microRNAs involved in psoriasis and cardiovascular diseases

Sara Sileno, Sara Beji, Marco D'Agostino, Alessandra Carassiti, Guido Melillo and Alessandra Magenta

1Istituto Dermopatico dell’Immacolata, IDI-IRCCS, Experimental Immunology Laboratory, Via Monti di Creta, Rome, Italy
2Unit of Cardiology, IDI-IRCCS, Via Monti di Creta, Rome, Italy
3Institute of Translational Pharmacology (IFT), National Research Council of Italy (CNR), Via Fosso del Cavaliere, Rome, Italy

Correspondence should be addressed to A Magenta: ale.magenta@gmail.com

*(S Sileno, S Beji and M D’Agostino contributed equally to this work)

Abstract
Psoriasis is a chronic inflammatory disease involving the skin. Both genetic and environmental factors play a pathogenic role in psoriasis and contribute to the severity of the disease. Psoriasis, in fact, has been associated with different comorbidities such as diabetes, metabolic syndrome, gastrointestinal or kidney diseases, cardiovascular disease (CVD), and cerebrovascular diseases (CeVD). Indeed, life expectancy in severe psoriasis is reduced by up to 5 years due to CVD and CeVD. Moreover, patients with severe psoriasis have a higher prevalence of traditional cardiovascular (CV) risk factors, including dyslipidemia, diabetes, smoking, and hypertension. Further, systemic inflammation is associated with oxidative stress increase and induces endothelial damage and atherosclerosis progression. Different miRNA have been already described in psoriasis, both in the skin tissues and in the blood flow, to play a role in the progression of disease. In this review, we will summarize and discuss the most important miRNAs that play a role in psoriasis and are also linked to CVD.

Introduction
Psoriasis is a complex and chronic inflammatory disease affecting 2–3% of the world’s population (1). The etiology of psoriasis is complex, and still debated, as the disorder is caused by the interaction among multiple genes, the immune system and environmental factors (2, 3).

From a dermatological point of view, psoriasis is characterized by hyperproliferative epidermis and cutaneous lymphocytic infiltration that can also involve joints causing a form of arthritis, known as psoriatic arthritis (PsA) (3).

A prominent role is played by the increased risk in these patients of major adverse cardiovascular events: this evidence has received increasing attention in the last decades (4, 5). This finding cannot be explained only on the basis of high prevalence of traditional cardiovascular risk factors seen in psoriatic patients (6); additional and independent factors such as the systemic inflammation associated with psoriasis, the presence of psoriasis-related comorbidities (7, 8) and the atherogenic side-effects of systemic therapies for psoriasis have also been reported (9).

Atherosclerosis and inflammation in psoriatic patients
Ample research work has demonstrated that inflammation is a key driver of atherosclerosis.
Indeed, the risk of cardiovascular events is not sufficiently indexed by cholesterol and other traditional risk factors. High-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL6) levels, despite significant reductions in low-density lipoprotein cholesterol (LDL-C) obtainable with maximal medical therapy, are associated with 'residual inflammatory risk'. Control of inflammation has increasingly become a viable pharmacologic target for primary and secondary prevention of atherosclerotic disease (10).

The inflammatory process seen in psoriasis shares many features with atherosclerosis including T helper 1-mediated inflammation, alterations in angiogenesis, and endothelial dysfunction that may link the pathogenesis of psoriasis with the development of atherosclerosis and cardiovascular disease (CVD) (11).

The typical histological features of the psoriatic plaque with dermal inflammation and leucocyte infiltration are similar to those of the atherosclerotic plaque. The theory of 'two plaques for one syndrome' has been hypothesized given the similarities in the molecular mechanisms and pro-inflammatory cytokine profile found in psoriatic lesions and those of atherosclerotic ones, with a comparable inflammatory infiltrate of T cells, macrophages and monocytes (9, 12).

Both atherosclerosis and psoriasis are characterized by immune system activation, involving T helper-1, T helper-17, regulatory T cells and inflammatory cytokines such as INFG, IL2, TNF and IL17 (13). These mediators play a key role in the development of psoriatic plaques, stimulating angiogenesis and keratinocyte proliferation and promote insulin resistance, metabolic abnormalities and endothelial dysfunction, which contribute to atherosclerotic plaque formation and progression (14, 15). In support of this theory, large epidemiologic studies have found increased rates of cardiovascular mortality, myocardial infarction (MI) (4, 5), atrial fibrillation and stroke (16) among patients with both mild and severe psoriasis. Recent comprehensive meta-analysis and cohort studies have confirmed that the association is statistically significant (16). For a definitive evaluation of the association, more long-term prospective studies will be needed.

Psoriatic patients, therefore, appear to have a shorter life expectancy, estimated as approximately 5 years (17). These subjects have increased prevalence of traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, tobacco use and obesity (7, 8). Psoriasis, as already pointed out and mainly if severe, appears to be an independent risk factor for atherosclerotic CVD, as the risk persists even after adjusting for the traditional risk factors, probably due to the role that systemic inflammation plays in determining premature atherosclerosis in these patients (4, 5).

The impact of psoriasis duration on aging and cardiovascular risk

Estimation of cardiovascular risk based on the traditional score system has limitations in peculiar clinical contexts. These scores are known to underperform because traditional cardiovascular risk factors do not fully explain the increased cardiovascular risk in patients with psoriasis. Consequently, cardiovascular risk is often underestimated in these individuals (18).

Although the relative risk of major adverse clinical events is greater for young patients with severe psoriasis vs old ones with mild disease, the greater population prevalence of mild psoriasis translates into a greater population-attributable risk of mild psoriasis for both MI and stroke. These findings emphasize that all patients with psoriasis, rather than only young patients with severe psoriasis, should be educated regarding the increased risk of CVD.

In addition, the risk of MI in psoriatic patients aged between 30 and 40 years vs tose between 50 and 60 years with a long history of psoriasis was compared (13). Attributable risk and excess risk calculated based on the adjusted relative risk of MI were much higher in the older group being roughly 70-fold higher.

Patients with psoriasis were more likely to have coronary artery disease (CAD) as visualized on coronary angiogram. This association was still evident after adjusting for established cardiovascular risk factors, leading the authors to conclude that psoriasis is independently associated with the presence of CAD (19). Finally, a strict correlation between the duration of psoriasis and the extension of CAD exists.

microRNA involved in psoriasis and CVDmiRNAs are short non-coding RNAs that inhibit translation and/or induce degradation of target messenger RNAs (mRNAs) (20).

The following miRNAs (summarized in Table 1) are the most important miRNAs modulated in psoriasis that are also involved in CVD.

miR-200 family

miR-200 family is composed of five members (i.e. miR200a, miR-200b, miR-200c, miR-429 and miR-141). This miRNA family has been shown to be induced in lesional skin (LS) of
### miRNAs modulated in psoriasis and CVD.

<table>
<thead>
<tr>
<th>miRNAs/ROS source or disease</th>
<th>Tissue/organ</th>
<th>Species</th>
<th>Modulation</th>
<th>Targets</th>
<th>References</th>
</tr>
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<td>ECs</td>
<td>Human</td>
<td>Upregulated</td>
<td>eNOS; SIRT1; FOXO1; ZEB1</td>
<td>(23, 24)</td>
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<td>Upregulated</td>
<td>eNOS; SIRT1; FOXO1; ZEB1</td>
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</tr>
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<td>ZEB1</td>
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<td>(46)</td>
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<td>CASP1</td>
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<td>CACNA1C</td>
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<td>H$_2$O$_2$</td>
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<td>Upregulated</td>
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<td>RECK; PDCD4</td>
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<td>miR-22</td>
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<td>(64)</td>
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<td>Psoriasis</td>
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<td>Human</td>
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<td>SIRT1, HDAC4</td>
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<td>(73)</td>
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<tr>
<td>AMI</td>
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<td>(74)</td>
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(Continued)
Table 1: miRNAs in psoriasis and cardiovascular risk

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<tr>
<th>miRNAs/ROS source or disease</th>
<th>Tissue/organ</th>
<th>Species</th>
<th>Modulation</th>
<th>Targets</th>
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<td>miR-369</td>
<td>Serum, LS vs HS</td>
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<td>(78)</td>
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<td>Atherosclerosis</td>
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<td>IGF1; TLR8</td>
<td>(80)</td>
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<td>ABCG1; SIRPA</td>
<td>(87, 88)</td>
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<td>miR-378a*</td>
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<td>VEGF</td>
<td>(80, 81)</td>
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<td>IGF1R; JAK2</td>
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<td>(36)</td>
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<td>Deep vein thrombosis</td>
<td>Venous tissue</td>
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<td>Downregulated</td>
<td>NFKB1</td>
<td>(92)</td>
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<td>MS</td>
<td>PBMCs</td>
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<td>ABCA1</td>
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<td>SDC2; OLR1</td>
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<td>miR-340</td>
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<td>Upregulated</td>
<td>Dystrophin</td>
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<td>Cardiac hypertrophy</td>
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<td>ATROGIN1, MURF1, PDE5A</td>
<td>(118)</td>
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<td>miR-19a</td>
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<td>Atherosclerosis</td>
<td>Plasma, atherosclerotic plaque</td>
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<td>Upregulated</td>
<td>HBP1</td>
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<td>Cardiomyocytes</td>
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<td>ATROGIN1, MURF1, PDE5A</td>
<td>(118)</td>
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<td>miR-424</td>
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<td>Atherosclerosis</td>
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<td>CRISPLD2</td>
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<td>miR-146a</td>
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miRNAs in psoriasis and cardiovascular risk

Further, miR-200c is the only one also induced compared to healthy subjects (HS). The entire miRNA family was assayed in the bloodstream of psoriatic patients, and miR-200c and miR-200a were upregulated significantly compared to healthy subjects. The correlation analysis with psoriasis area severity index (PASI) and the duration of disease showed that only miR-200c expression levels positively correlated with both, indicating that miR-200c could be considered as an inflammatory biomarker for this disease (21). Moreover, miR-200c correlated with different determinants of cardiovascular risk, such as relative wall thickness (RWT), left ventricular (LV) mass, and E/e' parameter, a marker of diastolic dysfunction (21). Circulating miR-200a correlated only with LV mass and augmentation index, a marker of stiffness, although not significantly (P = 0.06).

These data indicated that miR-200c increases in plaques and plasma of psoriatic patients and could be involved in the establishment of inflammation and CVD in psoriasis.

In another study, it has been shown that the upregulation of miR-200a in CD4+ T cells may induce immune dysfunction through Th17/Treg cells and relevant cytokines (i.e. IL17 and IL23) levels in psoriasis vulgaris patients and positively correlates with PASI (22).

miR-200c was upregulated in endothelial cells (ECs) upon oxidative stress exposure and is responsible for apoptosis, senescence (23), nitric oxide (NO) decrease and reactive oxygen species (ROS) increase, and all features associated with endothelial dysfunction (24). In particular, miR-200c targets zinc finger E-box binding homoeobox 1 (ZEB1) protein, inducing apoptosis and senescence of ECs (23) and disrupts the autoregulatory loop existing among Sirtuin1 (SIRT1), endothelial nitric oxide synthase (eNOS) and forkhead boxO1 (FOXO1), directly targeting all of them, causing NO decrease and ROS increase (24).

It is well known that endothelial dysfunction plays a key role in unstable plaques genesis. In keeping with this, miR-200c was increased in carotid plaques of atherosclerotic patients, and it is higher in unstable plaques vs stable plaques (25).

miR-200c was found to be elevated in the plasma of patients with atherosclerosis, although the circulating levels did not discriminate between stable or unstable plaques. Interestingly, the plasma levels were decreased after carotid endarterectomy (CEA), and after 1 month, the levels of miR-200c were increased in patients with unstable plaques, whereas 1 month after CEA miR-200c levels were still low in patients with stable plaques, indicating that...
increased levels of miR-200c are most probably associated with endothelial dysfunction and inflammation (25).

Interestingly, miR-200c levels positively correlate with biomarkers of plaque instability such as cyclooxygenase-2 (COX2), IL6, monocyte chemoattractant protein-1 (MCP1), metalloproteinase (MMP) 1, MMP9 and negatively correlated with stability biomarkers (i.e. ZEB1, eNOS, FOXO1 and eNOS).

Interestingly, miR-200c positively correlated with two important miRNAs, miR-33a/b (see following paragraph), which have been linked to atherosclerosis progression (26) and are key players of cholesterol homeostasis, since they are key regulators of high-density lipoprotein (HDL) cholesterol synthesis (27).

In conclusion, the miR-200 family is increased in psoriasis skin, and among its members, miR-200c plasma levels correlate with cardiovascular risk and inflammatory biomarkers (Fig. 1).

miR-33a/b

miR-33a and miR-33b share the same seed sequence and are embedded in introns of sterol regulatory element-binding protein (SREBP)2 and SREBP1 genes, respectively (28). SREBP genes are important transcription factors that regulate lipid metabolism, and their transcriptional upregulation induces miR-33a and miR-33b expression (28).

miR-33a was found to be higher in plasma of patients with plaque psoriasis compared to controls and correlated positively with plasma insulin and the homeostatic model assessment (HOMA)-insulin resistance index value. Moreover, psoriasis patients displayed greater carotid intima-media thickness (IMT) than controls (29).

miR-33 are known to directly target the cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), proteins implicated in the efflux of cholesterol from macrophages to generate HDL (27). miR-33a/b also regulate fatty acid oxidation and insulin signaling (30, 31).

Given their role in cholesterol and lipid metabolism, different studies evaluated miR-33 inhibition in animal studies. miR-33 inhibition has been shown to raise plasma HDL-cholesterol and to protect from atherosclerosis in mice (32). miR-33 inhibition in non-human primates upregulates the hepatic expression of ABCA1, increasing plasma HDL-cholesterol levels and suppressing the plasma levels of very-low-density lipoprotein (VLDL)-associated triglycerides (33).

Interestingly, as aforementioned, miR-33a and miR-33b were found to be increased in carotid atherosclerotic plaques, suggesting their role in advanced atherosclerosis in humans (26).

In keeping with this, miR-33a/b were also found to be upregulated in plasma of children with familial hypercholesterolemia, a disease that causes atherosclerosis in the pediatric age. miR-33a/b positively correlated with total cholesterol, LDL-cholesterol, apolipoprotein B, glycemia and CRP (34). Moreover, these miRNAs correlated also with miR-200c plasma levels, and the extracellular
release of miR-200c was mediated by miR-33 since the overexpression of miR-33a/b in vitro in different cells (i.e. ECs, hepatic cells and embryonic kidney cells) was mediated by a ZEB1-decrease mechanism (35).

The latter is a transcriptional inhibitor of miR-200c; hence, ZEB1-decrease causes an increase of both intracellular and extracellular miR-200c expression levels (35).

A positive correlation between miR-200c and miR-33a/b was also found in the plasma and plaques of atherosclerotic patients as mentioned previously (25) (Fig. 2).

Thus, a complex interplay among miRNAs is most probably the basis of metabolic dysfunction and inflammation and oxidative stress increase in psoriatic patients.

**miR-133a**

miR-133a was found to be downregulated in LS of psoriatic patients compared to NS (36). miR-133a expression levels increased after treatment with biologics.

Notably, miR-133a is muscle-specific miRNA, and it is involved in cardiac development and pathophysiology.

Interestingly, miR-133a is downregulated in both the infarcted area and the border zone both in humans, as well as in experimental animals (37, 38).

On the other hand, miR-133a levels in serum increased significantly in patients with acute myocardial infarction (AMI) or with unstable angina pectoris, and circulation increase of miR-133a positively correlates with the infarcted area (39).

Indeed, miR-133a decrease is involved in cardiac hypertrophy, and its overexpression inhibits hypertrophy (40). Moreover, miR-133a increase plays a major role in preventing cardiac fibrosis in chronic heart failure (HF) (41), and its increase in adult cardiac progenitor cells (CPCs) improves cardiac function, decreasing fibrosis and increasing cardiomyocyte proliferation and vascularization (42).

miR133a was found to be downregulated in plasma and in atherosclerotic plaques, and its decrease in vascular smooth muscle cells (VSMCs) results in the inhibition of proliferation and in the induction of apoptosis via MMP9 (43).

miR-133a has been shown to inhibit the osteogenic differentiation of VSMCs; therefore, its decrease induces arterial calcification (44).

Finally, miR-133a is also decreased in thoracic aortic aneurysms (TAA), and its decrease negatively correlates with aortic diameters (45).

Thus, miR-133a decrease in psoriasis could be involved in the onset of different CVD.

**miR-135b**

miR-135b was upregulated in LS compared to NS (46), and after treatment with biologics, miR-135b was
miR-21

miR-21 was significantly upregulated in LS of patients with psoriasis compared to healthy skin (50), and narrow-band UV phototherapy treatment decreased its expression in skin biopsies derived from psoriatic patients (51). Moreover, a specific single nucleotide polymorphism in 3'UTR of integrin alpha-M (ITGAM) is associated with a binding site improvement for miR-21 that can manifest an aberrant function of innate immune cells, resulting in higher risk insurgence of psoriasis in women (52). Other data suggest that miR-21 upregulation could increase the inflammatory process, by suppressing the apoptosis pathway in dermal T-cells of psoriatic patients (53). A recent study has shown that the interaction between miR-21 and IncRNA maternally expressed gene3 (MEG3) can influence the apoptotic axis in human psoriatic keratinocytes (54).

miR-21 inhibition was able to reduce psoriatic phenotype in a mouse model of psoriasis (55).

miR-21 has been widely studied in CVD. miR-21 was shown to be upregulated by oxidative stress in rat VSMCs. Its upregulation was found to be protective from apoptosis since programmed cell death 4 (PDCD4) is a direct target of miR-21 (56). PDCD4, in fact, is a pro-apoptotic protein that inhibits the activity of the transcription factor AP-1 (57). The latter is a signaling molecule, which determines cell fate based on extracellular stimuli, including ROS.

Interestingly, miR-21 is upregulated by shear stress and also protects ECs from apoptosis, increasing eNOS and NO production (58).

miR-21 upregulation also occurs in atherosclerotic plaques, decreasing the function of superoxide dismutase-2 (SOD2) antioxidant enzyme and targeting a negative regulator of the branching morphogenesis, sprouty homolog 2 (SPRY2). This, in turn, leads to the activation of ERK/MAP kinase provoking ROS increase and angiogenic progenitor cell (APC) migratory defects (59).

Moreover, miR-21 expression is increased in myocardial tissue and plasma of patients with aortic stenosis (60), in a mouse model of cardiac hypertrophy induced by aortic banding, and in neonatal rat cardiomyocytes after stimulation with hypertrophic agents (61); miR-21 upregulation in cardiac hypertrophic growth caused SPRY2 downregulation, enhancing the formation of various cellular protrusions and gap junction remodeling, enhancing conduction velocity (62).

miR-21 circulating levels have been also used as excellent biomarkers for the diagnosis of heart dysfunction (63).

In conclusion, miR-21 increase in psoriasis could be a possible link to CVDs such as atherosclerosis and cardiac hypertrophy.

miR-22

miR-22 circulating expression levels were significantly downregulated in the blood of patients affected by psoriasis vulgaris compared to healthy subjects (64). In addition, plasma levels of miR-22 were evaluated in PsA and ankylosing spondylitis, two chronic inflammatory rheumatic disorders. miR-22 circulating expression was found to be markedly lower in PsA subjects than in ankylosing spondylitis patients (65).

Psoriasis is widely regarded as a classical autoimmune disease. Interestingly, it has been shown that miR-22 levels are upregulated in the spleen and spinal cords of mice that developed autoimmune encephalomyelitis, and its high expression in inflammatory Th17 cells could protect mice from autoimmunity (66).

miR-22 also plays a pivotal role in CVD. miR-22 is a pro-hypertrophic miRNA, and in fact, miR-22 levels were increased in cardiomyocyte hypertrophy and in different cardiac hypertrophy mice models (67, 68). Moreover, cardiac-specific deletion of miR-22 inhibits stress-induced cardiac hypertrophy and remodeling (68, 69), whereas...
cardiac-specific overexpression of miR-22 elicited cardiac dilation and HF (70).

Moreover, pharmacological inhibition of miR-22 promoted cardiac functional recovery after MI by eliciting cardiac autophagy (71).

Ischemia-reperfusion (IR) in rat cardiomyocytes induced down-modulation of miR-22 and an increase of pS3-upregulated-modulator-of-apoptosis (PUMA), thus increasing apoptosis (72).

Moreover, miR-22 expression is decreased in human femoral arteries with atherosclerotic plaques compared to healthy arteries (73). miR-22 plays a regulatory role in VSMC phenotype switching and vascular neointima lesion formation, by regulating multiple target genes (i.e. HDAC4, methyl-CpG binding protein 2 and ecotropic viral integration site-1). Overexpression of miR-22 can reverse the process of VSMC phenotype switching in the injured arteries and prevent postangioplasty restenosis, supporting a potential role for miR-22 and its target genes in a variety of proliferative vascular diseases (73).

Further, miR-22 circulating levels were significantly decreased in patients affected by AMI compared to controls, suggesting that it could be considered as a promising diagnostic biomarker (74).

All the previously described studies underlined a decrease in psoriasis of miR-22 that is likely associated with atherosclerotic plaques, whereas in cardiac tissues, the miR-22 decrease has a protective function, and its increase induces cardiac dilation and failure.

**miR-369**

miR-369 expression levels were found to be increased in serum samples and skin tissues deriving from psoriatic patients compared to healthy subjects, and a positive correlation existed between skin miR-369 levels and PASI (64, 75).

miR-369 has emerged as a key regulator of inflammatory response in dendritic cells since it decreases LPS-induced NO production, by directly targeting iNOS expression and simultaneously inhibiting nuclear translocation of NFKB (76). In keeping with this, miR-369 overexpression in these cells significantly decreased cytokine production (i.e. TNF, IL6, IL12, IL1A and IL1B) in response to LPS, and some anti-inflammatory cytokines, such as IL-10 and IL-1RA, were indirectly increased (76).

In line with its anti-inflammatory role, miR-369 overexpression is able to suppress cardiomyocyte apoptosis and inflammation pathways triggered by hypoxia (77).

Furthermore, plasma of patients with HF, following AMI, exhibited higher miR-369 expression levels, compared to subjects affected by MI without HF (78).

These observations suggest that miR-369 upregulation in psoriasis and CVD seems to play a protective role against the deleterious effect inflammatory pathways elicited in these diseases.

**miR-378a/378a***

miRNA-378a, known also as miR-378 or miR-422b, originates from the first intron of the peroxisome proliferator-activated receptor gamma coactivator 1 beta (PPARGC1B) gene encoding PGC1B, a transcriptional regulator of oxidative energy metabolism. The complementary strand named miR-378a* is also miRNA active (79).

High levels of miR-378a were detected in the LS compared to NL. Further, biological treatment can restore its levels of expression to those in NS (36). Moreover, miR-378a was found to be upregulated in keratinocytes from LS of psoriasis compared to paired NL samples and also vs healthy keratinocytes (80).

miR-378a* was also found to be upregulated in LS keratinocytes compared to NL keratinocytes (80).

Interestingly, miR-378a* induces vascular endothelial growth factor expression (VEGF) competing for the same binding site with miR-125, which, in fact, is downregulated in psoriatic plaque (81).

A growing body of studies suggests that miR-378a/378a*, encoded within PGC1B, plays a mediatory role in lipid pathway metabolism (82).

miR-378a has been shown to play a protective role against hyperlipidemia. It has been shown that miR-378a/378a* adipose tissue-specific transgenic mice counteract genetic and high-fat diet (HFD)-induced obesity, through the expansion of brown fat (BAT) (83), which is known to reduce plasma triglyceride and cholesterol levels (84).

On the other hand, knockout mice for miR-378a/378a* are also resistant to HFD-induced obesity and show a mitochondrial fatty acid metabolism and oxidative capacity increase in insulin-target tissues (e.g. liver, muscles, and adipose tissues). This occurs since miR-378 and miR-378a* counterbalance the metabolic actions of PGC1B (85).

miR-378a also plays a major role in atherosclerosis. In VSMCs of human atherosclerotic plaques, a positive correlation between miR-378a expression, PGC1-α levels and the media were found and were decreased compared to healthy subjects (86).
miR-378a induction is regulated by transcription factors such as nuclear respiratory factor 1 (NFR1) via interaction with PGC1A. Thus PGC1A decrease determines miR-378a suppression. Interestingly, miR-378a overexpression plays an anti-atherogenic role in inhibiting free fatty acid-induced VSMC proliferation, migration and inflammation directly targeting insulin growth factor 1 (IGF1) and toll-like receptor 8 (TLR8), which are two genes aberrantly upregulated in atherosclerotic vessels (86).

On the other hand, miR-378a has been shown to directly target ABCG1, a transporter casquette implicated in macrophage reverse cholesterol efflux to generate HDL (87). In line with previous studies, miR-378a was found to be decreased in atherosclerotic plaques in low-density lipoprotein receptor-deficient mice (ApoE−/−) vs WT aortas (88).

miR-378a targets directly signal regulatory protein α (SIRPA), a negative modulator of macrophage phagocytosis and inflammation. Thus, miR-378a levels decrease in ApoE−/− mice atherosclerotic plaques, promotes inflammation, increases macrophage phagocytosis, and increases macrophage reverse cholesterol efflux.

According to a recent study, miR-378a has antihypertrophic activity in the heart, playing an important role in the regulation of myocardial remodeling (89).

Thus, miR-378a dysregulation in psoriasis could modulate cardiometabolic diseases associated with this disease.

**miR-9**

miR-9 was found to be downregulated in the LS compared to NL in psoriasis (36).

miR-9 plays a major role in the modulation of inflammatory pathways. In fact, it is not only induced by an NFKB1-dependent pathway in human monocytes (90), but it also targets NFKB1 (91), and thus a negative feedback loop exists between miR-9 and NFKB1.

Interestingly, in a peripheral artery disease rat model, it was found that deep vein thrombosis miR-9 decreased and NFKB1 increased, eliciting inflammation. Moreover, its overexpression alleviates inflammation and thrombosis in rats (92).

In metabolic syndrome, miR-9 was found to be upregulated in peripheral blood mononuclear cells (PBMCs) causing the decrease of its target ABCA1, diminishing cholesterol efflux and HDL production (93).

miR-9 was found to be decreased in PBMCs isolated from patients with the acute coronary syndrome (ACS) compared to healthy subjects and in aortic lysates of HFD-

ApoE−/− mice compared to normal diet-fed ApoE−/− mice. miR-9 overexpression in HFD ApoE−/− mice reduced inflammation and atherosclerotic plaques, acting as a negative regulator of SDC2-dependent FAK/ERK signaling pathway activated in these mice (94).

In keeping with this, it was found that miR-9 can decrease atherosclerosis in an ACS mouse model, via oxidized low-density lipoprotein (lectin-like) receptor 1 direct targeting that inhibits p38MAPK, thus promoting vascular remodeling (95).

miR-9 was also found to be downregulated in rat hypertrophic cardiomyocytes, and its overexpression counteracts hypertrophy in a mouse cardiac hypertrophy model since myocardin is a direct target of miR-9 (96).

In contrast, inhibition of miR-9 in mice prevented cardiac remodeling following MI through the upregulation of its target follistatin-like 1 (FSTL1) that is known to protect cardiomyocytes from different pathologic injuries including MI (97).

Interestingly, miR-9 also plays an angiogenic role. ECs exposed to high glucose (HG) showed a decrease in miR-9 and an increase in chemokine receptor-4 (CXCR4). miR-9 overexpression in HG-treated cells increases cell proliferation, tubule formation, decreases apoptosis and inflammation targeting CXCR4 (98).

Thus, miR-9 is deeply involved in inflammatory and metabolic regulation, and its downregulation is also associated with different CVD.

**miR-375**

miR-375 was found to be downregulated in the LS of psoriasis patients compared to NL. Further, the biological treatment restores its levels of expression (36).

IGF receptor 1, which is overexpressed in psoriatic epidermis, regulates the keratinocyte proliferation, apoptosis, and differentiation (99) and has been shown to be a direct target of miR-375 (100).

miR-375 also targets Janus kinase 2 (JAK2) (101), which plays a pivotal role in both inflammatory and anti-inflammatory signaling in keratinocytes.

Patients with HF have high levels of miR-375 (102). In addition, it has been shown that the inhibition of miR-375 decreases the inflammatory response after MI in a rodent model (103), and further, after MI, IL10 inhibits miR-375 improving murine EPC’s survival and function, promoting cardiac neovascularization and attenuating ischemic injury (104).

Thus, miR-375 decrease in psoriasis seems to play a protective role against inflammation and CVD.
miR-340

miR-340 is located in the intronic region of the ring finger protein 130 (RNF130) gene and is regulated by promoter hypermethylation (105).

miR-340 regulates the function and differentiation of immune cells and influences the progression of multiple autoimmune diseases, such as experimental immune encephalomyelitis (EAE), an animal model of brain inflammation and psoriasis (106).

Indeed, miR-340 inhibits the differentiation of Th2 cells through the downregulation of genes involved in the Th2 pathway, including IL4 (106).

Furthermore, miR-340 directly targets IL17A, a positive regulator of Th17 differentiation cells (107).

It was found that the expression of miR-340 was significantly decreased in mice treated with imiquimod (IMQ), the most widely accepted psoriasis animal model, with consequent upregulation of IL17A and development of psoriasis. Thus, miR-340 negatively regulates the IL17A expression and alleviates the severity of the disorder in the IMQ-induced psoriasis mouse model, giving an important role for Th17 cells in psoriasis development (108).

For these reasons, miR-340 has been suggested as a therapeutic target for the treatment of psoriasis and other IL17A-mediated autoimmune diseases (108).

Moreover, miR-340 has an important role in CVDs, such as eccentric hypertrophy, HF and cardiomyopathy. In particular, miR-340 upregulation is induced by cardiotoxin-1 (CT1) stimulation, a member of the IL6 family which initiates cardiac hypertrophy through the gp130/LIF receptor signaling pathway, which has a pivotal role in eccentric hypertrophy (109, 110).

miR-340 results in a downstream factor of gp130/LIF receptor pathway, and knockdown of miR-340 decreases the signal of CT1 and the hypertrophic response. At the same time, miR-340 is necessary for the induction and mediation of eccentric hypertrophy (111, 112).

Dystrophin is a structural protein present in the subsarcolemmal layer of cardiomyocytes and protects cells from stress during contraction and relaxation, and thus dystrophin deficiency results in the disruption of the sarcolemmal membrane and disorganization of the cytoskeleton (113).

It was found that dystrophin mRNA is a direct target of miR-340. miR-340 was found to be upregulated in failing heart caused by volume overload that in turns lead to alteration of cardiomyocytes sarcolemmal integrity and decompensation (111, 113).

Therefore, heart volume overload causes CT1 release which subsequently induces miR-340 upregulation that inhibits dystrophin, exacerbating eccentric hypertrophy and HF (111).

All the aforementioned studies show that alterations of miR-340 expression play a major role in inflammatory diseases and in cardiac pathogenesis.

miR-19a

miR-19a is a member of the miR-19 family together with miR-19b1 and miR-19b2, and they all share the same seed sequence. This family is located in the miR-17-92 polycistronic cluster that encodes miRNAs belonging to the miR-17, miR-18, miR-19 and miR-92 families.

Interestingly, IMQ-treated skin in mice differentially regulates the expression of the miR-17-92 cluster: miR-17 and miR-19 families are upregulated, while miR-92 is downregulated. However, overexpression or deletion of this cluster in keratinocytes or T cells does not have a relevant influence in IMQ-induced psoriasis, suggesting different functions and roles of miRNA families in T cells and keratinocytes (114).

Since miR-19a directly targets TNF (115), its expression levels were assayed in psoriasis to determine whether it could be a biomarker of this inflammatory disease.

It was found that miR-19a was upregulated in hair roots of psoriasis patients compared to healthy subjects. Moreover, miR-19a levels were negatively correlated with the duration of symptom onset in psoriasis patients (116).

Interestingly, miR-19a was found to be upregulated in sera of patients with coronary atherosclerosis vs healthy controls. miR-19a was shown to promote vascular inflammation and foam cell formation. In ApoE−/− mice fed with HFD, inhibition of miR-19a decreased atherosclerotic plaques and lipids load (117).

The miR-19 family has been shown to regulate cardiac hypertrophy. It was shown that the miR-19 family has a pro-hypertrophic role in rat neonatal cardiomyocytes since it directly targets the anti-hypertrophic proteins ATROGIN1 and MURF-1 (118).

On the contrary, another study showed that in a mouse model of cardiac hypertrophy, miR-19a/b expression was reduced in hypertrophic hearts. In keeping with this, miR-19a/b transgenic mice prevented cardiac hypertrophy and cardiac progression in response to angiotensin II via direct targeting of cardiac phosphodiesterase 5 (PDE5A) that regulates cardiac tone and vascular function (119).
miR-19a modulation is involved in psoriasis and in CVDs although discrepancies on its role are present in the literature.

**miR-424**

miR-424(322)/-503 are mammal-specific members of the extended miR-15/107 miRNA family, present on chromosome X.

miR-424 was found to be markedly decreased in psoriasis skin, although no significant difference in the sera of psoriasis patients vs healthy controls was found. miR-424 targets mitogen-activated protein kinase 1 (MEK1) and CYCLIN E1 that indeed were increased in psoriatic skin, leading to cell proliferation (120).

Hair shaft miR-424 levels, on the contrary, were significantly higher in psoriasis patients vs normal subjects. miR-424 levels do not correlate with other clinical psoriasis markers, disease duration or body surface area (120).

Interestingly, miR-424 was found to be decreased in the peripheral blood of atherosclerotic patients and in rat models of atherosclerosis (121).

miR-424 targets apolipoprotein C3 (APOC3) gene directly, whose decrease causes NFKB1 signaling pathway repression. Thus, miR-424 upregulation or APOC3 silencing suppressed inflammation, proliferation, migration and induced aortic smooth muscle cells apoptosis.

In keeping with this, miR-424 upregulation decreases atherosclerosis progression, blocking APOC3-mediated NFKB1 signaling pathway, whereas miR-424 downregulation accelerates atherosclerosis progression (121).

miR-424 upregulation was reported in cardiac IR injury in mice. In particular, IR in heart tissue and hypoxia/reoxygenation-injury in rat cardiomyocytes lead to miR-424 upregulation and repression of its direct target cysteine-rich secretory protein LCCL domain-containing 2 (CRISPLD2) (122). Decrease in CRISPLD2 expression triggers cardiac pyroptosis, associated with cytokine increase and activation of pro-inflammatory immune mediators, that finally leads to ischemic heart disease (122).

miR-424 is modulated in psoriasis and in CVDs, and its levels control proliferation and inflammatory pathways.

**miR-146**

The human miR-146 family is composed of two members, miR-146a and miR-146b, that share almost identical sequences and seed regions, located on different chromosomes.

miR-146a was found to be upregulated in psoriatic plaque epidermis vs healthy skin (123). It was observed that both miR-146a and miR-146b were upregulated in LS of psoriatic patients vs NL and vs HS (124). In that study, it was demonstrated that miR-146a targets and inhibits the proliferation marker fermitin family member 1 (FERMT1) that is also involved in the linkage of the actin cytoskeleton to the extracellular matrix, thus in the formation of a normal skin structure (125). Consequently, in human primary keratinocytes, overexpression of miR-146a inhibited cell proliferation.

miR-146a was found to be increased in PBMCs of psoriasis patients compared to healthy controls and correlated with PASI, suggesting that it could potentially act as a biomarker (126).

miR-146a has been found to be upregulated in valvular tissue from patients with atherosclerosis compared to controls (127), whereas in ApoE−/− mice, miR-146a was found to be decreased in both monocyte/macrophages and miR-146a delivery in ApoE−/−Ldlr(−/−) and Ldlr−/− mice decreased atherosclerosis reducing monocyte/macrophage activation in the absence of plasma lipid reduction (128).

This occurs since miR-146a acts as a negative regulator of NFKB1 signaling (128).

Interestingly, miR-146b also was found to be upregulated in the aortic plaques of ApoE−/− mice and in response to inflammatory cytokines. It was found that miR-146b repressed proliferation and migration of VSMCs by downregulating BCL2-associated athanogene 1 (BAG1) and matrix metalloproteinase (MMP)16, respectively (129).

Interestingly, in transgenic mice overexpressing TNF in the heart, miR-146a levels were increased in cardiac ventricular tissue and also in a human cardiomyocyte cell line exposed to TNF (130).

miR-146a targets Fos and thus the Fos-containing transcription factor complex the activator protein 1 (AP1), which transcribes MMP9. Therefore, miR-146a increase downregulates the AP1-MMP9 pathway, whose activation is correlated to HF and myocardial dysfunction. Therefore, miR-146a has been proposed as a therapeutic tool for treating CVD associated with enhanced inflammation in the heart (130).

In a recent study, miR-146a was found to be upregulated in human hearts in HF patients compared to nonfailing ones. A negative correlation was found with small ubiquitin-like modifier 1 (SUMO1) mRNA that was identified as a target of miR-146a. SUMO1 is a positive regulator of the sarcoplasmic reticulum Ca2+-ATPase pump (SERCA2A).
SERCA2A, in fact, undergoes SUMOylation that confers stability and increased activity to SERCA2A, restoring cardiac function in both mouse and swine HF models (131).

Thus, miR-146 is involved in psoriasis and CVD, where it plays anti-inflammatory roles in atherosclerosis but detrimental roles in HF.

miR-143/145

miR143/145 cluster is composed of two co-transcribed miRNAs.

It was shown that miR-143 upregulated in PBMCs of patients with psoriasis compared to healthy subjects, and significantly correlated with PASI (132). Interestingly, miR-143 decreased after treatment in psoriatic patients, suggesting that miR-143 could serve as an early biomarker for psoriasis severity and treatment response (132).

Indeed, miR-145 is also downregulated in psoriatic LS vs healthy skin and inhibits proliferation and chemokine secretion in keratinocytes (133).

miR-145 was significantly reduced in plasma of CAD patients who received state-of-the-art pharmacological treatment compared to healthy subjects (134).

In another study, circulating miR-145 was induced in unstable CAD compared with healthy controls. miR-145 was not modulated in stable CAD (135) and was also upregulated in patients with symptomatic vs asymptomatic carotid atherosclerosis (136).

miR-145a levels were found to be decreased in the aortas of ApoE−/− fed with western diets compared to controls and in human carotid atherosclerotic plaques compared to segments without plaques (137, 138).

Since miR-145 is highly expressed in VSMC, a VSMC-specific overexpression was used to determine its role in ApoE−/− mice fed with a western diet to induce atherosclerosis. miR-145a overexpression reduced plaque size, necrotic core and inflammation, whereas fibrous cap and collagen content increased, all features associated with plaque stability. It was found that miR-145a promotes VSMC differentiation toward the contractile phenotype via a mechanism that involves downregulation of its target Kruppel-like factor 4 and myocardin increase (137, 138).

In keeping with this, overexpression of miR-145 in the aorta of ApoE−/− mice reduced plaque size and decreased proliferation and apoptosis by direct targeting of osteoprotegerin (OPG) and KLF5 that are known to induce the NFκB1 signaling pathway, therefore reducing inflammation, as well (139).

Indeed, it was found that KLF2 induces the transcriptional upregulation of the miR-143/145 cluster.

Extracellular vesicles secreted by KLF2-transduced ECs or shear-stress-stimulated ECs are enriched in miR-143/145 and are able to control gene expression in co-cultured VSMCs. Interestingly, extracellular vesicles derived from KLF2-expressing ECs reduced atherosclerotic lesion formation in ApoE−/− mice (140).

Moreover, circulating miR-145 was found to be upregulated in MI patients, and miR-145 levels correlated with infarct sizes estimated by troponin T release (141).

miR-143 was shown to be the most abundant miRNA released in exosomes by rat cardiomyocytes cultured in ischemic conditions. The exosomes released were found to improve angiogenesis in matrigel plug assays. Finally, intramyocardial delivery of ischemic exosomes induced neovascularization following MI (142).

miR-143-145 modulation in psoriasis could be the basis of atherosclerosis and CVD in these patients.

Let-7 a/b

Let-7a and b belong to let-7 family of miRNA composed of nine isoforms (i.e. let-7a-1, 7a-2, 7a-3, 7b, 7c, 7d, 7e, 7f-1, 7f-2, 7g, 7i, and miR-98) encoded by 12 different genomic loci.

Interestingly, in the mice model of psoriasis, let-7b was also found to be downregulated in keratinocytes. In such a model, let-7b overexpression led to the decrease of its target IL6, promoting keratinocytes differentiation which resulted in improvement of psoriasis (143).

Plasma-derived extracellular vesicles were isolated and sequenced in PsA compared to cutaneous psoriasis only. It was found that let-7b extracellular levels were significantly decreased in PsA patients compared to psoriatic patients, suggesting that this miRNA could act as a promising biomarker for arthritis development (144).

Interestingly, let-7a also was found to be lower in T cells of psoriatic patients vs control and negatively correlated with signal transducer and activator of transcription 3 (STAT3) expression; further, let-7a overexpression decreased IFNG in T cells (145).

In human carotid plaque tissues, let-7b was downregulated in symptomatic compared to asymptomatic atherosclerotic patients. Diabetes is a condition that is considered to accelerate the atherosclerosis process, and let-7b decreased levels were also confirmed in diabetic plaque tissues compared to non-diabetic tissues (146). Interestingly, such decreased levels were also confirmed in the aortic tissue from diabetic ApoE−/− mice models compared to non-diabetic mice (146).
Interestingly, let-7a was decreased in Ang II-induced cardiac hypertrophy in vitro and in vivo, and its overexpression attenuated hypertrophy in mice (147).

let-7a downregulated the expression of its target Ccalmodulin (CALM) protein that together with Ca^{2+} induces the transcription of the hypertrophic genes (147).

let-7a was found to be downregulated in the myocardium of pigs after MI and also in the plasma of humans and pigs after MI (148). In this study, a let-7a overexpression was shown to be cardiac protective via inhibition of TGFBR3-p38 MAPK signaling pathways that regulate cardiomyocyte apoptosis (148).

The aforementioned papers showed that let-7a/b decrease seems to play a detrimental role in psoriasis and in eliciting CVD.

miRNA-based treatment of CVDGiven their importance in CVD, different miRNAs are currently used in preclinical studies and some of them could eventually be included in clinical trials.

This miRNA-based strategy holds good promise and has been demonstrated to be effective for hepatitis C therapy, where the feasibility of using miRNAs as a therapeutic tool is confirmed by the fact that a phase 2a clinical trial adopting anti-miR-122 has been completed successfully (149). This trial showed that the locked nucleic acid (LNA)-anti-miRNA is safe, not toxic and well-tolerated.

Different miRNAs modulations have been used in preclinical studies to counteract CVD insurgence by systemic delivery.

As mentioned earlier, miR-33 inhibition by anti-miRNA oligonucleotide that targets both miR-33a and miR-33b in non-human primates raises plasma HDL and lowers VLDL triglyceride levels and is a promising strategy for the treatment of dyslipidemias that increase CVD (33).

Moreover, systemic delivery of miR-9 mimics was shown to reduce isoproterenol-induced cardiac hypertrophy in mice and improve cardiac function (150); the systemic delivery of an LNA-oligonucleotide targeting the entire miR-15 family, which is upregulated in different forms of heart disease in both murine and porcine cardiac tissue, reduced infarct size and inhibited cardiac remodeling in the injured heart (151). Interestingly, the injected animals showed no evidence of LNA-associated toxicity or histopathologic abnormalities in the heart, liver, or kidneys.

miRNAs inhibition by antagonirs and sponges was successfully used in mice; in a cardiovascular setting, the in vivo inhibition of miR-133 by infusion of an antagonist or a sponge caused marked and sustained cardiac hypertrophy in mice, associated with a re-induction of fetal gene expression (40).

A drawback of the systemic delivery of miRNA therapy is that it targets predominantly the liver, although it has also been largely utilized to target the heart, and different strategies have been adopted to modulate miRNAs in a specific tissue or organ. Specific delivery is one of the most important problems due to the lack of clinical trials with miRNA-based technology (152).

To circumvent this problem, the delivery of miRNA mimics or anti-miRNA in a cardiac-specific or tissue-specific manner could be performed using serotype-specific adeno-associated virus 9 (AAV9) genetically modified to express a given miRNA mimic or antimir under a cardiac-specific or other tissue-specific promoters (153). AAV9 has been successfully used to deliver miRNAs to cardiac tissue, an additional advantage is that AAVs preferably infect nondividing cells, such as cardiomyocytes. Although many preclinical and phase I clinical studies have provided encouraging results regarding the safety of AAVs in humans, the clinical use of AAVs is still a challenge since they can induce the host immune response, and the AAV DNA can randomly integrate into the host genome. Although it occurs at a low rate, it was reported to occur.

Another possibility is minicircle; nonviral vectors that lack both the origin of replication and the antibiotic selection marker, carrying only short bacterial sequences, can be used to overexpress a miRNA. Their small size confers greater transfection efficiency, and the lack of bacterial backbone creates less immunogenicity and a longer time of expression.

Minicircles carrying an miR-210 expression cassette were injected intramyocardially in adult mice that underwent coronary ligation in order to demonstrate that miR-210 overexpression was able to improve cardiac function by upregulating angiogenesis and inhibited apoptosis (154).

Many strategies have been developed to ameliorate the uptake of nucleic acids into tissues and cells.

In order to facilitate the lipid bilayer crossing of the target cell membrane, the oligonucleotide needs to be packaged into liposomes or nanoparticles (155).

A class of liposomes, termed ‘lipidoid’, has been developed, showing high levels of specific silencing of endogenous gene transcripts (156). Preliminary studies with lipidoids tested in animal models (mice, rats and non-human primates) met the safety and specificity standards.

Finally, nanotechnology offers an attractive drug delivery system, with comparable efficacy and less toxicity compared to other vehicles (157).
Since in psoriasis, the predominant tissue involved is the skin, the topical delivery of miRNA mimics or anti-miRNA is easier to achieve, although topically applied miRNA-based therapeutics show difficulties in penetrating the stratum corneum barrier of the skin. To circumvent this problem, the following approaches have been used:

(i) Ultra-deformable liposomes (UDLs) are liposomes with augmented skin penetration capability: ethosomes and transerosomes (158); (ii) surfactant-ethanol cholesterol-osomes (SECosomes) comprising a cationic lipid, a helper lipid, cholesterol, a single-chain surfactant and ethanol that help to penetrate the skin barrier (159); (iii) finally, cell-penetrating peptides (CPPs) that bind nucleic acids and facilitate their entry through the skin could be used to deliver miRNA (160).

Nowadays, no trials on specific miRNAs are currently ongoing in psoriasis. This is probably due to the fact that miRNA modulation and regulation during psoriasis treatment have only been sparsely studied.

Further studies on miRNA involved in psoriasis and their possible involvement in CVD associated with this disease are needed in order to generate an individualized miRNA-based treatment of psoriasis.

Conclusions

Nowadays, miRNAs have been linked to many pathological conditions, and it is now clear that molecular circuits exist among miRNAs. Thus, the modulation of miRNAs caused by a disease in a specific tissue region or in a different tissue could either systemically or non-systemically induce a deleterious effect that could result in causing successive evident comorbidities associated with that disease.

In this review, we summarized those miRNAs that have been associated with psoriasis either in the skin and or in the blood flow that are known to play a role in CVD, and hence, could contribute to the establishment of secondary effects of psoriasis that shorten life expectancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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