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MicroRNAs as regulatory elements in psoriasis

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Abstract: Psoriasis is a chronic, autoimmune, and complex genetic disorder that affects 23% of the European population. The symptoms of Psoriatic skin are inflammation, raised and scaly lesions. microRNA, which is short, nonprotein-coding, regulatory RNAs, plays critical roles in psoriasis. microRNA participates in nearly all biological processes, such as cell differentiation, development and metabolism. Recent researches reveal that multitudinous novel microRNAs have been identified in skin. Some of these substantial novel microRNAs play as a class of posttranscriptional gene regulator in skin disease, such as psoriasis. In order to insight into microRNAs biological functions and verify microRNAs biomarker, we review diverse references about characterization, profiling and subtype of microRNAs. Here we will share our opinions about how and which microRNAs are as regulatory in psoriasis.

Keywords: microRNAs, Psoriasis.

1 Introduction

Human skin is the outermost bodily barrier; it protects inner organs from stress and hazards [1, 2]. Human skin tends to rapidly repair when injured, although that involves a complex healing process. These functions of skin are maintained by a system of regulatory mechanisms that involves various mediators [3,4]. Some reports indicate that epigenetic regulatory mechanisms are contributing factors [5].

Skin diseases, including skin cancer and psoriasis, exert more and more severe influence on public health, for example psoriasis, a common skin disease. It characterized by a chronic, autoimmune, and complex genetic disorder. Psoriasis undergoes three different processes of cellular alteration in skin: abnormal differentiation of keratinocyte, hyperproliferation of keratinocyte, and infiltration of immune into the dermis and epidermis [6]. Some common molecular components, genetic alterations of genes that participate in inflammatory pathways, and environmental risks can contribute to the pathogenesis of psoriasis [7,8].

Recent research reveals that microRNAs have an important influence on psoriasis. MicroRNAs (microRNAs) are single-stranded, noncoding, short RNA molecules; they act as regulators of gene expression and play critical roles in nearly all biological processes. One example is the differentiation, development, and metabolism of the human body cell [9,10], which is influenced complementary mRNAs by binding to a target. As recent reports have indicated, expression of distinct microRNAs is upregulated in psoriatic skin compared with healthy skin, and that this process is related to regulation of keratinocyte proliferation and/or differentiation or suppression of T-cell apoptosis in psoriasis [11]. A plethora of microRNAs have been reported to be related to regulation in psoriasis, and different microRNAs can play a vital role at different stages of the disease. For example, miR-31 can modulate inflammatory mediator production and leucocyte infiltration to skin, and thus be present in psoriatic keratinocytes and contribute to psoriatic inflammation [11]. miR-203 is upregulated during keratinocyte differentiation of psoriatic skin by regulating the expression of TNF-α, IL-8, IL-24. Whereas miR-21 can be suppressed during apoptosis, miR-146a is upregulated in Th1 cells from T cells [12]. Thus, an appropriate combination of microRNAs could act as a regulator of psoriasis and thereby could potentially provide biomarker, therapy and diagnostic information.

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2 MicroRNAs in skin

MicroRNAs are typically defined as the most abundant small RNAs on pre-microRNA hairpins. More and more diverse variants of microRNAs have been discovered, including canonical and noncanonical microRNAs [13-15], microRNA-like−RNA, [16] and microRNA isoforms [17]. The Drosha and Dicer pathways are the essential differences between canonical and noncanonical. For example, previously discovered noncanonical microRNAs, mirtrons that arise from disbranched intron lariats, serve as substrates for Dicer cleavage [18, 19]. Another less abundant variant of small RNAs, isoforms or isomiRs, that exiss in nearly all sepsis, also act as regular microRNAs [20, 21]. This small RNA regulates the same mRNA target as their companion microRNAs and accompany them to their exclusive target genes [22]. This phenomenon indicates that microRNA-mediated gene expression regulators have robustness and plasticity, and that they have abundant functions complementary to canonical microRNAs [23].

During skin development and cell differentiation, microRNAs play an important role in regulating different signaling pathways by interacting with their target mRNAs. Their regulated targets has been implicated in the pathogenesis of psoriasis [24, 25]. This evidence suggests that microRNA can be participate in early skin development and affect the psoriasis process. When knocking out either Dicer or Dgcr8, severe defects in murine embryonic skin development have emerged, which produce rough skin, body weight loss, defects in hair follicle downgrowth, and abnormal apoptosis [26]. Hyperproliferation that topically appears as a feature of psoriasis has been observed in the Dicer knocked-out epidermis, showing the close relationship between microRNA and epidermal proliferation [27]. Several microRNAs with functions in skin morphogenesis and homeostasis have been studied (Table 1). For example, miR-21 is up-regulated in diseased skin, as well as in psoriasis and squamous cell skin cancer [28]. The miR-199 family is highly expressed in hair follicles, which indicates a potential regulatory function in hair morphogenesis [29]. miR-203 is also upregulated when keratinocytes differentiate, inducing expression of TNF-a, IL-8, IL-24 and suppressing cytokine signaling 3 [30]. In addition, many studies have recognized that several other microRNAs are related to skin development and homeostasis (Table 1). For instance, the miR-200 family and miR-205 have been shown to target ZEB1 and ZEB2 and are highly expressed in normal skin. Downregulation of miR-200 and miR-205 will induce upregulation of ZEB1 and ZEB2 via epithelial-to-mesenchymal transition [31].

3 microRNAs in psoriatic skin

Psoriasis, which appears as white silvery scales, is a common skin disease with characteristics of a chronic, autoimmune, and complex genetic disorder. Many factors, both genetic and environmental, can contribute to its emergence. Humans with psoriasis may suffer from hyperproliferation, aberrant differentiation of keratinocytes, loss of the superficial granular layer, and thickening of the cornified envelope. Research over last few years suggests that epigenetic regulatory mechanisms may enable skin regeneration and execution of gene expression in skin. This theory may be applicable to processes of skin repair, regulation of keratinocyte proliferation, differentiation, and migration, along with dermal regeneration and neoangiogenesis [5]. The grainyhead-like 3 (Grhl3/Get1) transcription factor is one of the regulators in epidermal genes that control the expression of specific microRNAs [27]. As one of the most widely studied microRNAs, miR-21 is abundantly expressed in skin [34]. Some records have indicated that it is upregulated in pathological conditions such as psoriasis [35]. When miR-21 is upregulated, the differentiation and hyperplasia are impaired and Grhl3

Table 1: microRNAs involved in skin development

microRNA	Function
miR-203	Inhibit cell proliferation by repressing p63; as the regulation in transition from basal to suprabasal layer in epidermis [30]
miR-34a/c	Maintain cell cycle progression and expression of cyclin D1 and Cdk4 via repression by p63 in epidermal cells [32]
mir-125b	Contribute to self-renew and early lineage commitment of skin stem cell [33]
miR-200/miR-205	Maintains proliferation of progenitor cells and epithelial-mesenchymal transition to restrict basal layer [31]

tends to be down regulated [5]. microRNA-31, one of the most dynamic microRNAs, exists in the skin of psoriatic patients and of mouse models. Transcription of miR-31 will be triggered by activated NF-κB and then promotes the keratinocyte hyperproliferation in psoriasis. When the miR-31 seed sequence is blocked by antagomirs and its effects are tested on an imiquimod (IMQ)-induced psoriasis mouse model, we found that there was a pronounced decrease in acanthosis and dermal cellular infiltration [11]. Furthermore, the majority of the collected data suggest that more and more novel human microRNAs have been detected. For example, miR-4623 acts on TNFRSF1B that is reported existing in psoriatic arthritis [36]. As another intronic, miR-944 is encoded in KPT15, which acts as a downregulator in psoriatic skin [37]. miR-944 contributes to maintaining stemness in skin by located in an intron of p63 [38]. A very special microRNA, miR-203-AS, is identified as a distinct microRNA on the DNA strand at the locus antisense to miR-203 [39]. Another example is miR-103, it also encodes on both antisense and sense strands. As for noncanonical microRNAs and microRNA-like RNAs in psoriatic skin, has-miR-1983 as a t-RNA-derived microRNA expresses in psoriatic and normal human skin [40].

A systematic analysis has revealed that microRNA isoforms originate from diverse tissues and across species [41,42]. For example, 5'-isomiRs (Table 2). miR-142 and miR-233 with high 5'-heterogeneities in human psoriatic lesions is expressed in dendritic cells and neutrophils, respectively [43-45].

4 Summary and future

Although the study of microRNAs in mammalian skin, such as in psoriatic skin, is an early stage, the research has already provided new insights into a novel layer of gene regulation. In the present article, some microRNAs, along with their targets, have been discussed; this provide us increased knowledge of psoriasis mechanisms. Taking miR-203 as an example, it has an essential role in early skin development and a critical role in psoriasis (shown in Table 2). This knowledge gives us hope that we will eventually find an excellent candidate for treatment of psoriasis.

Although the science is incomplete, new threads for future research have emerged. To reveal the etiology of autoimmune skin disorders, psoriasis included, a high-quality and rapid analysis system should be put in place to find the complex genetic networks; this will require a comprehensive profile of the transcriptome. Finding these complex genetic networks bring along another challenge: to integrate the information of genotypic variations. These genotypic variations hold a potential to explore causal genetic variations and then to lead to a connection with disease phenotypes. Furthermore, detailed genetic knowledge of the mechanism behind psoriasis development will be beneficial to developing animal models for research.

No matter how great the challenge, we are optimistic regarding the future of this field and are willing to make efforts to contribute to it. We believe that there is a possible cure for skin-related disease in deeper understanding of small RNA- and microRNA-based therapies.

Table 2: Some of microRNAs that express aberrantly in human psoriatic skin

microRNA	Description	Fold Change (PP/NN)
miR-31	triggered by activated NF-κB to promotes keratinocyte hyperproliferation in psoriasis [11,23]	42.9
miR-21	Upregulated in pathological induced impaire in differentiation and hyperplasia and down regulation of Grhl3 [35,23]	4.0
miR-1983	tRNA-derived human homolog of murine miR-1983 [40]	4.9
miR-203-AS	Antisense to miR-203 [39]	2.7
miR-142	Highly expressed in dendritic cell and play vital roel in hematopoietic development [41]	2.5
miR-203	As the regulation in development of epidermis from basal to suprabasal layer [30, 23]	1.6
miR-205	Primarily in the basal layer expressed in normal skin and regulates the transcriptional[42]	1.6

Fold change is a value of microRNA expression in psoriatic skin (PP) divided by that in normal skin (NN).

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