSTRACT

microRNAs are being investigated as promising therapeutic targets and biomarkers for different disease conditions. miRNAs serve as essential regulators of cell differentiation, proliferation and survival. The involvement of miRNAs in the functioning and regulation of the skin cells and skin diseases is a rapidly advancing area in dermatological research. miRNAs have been identified to play a key role in the pathogenesis, diagnosis, and treatment of the skin diseases. Skin is one of the largest organs of the body, primarily functioning as the first line of defence against external insults including bacteria, virus and other pathogens. Various miRNAs have been identified to demonstrate significant effects in various skin inflammatory conditions such as wounds, cancer, psoriasis, scleroderma, dermatomyositis. The current review explores the possible roles of the miRNAs in skin disorders and reports relating to the clinical trials involving skin diseases and miRNAs. The review has also compiled the information of the databases available, which correlates the miRNAs with different diseases and give details about targeting interactions of miRNA.

1. Introduction

Skin is the primary defence structure of the body and is the largest and important part of the human body comprising around 15% of the total human body weight. Human skin consists of three different tissue layers i.e. the epidermis, dermis, and hypodermis. The epidermis is made up of keratinocytes (primarily), melanocytes and the Merkel cells (mechanical stimuli-sensitive) [1]. The dermis delivers nutrients and supports circulation. Skin is introduced to various environmental hazards. Almost 30,000 cells of the outermost skin die every minute [2]. Its development and normal physiology is the highly adapted process which involves a number of factors and network of genes, regulating its functions, both acting in integration [3]. Whenever the skin gets affected, aging of the skin and its failure becomes evident which is mainly due to the faulted physiology causing deterioration of the skin [4].

Around 20,000–25,000 protein-coding genes make up the human genome. These genes encode proteins that dictated the cell functions. However, since the discovery of the miRNAs, there had been reports highlighting the existence of various non-coding RNAs, which is not translated into proteins (earlier thought to be junk DNAs) but transcribe the mammalian and other organisms genomes. Though the functional and physiological relevance of ncRNA is not clearly understood, they are believed to exhibit catalytic activity and regulate chromosomes at the transcriptional site. ncRNAs are majorly categorized as housekeeping and regulatory ncRNAs. The housekeeping ncRNAs are further divided into transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs). Based on the number of nucleotides, regulatory ncRNAs are classified into small ncRNAs with 18–200 nucleotides and long ncRNAs with more than 200 nucleotides [5]. Long ncRNAs includes natural antisense transcripts, transcribed ultra-covered regions, long intergenic ncRNAs, pseudogenes, circular RNA's. Small ncRNAs include miRNAs, P-element-induced wimpy testis-interacting RNAs (piRNAs), and small interfering RNAs (siRNAs) [6], where miRNAs are the most widely studied subset. miRNAs represent almost 4% of the genes in the human genome and regulate more than one-third of the expressed genes post-

Abbreviation: ds, double stranded; ECM, extracellular collagen matrix; FGF, fibroblast growth factor; HS, hypertrophic scaring; HSFBs, hypertrophic scaring affected fibroblasts; miR, microRNA; PCR, polymerase chain reaction; PDGF, platelet-derived growth factor; PremiRNA, precursor miRNA; Pri-miRNA, primary miRNA; RISC, RNA induced silencing complex; RUNX3, runt-related transcription factor 3; ss, single-stranded; TGF, transforming growth factor

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transcriptionally [7–9].

miRNAs are being recognized as critical regulators of the genes and biomarkers for the number of diseases. While, naturally occurring miRNAs serve as essential regulators of cell differentiation, proliferation and survival, the aberrant and altered miRNA expression have been linked to various pathological and immune related disorders like psoriasis, schizophrenia, Alzheimer's, Parkinson's, diabetes, cardiovascular diseases and cancer [10]. miRNAs regulate gene expression by acting on messenger RNA(mRNA) by sequence-specific hybridization at 3′untranslaated region. Additionally, the interaction between miRNA and mRNA could inhibit mRNA translation or even directly degrade the mRNA [11]. At the post-transcriptional level, they serve as negative regulators of the gene expression [12,13]. In addition, the biogenesis and function of miRNAs are associated with the underlying molecular mechanisms of different diseases where they are involved in regulating the biological activities like differentiation and development, metabolism, proliferation, apoptosis, viral infection and tumorgenesis at the cellular level [14]. With the recent advances, various classes of miRNAs have been identified to play a crucial role in diseases progression such as extracellular miRNAs in hepatic diseases [15,16], circulating miRNAs in ageing and ageing-related-diseases [17], pulmonary hypertension etc [18]. Such advanced miRNAs are under investigation for their cell-cell signalling functions.

Innovation in the skin technology and the research in the miRNA field collectively shows the role of the miRNAs in the functioning of the skin cells, most importantly in the diseases related to the skin [4]. miRNA affect different activities of the cell such as proliferation, migration due to changes in the gene expression, immune response or the tumor formation. miRNAs present in extracellular space are packed and exosomes protect them from the harsh conditions are found. They are present in the extracellular fluids of the body like saliva, serum or urine. Levels of miRNA in extracellular fluids, more prominently in the serum has become biomarkers in several human disorders mainly in tumors. Lefkowitz et al. have shown the presence of RNAs in shafts and roots of hair [19]. Studies have been reported which show the possibility of the use of the hair miRNA levels in the treatment of the diseases [20]. As miRNA expression is different in the hair shafts from the hair roots or sera, they can also be used as the biomarkers. In patients having diseases related to the collagen or in the babies, the miRNA can be easily accessed in the hair, as the collection of blood samples become difficult in them [21].

Generally, for the treatment of the disease with the help of miRNAs, the miRNAs which are downregulated must be augmented with the mimics of the miRNA whereas those miRNAs which are not upregulated normally must be supplemented with miRNA inhibitors. Thus, miRNAs play a key role in the clarification of the pathogenesis, diagnosis, and treatment of the disease [22]. miRNAs affect several diseases like vitiligo, psoriasis, bullous disease, sclerosis etc (Fig. 1) out of which, some are explained here [23].

2. The maturation process of microRNA

miRNA regulates gene expression in the cell cytoplasm through the degradation or translation repression of mRNA. In presence of RNA polymerase II and III, long primary miRNA (pri-miRNA) is formed in the nucleus. Pri-miRNA consists of a terminal loop, two flanking unstructured single stranded tails and a double stranded stem which consist of base pairs (upto 30). Pri-miRNAs get converted into precursor miRNA (pre-miRNAs) in presence of protein complex, microprocess complex which consists of RNase III enzyme dorsha and double stranded RNA binding protein. The precursor miRNA consist of 70 nucleotides. Translocation of pre-miRNA into cytoplasm takes place by Exportin5 (XPO5), which belongs to karyopherin β family, complex with Ran GTPase. Precursor miRNA get converted into duplexes-miRNA (ds-miRNAs) with phosphate at 5′ end and a two nucleotide overhang with a hydroxyl group at 3′ end in presence of RNase III enzyme dicer. In presence of RNA induced silencing complex (RISC), miRNA duplex gets loaded onto argonaute (AGO). RISC is a complex comprising of dicer, trans-activation response RNA-binding protein(TRBP) and AGO. AGO helps in retaining mature miRNA by unwinding duplex and removing the passenger strand. A partially complimentary portion of mature miRNA act on 3' untranslated regions of mRNA which leads to the subjugation of mRNA. The maturation process of microRNA is represented in Fig. 2 [24,25]. miRNA act on 3' untranslated region of target mRNA. miRNA exhibits two mechanisms of action on mRNA i.e. mRNA degradation and target mRNA translational inhibition. When miRNA found the most complimentary with mRNA, deadenylation and subsequent degradation of target mRNA take place. Apart from complimentary degradation of mRNA by miRNA multiple factors are expected for miRNA action which includes, impaired processing, methylation, gene polymorphisms, gene amplification, deletion of dicer and translocation. Generally, the expression of target suppresses due to miRNA upregulation while its down-regulation causes target induction [26,27].

3. microRNAs in wound healing

Wound healing is the biological process which includes hemostasis, inflammation, proliferation, and remodeling. Out of these four phases, the proliferation phase is the most important and maximum healing takes place in this phase. After the skin injury, this phase can occur for 3 days to 2 weeks [28]. It has three main phases:

3.1. Re-epithelialization

At the edges of the wound, keratinocytes proliferate and get migrated at the wound site [29]. Along with the keratinocytes, stem cells, obtained from the sweat glands or the hair follicles adjacent to the wound, also contribute to re-epithelialization [30]. Keratinocytes reorganize the cell skeleton for migrating to the wound site after which they go back and get attached to the basement membrane and the dermis [29]. According to Wang *et. al.*, miRNA-204 is found to be expressed in the different tissues of the eye such as lens, cornea, and retina. It is important for the growth of both lens and retina. Its downregulation has been found during the healing of the wound of the cornea [31].

3.2. Angiogenesis

The process of the formation of the new blood vessels from the preexisting ones is known as angiogenesis. It occurs as the formation of the hemostatic plug take place and the TGF-b (transforming growth factor), FGF (fibroblast growth factor) and the PDGF (platelet-derived growth factor) get released by the platelets [32]. Various miRNA has been identified to be useful at this stage. For example, Studies have reported that miR-21 is over-expressed in the multiple tumors which results in the inhibition of the proliferation, tube formation and migration of endothelial cells [28].

3.3. Granulation tissue formation

After the angiogenesis, the induction of the fibroblasts migration and proliferation takes place. Fibroblasts form the matrix of collagen, hyaluronic acid, glycosaminoglycans, proteoglycans and fibronectin [33]. As a result, the granulation tissue is formed after the replacement of the hemostatic clot and a myofibroblast is formed from the fibroblasts [34].

Studies have shown the importance of various miRNAs in the normal functioning of the skin and so its wound healing process. Fig. 3 has demonstrated the role of various miRNAs in wound healing. The roles of the miRNAs along with their site of action have been summarized in Table 1 [35–53].