microRNAs in Psoriasis

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Psoriasis is a chronic inflammatory skin condition resulting from a complex interplay among the immune system, keratinocytes, susceptibility genes, and environmental factors. However, the pathogenesis of psoriasis is not completely elucidated. microRNAs represent a promising class of small, noncoding RNA molecules that function to regulate gene expression. Although microRNA research in psoriasis and dermatology is still relatively new, evidence is rapidly accumulating for the role of microRNAs in the pathogenesis of psoriasis and other chronic inflammatory conditions. In this article, we present a comprehensive review of what is known about microRNAs and their role in the pathogenesis of psoriasis.

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INTRODUCTION

Psoriasis is a chronic immunoinflammatory skin condition that affects approximately 2% of the Caucasian population (Kurd and Gelfand, 2009). The pathogenesis of psoriasis is the result of a complex interplay between the immune system, keratinocytes, genes, and environmental factors. Dendritic cells (Glitzner et al., 2014), antimicrobial peptides (Lande et al., 2014), and the T helper (Th-1, Th-17) cell population (Kryczek et al., 2008; Lowes et al., 2008) with their respective cytokines (e.g., IFN-γ, IL-17, IL-22, IL-23) (Johansen et al., 2009; Kryczek et al., 2008; Langrish et al., 2005; Nair et al., 2008, 2009) have all been shown to be essential to the pathogenesis of psoriasis. However, significant research gaps still exist.

microRNAs (miRNAs) represent an abundant class of small, evolutionarily conserved, noncoding RNA molecules that posttranscriptionally regulate gene expression. These noncoding RNAs are fundamental to human life and disease states (Esteller, 2011). Evidence is rapidly accumulating for the role of miRNAs in the pathogenesis of inflammatory skin disorders. However, miRNA research in dermatology and psoriasis is still relatively new. Here, we present a comprehensive review of the developments, implications, and future directions of miRNA research on the study of psoriasis pathogenesis.

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Abbreviations: IRAK1, interleukin-1 receptor-associated kinase 1; miRNA, microRNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PBMCs, peripheral blood mononuclear cells; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; TNF-α, tumor necrosis factor-α

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ORIGIN OF miRNAs

First discovered in *Caenorhabditis elegans*, miRNAs are small (approximately 22 nucleotides) noncoding RNAs derived from larger primary RNA transcripts in the human genome (Lee et al., 1993). Individual miRNA genes are transcribed by polymerase II or III into primary miRNA (pri-miRNA) transcripts (Borchert et al., 2006; Cai et al., 2004; Lee et al., 2004) and subsequently processed into a precursor miRNA (pre-miRNA) by Drosha (RNASEN) and DGCR8 (DiGeorge syndrome critical region 8) enzymes (Figure 1) (Han et al., 2004; Landthaler et al., 2004; Lee et al., 2003). 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 (Leuschner et al., 2006; Matranga et al., 2005). The loaded miRNA–RNA-induced silencing complex is then guided to the 3′ untranslated region of target mRNA genes where it binds and disrupts translation or triggers mRNA degradation (Lee et al., 1993; Yekta et al., 2004).

Since their discovery, more than 2,500 miRNAs have been reported in public repositories and are thought to regulate more than one-third of all protein-coding genes (Lewis et al., 2005). This makes miRNAs one of the most abundant regulators of gene expression in humans. miRNAs have now been associated with a broad range of normal and disease processes, including chronic inflammatory skin diseases (Esteller, 2011; O'Connell and Baltimore, 2012; O'Connell et al., 2012).

ABERRANT miRNAs IN PSORIASIS

The link between miRNAs and psoriasis was first described in 2007 (Sonkoly et al., 2007). To date, more than 250 miRNAs have been reported as aberrantly expressed in psoriasis tissue, the majority of which are found in peripheral blood or involved psoriatic skin (Supplementary Table S1 online). Several studies have compared the miRNA profiles of uninvolved psoriatic skin versus normal healthy skin, but failed to identify reproducible differences between these tissues (Joyce et al., 2011; Lerman et al., 2011; Raaby et al., 2015; Zibert et al., 2010). In addition, only small subsets of these dysregulated miRNAs in psoriasis have confirmed mRNA targets with established biological functions in the skin (Table 1). Here, we review the miRNAs most strongly implicated in the immunopathogenesis of psoriasis.

miR-203

Multiple studies have reported miR-203 as being dysregulated in patients with psoriasis (Lerman et al., 2011; Sonkoly et al., 2007; Zibert et al., 2010). The first skin-specific miRNA

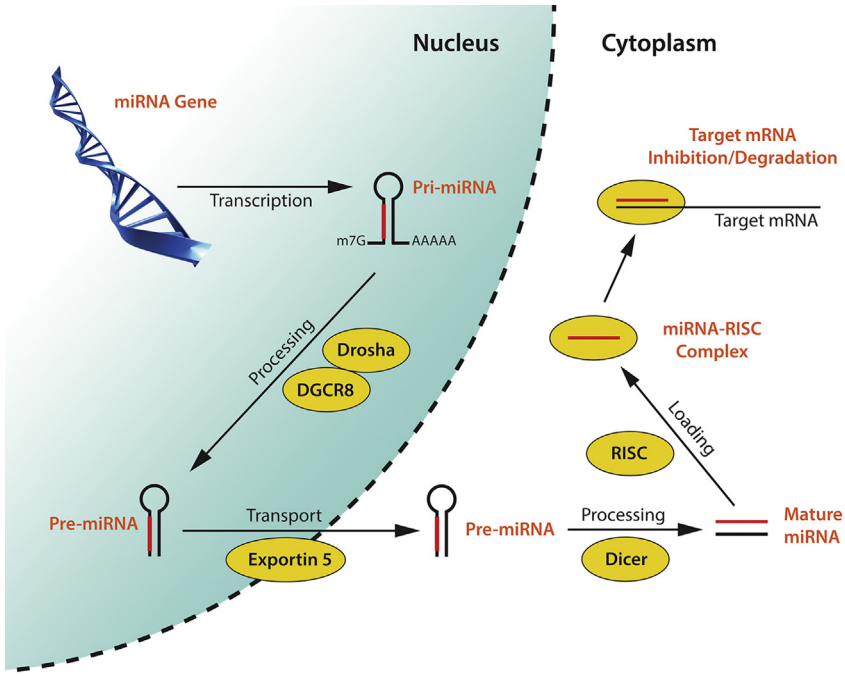

Figure 1. Model of miRNA biogenesis and posttranscriptional regulation of genes. miRNA genes are transcribed by either RNA polymerase II or RNA polymerase III into primary miRNA transcripts, known as pri-miRNA. The pri-miRNAs are then folded into hairpins, which serve as substrates for an RNase III enzyme, Drosha (RNASEN) and its partner DGCR8 (DiGeorge critical region 8). Drosha endonucleotically cleaves the long chain pri-miRNAs into ~70-nucleotide pre-miRNA. The pre-miRNAs are then exported into the cytoplasm by XPO5 (Exportin 5). Once outside the nucleus, the loop of pre-miRNA is cleaved off by another RNase family enzyme known as Dicer, generating an ~22-nucleotide miRNA duplex. One strand of this miRNA duplex is then loaded into the RNA-induced silencing complex (RISC). The loaded miRNA-RISC complex then interacts with the 3′ untranslated region (3′UTR) of target mRNA genes where it binds and disrupts translation or triggers mRNA degradation.

identified, miR-203, is made almost exclusively by keratinocytes and regulates cell differentiation in a protein kinase C–dependent manner (Sonkoly et al., 2007, 2010). Increased miR-203 in psoriatic tissue strongly correlates with a decrease in suppressor of cytokine signaling 3 (SOCS3) and subsequent elevation in signal transducer and activator of transcription-3 (STAT3), a transcription factor in keratinocytes that is fundamental to the development of psoriatic skin lesions (Sonkoly et al., 2010). miR-203 may also dampen the pro-inflammatory response by direct targeting and repression of tumor necrosis factor-α (TNF-α), IL-8, and IL-24 mRNA (Primo et al., 2012; Wei et al., 2013). The importance of miR-203 on skin morphogenesis and keratinocyte differentiation was further corroborated by showing that its upregulation in suprabasal keratinocytes results in inhibition of p63, a key regulator of basal cell "stemness" (Yi et al., 2008).

miR-146a

One of the most highly upregulated miRNAs in psoriatic skin is miR-146a (Sonkoly et al., 2007; Xia et al., 2012; Zibert et al., 2010). miR-146a is a crucial negative regulator of inflammation, autoimmunity, and the innate immune response (O'Connell et al., 2012; Taganov et al., 2006). This miRNA promotes resolution of the immune response by negatively regulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-dependent inflammatory signals via direct targeting of TNF receptor–associated factor 6 and IL-1 receptor–associated kinase 1 (IRAK1) (Meisgen et al., 2014; O'Connell et al., 2012). TNF receptor–associated factor 6 and IRAK1 are key signaling mediators involved in the production of pro-inflammatory cytokines (e.g., IL-6 and TNF-α) after toll-like receptor and IL-1 receptor activation (O'Connell et al., 2012).

Increased miR-146a is found in both the epidermal and dermal compartments of psoriatic skin, as well as the peripheral blood mononuclear cells (PBMCs) (Lovendorf et al., 2015; Xia et al., 2012). High levels of miR-146a in the skin and PBMCs of patients with psoriasis have a strong positive correlation with IL-17, an increasingly important cytokine in the pathogenesis of psoriasis (Xia et al., 2012). Given the strong link between miR-146a, inflammation, and the immune responses, it is not surprising that this miRNA associates with pathogenic processes of psoriasis.

miR-21

miR-21, an important oncogene (i.e., oncomiR) that functions to promote inflammation and inhibit apoptosis, is also elevated in psoriatic skin (Guinea-Viniegra et al., 2014; Ichihara et al., 2011; Joyce et al., 2011; Lovendorf et al., 2014, 2015; Meisgen et al., 2012; Sonkoly et al., 2007; Zibert et al., 2010). Increased miR-21 has been localized to keratinocytes and infiltrating inflammatory cells (Guinea-Viniegra et al., 2014; Meisgen et al., 2012). Further, it is upregulated in proliferative states due, in part, to the disruption of the degradation pathway of miR-21 (Boele et al., 2014). Elevated miR-21 in psoriatic skin correlates with enhanced TNF-α mRNA expression, and its inhibition in mice with psoriasis xenotransplants results in improved skin disease (Guinea-Viniegra et al., 2014). Further, inhibition of miR-21 in activated primary $CD4^+$ human T cells results in increased apoptosis suggesting that miR-21 in psoriatic skin may contribute to the persistence of infiltrating T-cell populations and chronic skin inflammation (Meisgen et al., 2012). These studies provide strong evidence for a role of miR-21 in the pathogenesis of psoriasis and its potential as a future therapeutic target.

Table 1. Aberrantly expressed miRNAs in psoriasis with established biological targets and functions in skin

miRNA	Tissue/cell type	Expression	Target genes	Biological function	References
miR-21	Human skin, human PBMCs	Increased	*TIMP3, TPM1, PDCD4, PTEN, IL12A, RECK, RTN4, NFIB*	Regulation of keratinocyte proliferation, inflammation, T-cell apoptosis, and angiogenesis	(Ichihara et al., 2011; Joyce et al., 2011; Liu et al., 2011; Lovendorf et al., 2014, 2015; Meisgen et al., 2012; Sonkoly et al., 2007; Zibert et al., 2010)
miR-31	Human skin	Increased	*FIH-1, STK40*	Regulation of keratinocyte differentiation, NF-κB activity, angiogenesis, and leukocyte migration to the skin	(Joyce et al., 2011; Peng et al., 2012; Sonkoly et al., 2007; Xu et al., 2013; Zibert et al., 2010)
miR-135b	Human skin, primary human keratinocytes	Increased	*COL4A3*	Regulation of keratinocyte differentiation and proliferation	(Choi et al., 2013; Joyce et al., 2011)
miR-136	Human skin, primary human keratinocytes	Increased	*PPP2R2A*	Regulation of TGF-β1-induced keratinocyte proliferation arrest	(Zhang et al., 2015; Zibert et al., 2010)
miR-138	Human PBMCs	Increased	*RUNX3*	Regulation of the Th-1/Th-2 balance in $CD4^+$ T cells	(Fu et al., 2015)
miR-146a	Human skin, human PBMCs, primary human keratinocytes	Increased	*IRAK1, TRAF6, EGFR*	Regulation of hematopoietic development, inflammation, immune cell mediators, and keratinocyte proliferation	(Lovendorf et al., 2015; Meisgen et al., 2014; Sonkoly et al., 2007; Xia et al., 2012; Zhang et al., 2014; Zibert et al., 2010)
miR-155	Human skin	Increased	*CTLA-4*	Regulation of hematopoietic development and inflammation	(Ichihara et al., 2011; Lovendorf et al., 2015)
miR-184	Human skin	Increased	*AGO2*	Regulation of posttranscriptional modification of mRNA and miRNA biogenesis via the miRISC complex	(Roberts et al., 2013)
miR-203	Human skin, primary human keratinocytes	Increased	*SOCS-3, SOCS-6, p63, TNFα, IL8, IL24*	Regulation of inflammation, STAT3 signaling, and keratinocyte proliferation/differentiation	(Lerman et al., 2011; Primo et al., 2012; Raaby et al., 2015; Sonkoly et al., 2007; Wei et al., 2013; Yi et al., 2008; Zibert et al., 2010)
miR-210	Human PBMCs	Increased	*FOXP3*	Regulation of regulatory T cells and their cytokine production	(Zhao et al., 2014)
miR-221/222	Human skin	Increased	*TIMP3, c-KIT, p57*	Regulation of keratinocyte and immune cell proliferation	(Joyce et al., 2011; Zibert et al., 2010)
miR-424	Human skin	Increased	*MEK1, Cyclin E1*	Regulation of keratinocyte proliferation	(Ichihara et al., 2011; Lerman et al., 2011)
miR-99a	Human skin	Decreased	*IGF-1R*	Regulation of keratinocyte proliferation and differentiation	(Ichihara et al., 2011; Lerman et al., 2011; Lovendorf et al., 2015)
miR-125b	Human skin, human serum	Decreased	*FGFR2, TNF-α*	Regulation of keratinocyte proliferation/ differentiation and inflammation	(Koga et al., 2014; Lovendorf et al., 2015; Sonkoly et al., 2007; Xu et al., 2011)

Abbreviations: NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PBMCs, peripheral blood mononuclear cells; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor-β1.

miR-184

miR-184 has been shown to be upregulated in psoriatic skin (Joyce et al., 2011) and may have a unique role in keratinocytes and keratinocyte-related diseases by directly affecting the expression of other miRNAs (Roberts et al., 2013). miR-184 directly targets argonaute RNA-induced silencing complex catalytic component 2, a fundamental protein involved in the RNA-induced silencing complex, and, ultimately, miRNA biogenesis (Roberts et al., 2013). miR-184 also inhibits miR-205 to maintain expression levels of keratinocyte SH2—containing phosphoinositide 5′-phosphatase 2, a regulator of Akt signaling and cell survival (Yu et al., 2008). However, the significance of this specific miRNA in psoriasis remains unclear because prior miRNA profiling studies did not find miR-184 to be significantly dysregulated in psoriatic skin.

miR-210

Upregulation of miR-210 in psoriasis has been reported (Lerman et al., 2011) and appears to contribute to inflammation by interfering with the immunosuppressive effects of regulatory T cells (Zhao et al., 2014). miR-210 is increased in $CD4^+$ T cells in patients with psoriasis and leads to increased pro-inflammatory cytokines (i.e., IFN-γ and IL-17) via direct targeting of FOXP3, a master regulator of the development of regulatory T cells (Zhao et al., 2014). These findings provide support for regulatory T-cell dysfunction and miRNA-mediated regulation of this cell population in psoriasis. Additional studies are needed to further validate and establish the role of this miRNA in psoriatic disease.

miR-221 and miR-222

Increased levels of miR-221 and miR-222 have also been observed in psoriasis skin lesions (Joyce et al., 2011; Zibert et al., 2010). Increased levels of these miRNAs correlate with a reduction in tissue inhibitor of metalloproteinase 3, a member of the matrix metalloprotease family (Zibert et al., 2010). Matrix metalloproteases are a group of enzymes involved in a broad range of cellular activities (e.g., cell proliferation, angiogenesis, and inflammation) and are altered in psoriasis tissues (Fleischmajer et al., 2000). Therefore, increased miR-221 and miR-222 are thought to contribute to psoriasis by promoting epidermal proliferation via activated matrix metalloproteases (Zibert et al., 2010). Other psoriasis-associated miRNAs (e.g., miR-21) also target tissue inhibitor of metalloproteinase 3 (Zibert et al., 2010). These findings underscore the potential importance of tissue

inhibitor of metalloproteinase 3 and matrix metalloproteases in the immunopathogenesis of psoriasis.

miR-31

miR-31 is upregulated in psoriatic skin (Joyce et al., 2011; Sonkoly et al., 2007; Xu et al., 2013; Yan et al., 2015; Zibert et al., 2010) and directly inhibits serine/threonine kinase 40 (Xu et al., 2013) and protein phosphatase 6 (Yan et al., 2015). By direct targeting of serine/threonine kinase 40, miR-31 regulates NF-κB signaling and the leukocyte-attracting and endothelial cell—activating signals produced by keratinocytes (Xu et al., 2013). Similarly, Yan et al. (2015) showed that activation of NF-κB signaling results in the upregulation of miR-31 and subsequent enhanced keratinocyte proliferation through direct targeting of protein phosphatase 6. miR-31 is also induced by transforming growth factor-β1, a cytokine previously implicated in psoriasis (Han et al., 2010; Xu et al., 2013). Of interest, miR-31 also has regulatory effects on vascular differentiation, keratinocyte migration during wound healing, and promotion of hair growth (anagen) by inhibition of the catagen and telogen stages of hair development (Peng et al., 2012; Xu et al., 2013). These reports place miR-31 at the center of keratinocyte biology and skin development, supporting the notion that its dysregulation may directly contribute to the development of proliferating skin diseases, such as psoriasis.

miR-125b

In contrast to the upregulated miRNAs in psoriasis, miR-125b is decreased in the skin (Lovendorf et al., 2015; Sonkoly et al., 2007; Xu et al., 2011) and serum of patients with psoriasis (Koga et al., 2014). Decreased expression of miR-125b in psoriasis skin compared with normal skin is primarily the result of decreased expression in keratinocytes (Xu et al., 2011). This decrease in miR-125b results in increased proliferation and decreased differentiation of keratinocytes and is mediated through direct targeting of Fibroblast growth factor receptor 2 (FGFR2) (Xu et al., 2011). In macrophages, decreased levels of miR-125b also correlate with increases in TNF-α, a direct target of miR-125b (Tili et al., 2007). Decreases in miR-125b may, therefore, directly contribute to psoriasis skin lesions via its regulation of keratinocyte proliferation and TNF-α signaling. The central role of TNF-α in psoriasis has already been established by the clinical efficacy of anti-TNF-α biologic therapies.

miR-99a and miR-424

miR-99a and miR-424 also play a role in the development of psoriatic skin. miR-99a is decreased in psoriatic skin (Ichihara et al., 2011; Lerman et al., 2011; Lovendorf et al., 2015) and reciprocally expressed in the epidermis with one of its direct targets, insulin-like growth factor-1R, a known promoter of keratinocyte proliferation and inhibitor of cell differentiation (Lerman et al., 2011). On the other hand, miR-424 is decreased in psoriatic skin and promotes abnormal keratinocyte proliferation by allowing for increases in the protein expression of MEK1 and cyclin E1, two key regulators of cell proliferation (Ichihara et al., 2011). Together, these findings suggest that the function of miR-99a and miR-424 in normal skin may help maintain epidermal homeostasis by the direct inhibition of their respective mRNA targets. Although no other studies have validated the decreased levels of miR-424 in psoriatic skin, this miRNA can regulate TNF-α production (Zhao et al., 2013) and has been shown to be increased in the hair shafts of patients with psoriasis (Tsuru et al., 2014).

miRNAs AND PSORIASIS SUSCEPTIBILITY

Genome-wide association studies have identified many psoriasis-associated genetic loci in the Caucasian population (Nair et al., 1997; Russell et al., 1972; Tiilikainen et al., 1980; Tsoi et al., 2012). However, most genome-wide association study signals lie within noncoding regions of the human genome (Maurano et al., 2012). miRNAs and other noncoding RNAs make up more than 70% of noncoding RNA (Venter et al., 2001). Thus, it will be important to examine whether psoriasis-associated variants also disrupt or alter the expression of specific miRNAs and determine if they contribute to psoriasis susceptibility.

In 2010, Chatzikyriakidou and colleagues studied the association between psoriatic arthritis risk in a cohort of patients with psoriasis from Greece and specific polymorphisms found in miR-146a (rs2910164) and one of its known targets, IRAK1 (rs3027898, rs1059703) (Chatzikyriakidou et al., 2010). There was no association between the rs2910164 miR-146a variant and psoriatic arthritis susceptibility, but a very strong association with the rs3027898 IRAK1 variant was observed (Chatzikyriakidou et al., 2010). Interestingly, the rs3027898 IRAK1 variant was also correlated with ankylosing spondylitis, suggesting a more general role for miR-146a and IRAK1 in inflammatory arthropathies (Chatzikyriakidou et al., 2010). In contrast, a separate study showed that the rs2910164 miR-146a allele was associated with increased psoriasis susceptibility in Han Chinese patients (Zhang et al., 2014). Specifically, the rs2910164G allele resulted in reduced levels of miR-146a and impairment of its ability to regulate endothelial growth factor receptor, an important proliferative signal in keratinocytes and psoriasis skin (Nanney et al., 1986; Zhang et al., 2014).

miRNAs may also help explain the link between psoriasis risk and polymorphisms in *BSG* (*basigin*), a gene located within the psoriasis susceptibility locus 6 region (Wu et al., 2011). Carriers of the rs8259 BSG polymorphism have lower BSG mRNA expression levels in their PBMCs and a decreased psoriasis susceptibility risk (Wu et al., 2011). Notably, the rs8259 BSG polymorphism was localized to the 3′ untranslated region miR-492-dependent binding site and completely abolished miR-492 binding (Wu et al., 2011). Although their study did not find a significantly elevated level of miR-492 in the PBMCs of patients with psoriasis, it suggests that the link between this gene variant and psoriasis susceptibility could be due to the disruption of miRNA binding of the *BSG* gene, warranting further investigation.

Finally, one report demonstrates the interplay between miR-148a and cell surface expression of HLA-C (Kulkarni et al., 2013), one of the strongest psoriasis susceptibility loci discovered to date (Bergboer et al., 2012). miR-148a binding with HLA-C mRNA directly affects cell surface expression of HLA-C and influences HIV control and Crohn's disease susceptibility (Kulkarni et al., 2013). Although these

findings do not establish a direct role for miR-148a in psoriasis, they do provide a mechanism whereby miRNAs interact with psoriasis susceptibility loci to ultimately impact disease phenotype. In this way, polymorphisms in specific miRNAs and/or their interaction with susceptibility genes may provide insights into the issue of "missing heritability" in complex, multigenic, chronic inflammatory diseases.

miRNAs AS POTENTIAL BIOMARKERS OF DISEASE

Multiple studies provide evidence supporting the utility of miRNAs as biomarkers of skin disease (Jinnin, 2014). An area of considerable interest is whether a single miRNA or group of miRNAs can serve as biomarkers of psoriatic disease. To date, more than 100 miRNAs are reproducibly detected and abundant in the serum of patients with plaque psoriasis (Pivarcsi et al., 2013). Specific miRNAs (i.e., miR-19a and miR-424) have also been isolated from more easily accessible tissue such as the hair of patients with psoriasis (Hirao et al., 2013; Tsuru et al., 2014). Ready access to miRNAs as potential biomarkers of psoriasis represents an important field of discovery.

Plasma miR-33 is increased in patients with psoriasis and positively correlates with insulin levels and calculated insulin resistance (Garcia-Rodriguez et al., 2014). A negative correlation between circulating levels of miR-126 and carotid intima-media thickness has also been described (Garcia-Rodriguez et al., 2014). Both of these findings are potentially important observations given the unclear mechanisms driving the increased risk of diabetes and cardiovascular disease in patients with psoriasis.

The serum levels of miR-1266, a putative regulator of IL-17A, are also significantly increased in patients with plaque psoriasis and inversely correlated with psoriasis-involved body surface area and Psoriasis Area Severity Index (PASI) scores (Ichihara et al., 2012). High levels of miR-146a in psoriatic skin and PBMCs are also positively correlated with IL-17 levels and PASI scoring (Xia et al., 2012). Similarly, levels of miR-369-3p (Guo et al., 2013), as well as miR-143 and miR-223 (Lovendorf et al., 2014), are upregulated in the serum and positively correlate with disease severity. However, there was no single miRNA identified in both studies that was elevated in the serum of patients with psoriasis.

The ability to isolate miRNA from small skin samples or blood represents a potentially useful, noninvasive method of diagnosing and/or monitoring systemic inflammatory conditions. However, the lack of correlation between the various tissues studied suggests an incomplete understanding of the regulatory mechanisms of miRNA expression in skin, blood, and the hair (Xia et al., 2012). Until research generates a more thorough understanding of the role of miRNAs in psoriasis, discordant results should be expected and highlight the limitation of skin and serum association studies. Further, it adds emphasis to the need for standardized study designs, isolation techniques, miRNA expression profiling platform, and data analysis.

ALTERATION OF miRNA PROFILES AFTER PSORIASIS TREATMENTS

The impact of systemic therapies on specific psoriasis–related miRNAs has also been explored. One report found that narrow-band ultraviolet B therapy results in epidermal decreases of miR-21 and increases in p53 and miR-125b (Gu et al., 2011). The role of miRNAs in the phototherapy response is further supported by the observation that miR-4516 mediates downregulation of STAT3 and apoptosis in keratinocytes exposed to psoralen plus UVA therapy (Chowdhari and Saini, 2014).

The alteration of miRNAs after treatment is not unique to phototherapy. miR-143 and miR-223 are significantly elevated in the PBMCs of patients with untreated psoriasis and subsequently decrease after methotrexate therapy (Lovendorf et al., 2014). Another report found that 38 miRNAs had increased in the serum after etanercept therapy (Pivarcsi et al., 2013). These posttreatment miRNA profile changes were observed in etanercept therapy responders, but were not observed in patients treated with methotrexate. In addition, the miRNA expression profile changes in the skin of patients with psoriasis treated with adalimumab were not seen at 4 days after the first injection, but changes were observed at 2 weeks (Raaby et al., 2015). Together, these findings suggest that the alteration of miRNA expression profiles after systemic psoriasis treatments is somewhat specific to each treatment, may be used as predictors of treatment efficacy, and can change at various time points during the treatment period.

CHALLENGES AND FUTURE DIRECTIONS

Although previous work suggests a functional role for miRNAs in the development of psoriasis, most studies to date involve small patient cohorts and are limited to association studies. Psoriasis-associated miRNAs need to be investigated further using comprehensive studies with in vitro and in vivo experiments designed to determine the molecular mechanisms and direct targets of specific miRNAs. A number of transgenic mouse models felt to closely resemble the phenotypic, histologic, and cytokine pathways of human psoriasis are available for such mechanistic studies (Gudjonsson et al., 2007; van der Fits et al., 2009). Recent psoriasis studies have begun to incorporate these mouse models into their miRNA profiling and screening studies (Guinea-Viniegra et al., 2014; Lerman et al., 2011; Raaby et al., 2015; Yan et al., 2015).

Studying the role and function of specific miRNAs along with global expression patterns of specific phenotypes will provide the clues that will lead to an understanding of central pathways and/or genes perturbed in this chronic inflammatory disease. However, a major limitation to the current miRNA studies in psoriasis is that they are almost completely exclusive to psoriasis vulgaris. Little is known about the miRNA profiles of the various psoriasis subtypes, including guttate, pustular, erythrodermic, thin/thick plaques, inverse, and the arthritis variants. Initial miRNA profiling studies on these variants may offer insight into the pathophysiology of psoriasis subtypes. Moreover, individual psoriasis-specific miRNAs may become the focus of new topical and systemic therapy development efforts. The use of topical miRNA-targeted therapies, including the use of cell-penetrating peptides and nanoparticles, has been demonstrated in pachyonychia congenital (Hickerson et al., 2008; Leachman et al., 2010; Smith et al., 2008) and melasma

(Yi et al., 2011). Inhibition of specific miRNAs has also been shown to be effective in preclinical mouse models of psoriasis (Guinea-Viniegra et al., 2014) and breast cancer (Devulapally et al., 2015). The potential benefit of miRNA-targeted therapies in humans has also been demonstrated by the development and use of Miravirsen, an antisense inhibitor of miR-122 for the treatment of hepatitis C infections (Janssen et al., 2013).

The considerable impact of psoriasis on patients and the comorbidities associated with this condition highlight the importance of elucidating the molecular details of the immunopathogenesis of this inflammatory disorder. It is crucial that ongoing psoriasis studies evaluate novel mechanisms of epigenetic regulation of gene expression, including miRNA-mediated posttranscriptional gene silencing. As our understanding of psoriasis pathophysiology increases, we anticipate that miRNAs will emerge as prominent players in the development of this and other chronic inflammatory skin conditions.

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CONFLICT OF INTEREST
KCD reports personal fees from AbbVie, Amgen, Lilly, Pfizer, Bristol Myers Squibb, Janssen, XenoPort, Novartis, and Celgene. GGK reports personal fees from Abbott, Amgen, ApoPharma, Astellas, Boehringer, Bristol Myers Squibb, Celgene, Idera, Isis, Janssen, Lilly, L'Oreal, Novartis, Pfizer, Vascular Biologics Limited, and UCB, and institutional support from Abbott, Amgen, and Janssen.

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SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1038/JID.2015.409.

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