Autoimmunity Reviews 24 (2025) 103739

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Current state of epigenetics in giant cell arteritis: Focus on microRNA dysregulation

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ARTICLE INFO

Keywords:
Giant cell arteritis
Epigenetics
microRNA
Inflammation
Vascular remodeling
Biomarker

ABSTRACT

Giant cell arteritis (GCA) is a primary systemic vasculitis affecting the elderly, characterized by a granulomatous vessel wall inflammation of large- and medium-sized arteries. The immunopathology of GCA is complex, involving both the innate and adaptive arms of the immune system, where a maladaptive inflammatory-driven vascular repair process ultimately results in vessel wall thickening, intramural vascular smooth muscle cell proliferation, neovascularization and vessel lumen occlusion, which can lead to serious ischemic complications such as visual loss and ischemic stroke. Over the past decade, microRNA (miRNA) dysregulation has been highlighted as an important contributing factor underlying the pathogenesis of GCA. Since current understanding of miRNA involvement in GCA remains largely based on extrapolation of previously determined miRNA functions in vitro or in loss- or gain-of-function studies, an overall insight into the role of miRNA alteration in GCA pathophysiology remains limited. In this narrative review, we summarize the current knowledge on aberrantly expressed miRNAs in GCA and thoroughly discuss the impact of their altered regulatory role in the context of GCA setting. Furthermore, we address challenges and future perspectives in utilization of miRNA-based diagnostic and prognostic biomarkers of GCA in clinical settings.

1. Introduction

Giant cell arteritis (GCA) is a primary systemic vasculitis, affecting individuals aged 50 years and older. It is a granulomatous arteritis mainly affecting large- and medium-sized arteries, with a predilection for the branches of the proximal aorta, including cranial and extracranial arteries [1,2]. Patients commonly display ischemic symptoms reflecting the vascular disease component of GCA (i.e. vascular wall inflammation), including a severe new-onset headache, scalp tenderness or necrosis, jaw claudication, visual disturbances or visual loss and ischemic stroke. Constitutional symptoms mainly reflect the extravascular disease component of GCA (i.e. systemic inflammation) and comprise fever, malaise, myalgia, anorexia and weight loss, along with elevated acute phase reactants, including erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP) levels [2–5]. GCA is recognized as a chronic disease and according to historical cohorts up to half of patients experience a relapsing disease course [6,7].

Current understanding of GCA pathogenesis is largely based on histopathological, immunopathological and molecular observational studies performed on temporal artery biopsies (TABs) obtained for diagnostic purposes, where implication of identified factors contributing to GCA pathogenesis and disease outcome has been mainly based on extrapolation of their previously determined functions, and their correlation with clinical or histological data [8]. Recent advances in elucidation of mechanisms underlying the pathogenesis of GCA revealed that epigenetics, including microRNA (miRNA) dysregulation, might crucially influence vascular inflammation and remodeling in arterial lesions of patients with GCA [9–12]. miRNAs are a class of small (~18–23 nt long) non-coding RNA (ncRNA) molecules involved in posttranscriptional regulation of gene expression through translational inhibition and/or degradation of their target messenger RNAs (mRNAs). Most miRNAs are transcribed from their coding genes as primary transcripts (pri-miRNAs) by RNA polymerase II and subsequently cleaved into precursor miRNAs (pre-miRNAs) in the nucleus by the microprocessor complex, comprising the nuclear RNase III Drosha and the RNA binding protein DiGeorge syndrome critical region 8 (DGCR8). Each generated pre-miRNA is then exported to the cytoplasm by exportin 5, and cleaved by the RNase III endonuclease Dicer to generate a mature

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https://doi.org/10.1016/j.autrev.2024.103739
Received 18 September 2024; Received in revised form 23 December 2024; Accepted 25 December 2024
Available online 26 December 2024

miRNA duplex. Only a single strand of the miRNA duplex, representing a functional mature miRNA, is then loaded onto an Argonaute (AGO) protein to form the RNA-induced silencing complex (RISC), where it serves as a guide strand that interacts with the 3′-untranslated region (UTR) of target mRNAs. The degree of complementarity between the miRNA "seed" sequence, located at the 5′ end of the guide mature miRNA strand and spanning from nt position 2–7, and the miRNA binding site on the 3′-UTR of target mRNAs determines the mechanism of miRNA-mediated gene regulation. As such, complete complementarity leads to direct mRNA degradation or cleavage, while moderate (partial) complementarity results in translational repression without affecting the amount of target mRNA [13–15]. Overall, miRNA regulatory networks show a high degree of complexity as a single miRNA can target several mRNAs, whereas a single mRNA transcript usually contains binding sites for multiple miRNAs. Moreover, multiple miRNAs may act either in a cooperative or antagonistic fashion, providing a positive or negative regulation of gene expression, and may function in positive or negative feedback loops. Since most protein-coding genes are likely under the influence of miRNA regulation, dysregulated miRNA expression is often associated with the development of various diseases, aberrant immune function and development of autoimmunity [13,15]. In this narrative review, we summarize recent findings on miRNA alteration and its involvement in GCA pathogenesis, and address challenges and future perspectives in miRNA utilization as diagnostic and prognostic biomarkers of GCA.

2. Immunopathology of GCA

The immunopathology of GCA is complex. The current immunopathological model describes GCA development as a cumulative process, involving initial loss of self-tolerance and development of autoimmunity, leading to the formation of a transmural granulomatous and self-renewing inflammation [3,6]. According to this concept, vasculitic lesions arise from stimulation and subsequent activation of resident vascular dendritic cells (vasDCs), which produce chemokines (including CCL18, CCL19, CCL20 and CCL21) and recruit circulating blood $CD4^+$ T cells and monocytes, the latter characterized by a spontaneous excessive production of matrix metalloproteinase-9 (MMP-9). The excessive monocyte MMP-9 production has been implicated in the digestion of the basement membrane of the *vasa vasorum*, enabling incoming inflammatory cells, predominantly $CD4^+$ T cells, to invade the vessel wall and enter the otherwise immune-privileged tissue niche [4,6,16–18]. Adhesion and transmigration of circulating $CD4^+$ T cells, characterized by an enhanced neurogenic locus notch homolog protein 1 (NOTCH1) expression, is facilitated through their interaction with Jagged1, a NOTCH1 ligand highly expressed on endothelial cells (ECs) of the *vasa vasorum* [4,6]. In addition, elevated expression of adhesion molecules, such as the intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), by adventitial microvessels further contributes to the influx of additional immune cells [3,16,19].

Recruited $CD4^+$ T cells that enter the protected tissue niche, interact with activated vasDCs, undergo metabolic reprogramming, take tissue residence, gain autonomy and polarize into multiple classes of effector cells, predominantly IFN-γ-producing Th1 and IL-17-producing Th17 cells [4,16,20]. Overall, lesional $CD4^+$ T cells are mainly polyfunctional and produce a broad spectrum of effector cytokines comprising IFN-γ (Th1), IL-17/IL-21 (Th17), IL-9 (Th9), IL-2 and IL-22, and thus coordinate immune cells and cellular constituents of the vessel wall in tissue destruction, inflammation-induced vascular remodeling and development of panarteritis [4,6]. High levels of IFN-γ, released mainly by Th1 cells, induce the production of several chemokines (CCL2, CXCL9, CXCL10 and CXCL11) by activated vascular smooth muscle cells (VSMCs) in the media, which recruit additional $CD4^+$ T cells, $CD8^+$ T cells and monocytes [16,17,20].

Once circulating monocytes settle in the developing lesion, they differentiate into macrophages (histiocytes) and form granulomas [4]. Under the strong pro-inflammatory stimuli, mediated predominantly by high levels of IFN-γ, macrophages form multinucleated giant cells (MGCs), which are present in about 50–75 % patients with transmural inflammation [6,21]. Macrophage populations in GCA are highly heterogeneous and their functions appear to relate directly to their spatial distribution in the vessel wall [4,16,22]. Macrophages resembling the pro-inflammatory (classically activated) M1 phenotype are prone to produce and release high levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-12 and IL-23), MMPs (MMP-2, MMP-7 and MMP-9) and reactive oxygen species (ROS), thus amplifying inflammation and tissue damage. In contrast, macrophages resembling the anti-inflammatory (alternatively activated) M2 phenotype produce growth and angiogenic factors (platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), respectively) and contribute to impaired tissue remodeling and neoangiogenesis. Aberrant overproduction of MMP-9 in medial macrophages and MGCs contributes to the atrophy of the media and digestion of the internal elastic lamina (IEL), a physical barrier separating the VSMC-rich media from the intima, fragmentation of which precedes the formation of intimal hyperplasia [4,16]. Under the influence of persistent intramural inflammation, VSMCs change their differentiated contractile phenotype into an undifferentiated, highly proliferative and migratory synthetic phenotype, characterized by excessive extracellular matrix production, and production of pro-inflammatory cytokines and chemokines, growth factors and MMPs, leading to VSMC hyperplasia and vascular occlusion [3,16,17,23]. In parallel, priming, activation and proliferation of ECs, mediated by macrophage- and MGC-derived VEGF, results in neoangiogenesis with further recruitment of infiltrating immune cells [3,4,16]. GCA lesions may eventually reach autonomy through acquired tissue-residency of a specialized pathogenic subset of memory T cell populations that maintain continuous repopulation of inflammatory $CD4^+$ T cells in inflamed vessel wall and drive regional autoimmunity [4]. In addition, several accompanying defects in peripheral immune tolerance in patients with GCA support the transition of granulomatous arteritis into a self-sustained, tissue-destructive lesion, including hyperactivity of the VEGF-NOTCH1-Jagged1 pathway, defect in the PD-1 (programmed cell death protein 1)/PD-L1 (programmed cell death ligand 1) immunoinhibitory pathway, enhanced CD28–CD80/CD86-mediated co-stimulatory pathway, a defect in $CD8^+$ Treg function, and an impaired functionality and decreased number of peripheral blood $CD4^+$ Tregs [4,6,16,24–27].

This sequence of events ultimately leads to the development and sustaining of self-renewing inflammatory lesions, vascular stenosis, luminal occlusion and tissue ischemia, which represent main causatives of clinical manifestations in patients with GCA.

3. miRNA implication in arterial immunopathology and vessel wall remodeling in GCA

Involvement of miRNA dysregulation in immunopathology and arterial wall remodeling in GCA has become evident mainly in the last decade. According to several studies, a total of 21 aberrantly expressed miRNA families, miRNA clusters and/or individual miRNAs have been identified and their expression profiles validated in either tissues or cells from patients diagnosed with GCA, including treatment-naïve patients [10–12,28]. Notably, these miRNAs comprise miR-21, miR-23b, the miR-30 family, miR-124, miR-125a, the miR-132/212 cluster, miR-142, the miR-143/145 cluster, miR-146a, miR-146b, miR-150, miR-155, miR-195, miR-210, miR-299, miR-326, miR-342, miR-365a, the miR-424/503 cluster and miR-511. As revealed, miRNA deregulation in GCA occurs mostly at tissue level [10], and altered expression profiles of different miRNAs in GCA arterial lesions have been associated with distinct cellular composition of the inflammatory infiltrate [12], extent of intimal hyperplasia [11,29] and several clinical features of GCA, including headache, jaw claudication and visual disturbances [12,28]. According to their previously determined functions, the majority of

identified aberrantly expressed miRNAs in GCA arterial lesions, primarily involving temporal arteries, display pleiotropic, multi-functional properties and appear to be crucially involved in diverse aspects of the disease. Overall, these comprise immune cell dysfunction, development of intimal hyperplasia through modulation of the VSMC phenotype, EC dysfunction, modulation of GCA-related signaling pathways, and altered production of cytokines, chemokines, MMPs and growth factors (summarized in detail in Table 1 and Fig. 1). Nevertheless, whether miRNA dysregulation actively participates in these events in GCA, still needs to be determined.

Below, we discuss how the aberrantly expressed miRNAs are likely to exert their altered regulatory role in the context of GCA setting, based on their previously determined functions in processes closely resembling GCA-related arterial pathophysiology.

3.1. Interrelation between aberrantly expressed miRNAs and signaling pathways involved in GCA pathogenesis

In GCA, multiple signal transduction pathways shape the inflammatory microenvironment in vascular lesions and mediate disease-relevant processes, predominantly through fine-tuning of vasculitis-inducing effector T cell functions [4,30]. Several aberrantly expressed miRNAs in inflamed temporal arteries of patients with GCA have been shown to either modulate, interact or be under the transcriptional regulation of these signaling pathways, including Toll-like receptor (TLR) signaling, downstream events of T-cell receptor (TCR) activation, NF-κB signaling, JAK/STAT pathway, eNOS/NO/sGC/cGMP pathway, MAPK/ERK pathway, CD28-PI3K-AKT-mTORC1-HIF-1α axis, Ca^{2+}/CaM/CaN/NFAT signaling pathway and the NOTCH pathway (Fig. 2).

3.1.1. TLR signaling

It has been demonstrated that peripheral blood mononuclear cells (PBMCs) from patients with GCA exhibit altered expression and function of several members of the TLR family [31], and the tropism of GCA for various arterial locations, primarily cranial arteries, might relate to distinct profiles of TLR expression in adventitial vasDCs, which vary across arterial territories [16,17,32]. Although different TLR ligands may induce distinct patterns of vascular inflammation, DCs from patients with GCA have been shown to express increased levels of TLR2 and TLR4 and their activation via TLR4 ligands triggered the recruitment of T cells into the arterial wall [16,33]. Upon TLR activation, induction of miR-21, miR-146a and miR-155 has been determined in various inflammatory settings, where these three miRNAs have been proven as key TLR modulators mainly functioning in feedback loops [10,34]. Noteworthy, miR-155 is a major pro-inflammatory miRNA upregulated by several TLR ligands, whose overexpression promotes pro-inflammatory macrophage responses, differentiation of effector $CD4^+$ Th1 and Th17 cell subsets, and production of cytokines that promote T cell-mediated autoimmune inflammation, predominantly IFN-γ and IL-17 [35–37]. In addition, miR-511 has been shown to modulate TLR4 expression in monocytes and DCs, depending on cell cycle dynamics [34], whereas miR-124, miR-125a-5p and miR-195 negatively regulate pro-inflammatory M1 macrophage functions through modulation of TLR6, TLR2/4 and TLR2 signaling, respectively [38–40], which may at least partly correspond to their determined under-expression in inflamed TABs from patients with GCA (Table 1).

3.1.2. The NF-κB, JAK/STAT, eNOS/NO/sGC/cGMP and MAPK/ERK signaling pathways

Presentation of vasculitogenic antigens by vasDCs to infiltrating T cells via the TCR complex and co-stimulatory receptors, triggers the downstream activation of NF-κB, crucial for inducing pro-inflammatory responses in T cells, their proliferation, differentiation and lineage commitment [30,41]. Dependence on NF-κB-mediated induction has been determined for several overexpressed miRNAs in GCA, including mainly miR-146a, miR-146b, miR-155 and miR-21 [42,43]. Upon TCR engagement, NF-κB-driven upregulation of miR-146a has been shown to modulate activation-induced cell death (AICD) in differentiated T lymphocytes, where it serves as an anti-apoptotic factor towards T cells, and might play a role in the timing of different T cell activation phases, mainly through impairing IL-2 production [44]. In contrast, upregulation of miR-146a and miR-146b has been shown to negatively regulate TCR-induced NF-κB signaling pathway in activated T cells and NF-κB signaling in macrophages, respectively, through a negative feedback loop, indicating to miR-146a/-146b inhibitory function towards NF-κB activation and participation in resolution of inflammation, mediated at least partly through repression of TRAF6 and IRAK1 [45–47]. Nevertheless, activation of the NF-κB pathway was not inhibited by miR-146a/-146b-mediated reduction of IRAK1 in an in vitro cell model of GCA, which suggests that the negative feedback loop is not functional in GCA [48].

The strength of TCR stimulation also affects miRNA upregulation. In human $CD8^+$ T cells, induction of miR-155 by NF-κB-dependent factors was proportional to the strength of TCR signaling, where miR-155-mediated targeting of SOCS1 resulted in accumulation of effector $CD8^+$ T cells and their enhanced cytokine responsiveness [49]. In addition, by downregulating SOCS1, overexpressed miR-155 directs $CD4^+$ T cell polarization towards the Th17 phenotype through activation of the JAK/STAT signaling pathway [50]. Overexpression of miR-155 also suppressed BCL6 expression in macrophages, which in turn activated NF-κB signaling and thus promoted pro-inflammatory macrophage activity and enhanced vascular inflammation [51]. Interrelationship between NF-κB signaling and miRNA induction has been also confirmed in VSMCs, where conjoined activation of the NF-κB pathway and overexpression of miR-146a or miR-155 affected VSMC viability and associated with characteristics of the synthetic VSMC phenotype [52–54]. As revealed in atherosclerotic lesions, NF-κB-induced upregulation of miR-155 in VSMCs inhibited endothelial nitric oxide synthase (eNOS) and soluble guanylyl cyclase β1 (sGCβ1) expression, and thus indirectly affected NO-dependent cGMP production, which results in VSMC phenotypic switching into the synthetic state, impaired vascular relaxation and induction of intimal hyperplasia [53,55]. Since the sGC/cGMP axis is essential for maintaining the contractile VSMC phenotype and NO-mediated vasorelaxation, the determined overexpression of miR-155 in inflamed TABs from patients with GCA suggests that impaired eNOS/NO/sGC/cGMP pathway might be involved in GCA pathogenesis. In addition, it has been revealed that overexpression of miR-155 in VSMCs from abdominal aortic aneurism lesions decreases VSMC viability and promotes VSMC apoptosis by suppressing FOS and ZIC3 [52]. This miR-155 function might be in line with VSMC apoptosis in the medial layer of inflamed arteries of patients with GCA, which associates with the atrophy of the media, destruction of elastic fibers, collapse of the inner elastic membrane and calcifications [56,57]. Therefore, overexpression of miR-155 in regulating VSMC function in GCA lesions might associate with both, proliferation of the synthetic VSMCs resulting in intimal hyperplasia, and apoptosis of medial VSMCs resulting in medial atrophy, with miR-155 function depending on the “geographic” location within the arterial lesion.

Overexpression of miR-21 in effector $CD4^+$ and $CD8^+$ T cells increases the production of pro-inflammatory cytokines, including IFN-γ and TNF-α, where both, the NF-κB and MAPK/ERK signaling pathways may upregulate miR-21 directly [58]. Furthermore, transcription factors NF-κB and Sp1, and the MAPK/ERK pathway cooperatively regulate miR-365, which serves as a negative regulator of IL-6 production [59]. In addition to the NF-κB signaling pathway, miR-146a induction in differentiated T cell subsets upon TCR stimulation was suggested to be under the regulatory influence of the activated MAPK/ERK and CaN/NFAT pathways [44], whereas miR-124-3p negatively regulates p38MAPK signaling pathway in macrophages and thus inhibits macrophage proliferation and invasion [60]. In line with determined altered expression profiles of miR-21/-124-3p/-146a/-365 in inflamed TABs from patients with GCA (Table 1), implication of the MAPK/ERK

Table 1
Aberrantly expressed miRNAs in GCA.

miRNA	Mature miRNA[a]	Study[b]	Expression[d]	Tissue/ cells	Function[f]	Reference[g]
miR-21	miR-21-3p	[11][c]	Up	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Regulation of T cell differentiation and cytokine production. • Overexpression determined in vascular neointimal lesions (promotion of neointimal lesion formation). • Overexpression promotes VSMC proliferation and migration. • Overexpression determined in effector $CD4^+$ T, $CD8^+$ T and Th17 cells. • Overexpression promotes IFN-γ, TNF-α and IL-17 production. • Age-related miR-21 overexpression promotes effector T cell differentiation in older individuals.	[58,75,113,152–154]
	miR-21-5p	[11][c], [28][c], [10]	Up	TAB		
	miR-21-5p	[10]	Up	PMNCs		
miR-23b	miR-23b-3p	[11][c]	Down	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Upregulation associates with reduction of MMP-9 production. • Downregulation promotes the synthetic VSMC phenotype and intimal hyperplasia.	[95]
miR-30 family	miR-30a-5p	[12][c]	Down	TAB	• Regulation of VSMC phenotype, intimal hyperplasia and autophagy. • Regulation of Ca^{2+}/CaN signaling pathway. • Regulation of MΦ polarization. • Overexpression inhibits VSMC proliferation and neointima formation. • Overexpression of miR-30a-5p inhibits autophagy-driven attaining of the synthetic VSMC phenotype. • Under-expression determined in synthetic VSMCs. • Downregulation induces activation of Ca^{2+}/CaN signaling. • Downregulation promotes M1 MΦ polarization.	[69,77,85,155]
	miR-30b-5p	[12][c]	Down	TAB		
	miR-30c-5p	[12][c]	Down	TAB		
	miR-30d-5p	[12][c]	Down	TAB		
	miR-30e-5p	[12][c]	Down	TAB		
miR-124	miR-124-3p	[12][c]	Down	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Regulation of the NFAT signaling pathway. • Regulation of MΦ activity, cytokine production, apoptosis and proliferation. • Overexpression inhibits NFAT signaling, VSMC proliferation and migration. • Overexpression inhibits pro-inflammatory cytokine production (IL-6, TNF-α), TLR signaling and MΦ proliferation, and promotes MΦ apoptosis. • Downregulation promotes the synthetic VSMC phenotype and intimal hyperplasia. • Downregulation determined in aortic lesions.	[38,60,70,86,156,157]
miR-125a	miR-125a-5p	[11][c]	Down	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Regulation of MΦ polarization. • Regulation of ET-1 production and angiogenesis. • Overexpression inhibits the NLRP3 inflammasome in VSMCs, thus attenuating inflammation. • Downregulation promotes the synthetic VSMC phenotype and intimal hyperplasia. • Downregulation promotes ET-1 production, EC dysfunction and angiogenesis. • Downregulation promotes M1 MΦ polarization and MΦ-mediated vascular dysfunction.	[39,87,88,104,158–160]
miR-132/212 cluster	miR-132-3p	[12][c]	Up	TAB	• Regulation of Th17 cell differentiation. • Regulation of EC function. • Regulation of VSMC function. • Upregulation promotes Th17 cell development and IL-17 production. • Upregulation promotes EC dysfunction and inhibits angiogenesis. • Upregulation promotes synthetic VSMC features and activity.	[102,111,161]
	miR-212-3p	[12][c]	Up	TAB		
miR-142	miR-142-3p	[12][c]	Up	TAB	• Regulation of VSMC proliferation and migration. • Regulation of MΦ polarization. • Regulation of Treg cell function. • Overexpression promotes VSMC proliferation and migration. • Upregulation promotes polarization of M2 MΦ and their pro-fibrogenic activity. • Overexpression promotes functional impairment of Tregs, by suppressing cAMP production.	[91,92,106,162]
	miR-142-5p	[12][c]	Up	TAB		

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Table 1 (*continued*)

miRNA	Mature miRNA[a]	Study[b]	Expression[d]	Tissue/ cells	Function[f]	Reference[g]
miR-143/145 cluster	miR-143-3p miR-143-5p miR-145-3p miR-145-5p	[11][c] [11][c] [11][c] [11][c], [28][c]	Down Down Down Down	TAB TAB TAB TAB	• Regulation of VSMC differentiation, phenotype and intimal hyperplasia. • Regulation of EC function. • Regulation of T cell differentiation, proliferation and activity. • Under-expression promotes the synthetic VSMC phenotype and intimal hyperplasia. • Under-expression determined in arterial lesions, whereas overexpression reduces neointimal lesion formation. • Downregulation promotes podosome formation, VSMC migration and invasiveness. • Upregulation and tunneling nanotube-mediated transfer of VSMC-derived miR-143/-145 reduces proliferation, migration and angiogenic properties of ECs. • Under-expression determined in effector $CD4^+$ T cells, whereas overexpression inhibits effector $CD4^+$ T cell proliferation, Th9 cell differentiation, IL-9 production, Th17 cell levels and pathogenic Th17 cell responses.	[71,72,82–84,90,99,100,110]
miR-146a	miR-146a-5p	[11][c], [28][c], [10]	Up	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Regulation of MΦ polarization. • Regulation of T cell activation and function. • Overexpression promotes VSMC proliferation, migration and intimal hyperplasia. • Overexpression promotes M2 MΦ polarization and activity, and suppresses M1 MΦ activation. • Overexpression promotes autoimmune Th1 cell responses. • Upregulation mediated by TCR stimulation regulates TCR-induced $CD4^+$ and $CD8^+$ T cell activation in a negative feedback loop. • Upregulation, determined in differentiated $CD4^+$ and $CD8^+$ T cells upon TCR stimulation, impairs IL-2 production and protects T cells from AICD.	[44,45,54,75,76,163,164]
miR-146b	miR-146b-5p	[11][c], [28][c], [10]	Up	TAB	• Regulation of VSMC proliferation and migration. • Regulation of MΦ polarization. • Regulation of EC function. • Overexpression promotes VSMC proliferation and migration. • Upregulation promotes M2 MΦ polarization and activity, and suppresses M1 MΦ differentiation and activation. • Overexpression and enrichment determined in $CD4^+$ T cells and $CD4^+$ T cell-derived EVs, respectively. • $CD4^+$ T cell-derived EVs carrying miR-146b-5p affect endothelial function.	[93,107,108,123]
miR-150	miR-150-5p	[10]	Up	TAB	• Regulation of EC migration. • Regulation of MΦ polarization and function. • Regulation of T cell differentiation and function. • Overexpression determined in vascular neointimal lesions. • Upregulation and enrichment determined in stimulated monocytes, stimulated VSMCs, monocyte- and synthetic VSMC-derived EVs. • Secreted monocyte- and VSMC-derived EVs carrying miR-150 promote recipient EC migration and angiogenesis. • Age-related overexpression of miR-150 promotes pathogenic MΦ-mediated inflammation and pathological angiogenesis in older individuals. • Upregulation promotes M2 MΦ polarization and activity, and miR-150 deficiency enhances the M1:M2 MΦ ratio. • Deletion of miR-150 decreases MΦ-driven inflammatory responses, MΦ infiltration and reduces the expression of pro-inflammatory mediators (TNF-α, IL-1β, IL-6, iNOS). • Deletion of miR-150 decreases the number of $CD3^+$, $CD4^+$ and $CD8^+$ T cells, and reduces pro-inflammatory cytokine expression (IL-1β, IL-6, IL-17, TNF-α). • Deletion of miR-150 diminishes $CD8^+$ T cell differentiation, proliferation and effector functions.	[80,94,114,116–119,165]
miR-155	miR-155-5p miR-155-5p	[12][c], [28][c], [10] [10]	Up Down	TAB PBMCs	• Regulation of T cell differentiation and function. • Regulation of MΦ function. • Regulation of VSMC phenotype, proliferation, migration, viability and apoptosis. • Overexpression promotes Th1, Th17 and Treg cell differentiation, Th17 function, and IL-17 and IFN-γ production in effector $CD4^+$ T cells. • Deletion of miR-155 decreases Th1 and Th17 cell responses, diminishes Th17 cell differentiation, and reduces IFN-γ and IL-17 production.	[36,37,49–53,55,166]

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Table 1 (*continued*)

miRNA	Mature miRNA[a]	Study[b]	Expression[d]	Tissue/ cells	Function[f]	Reference[g]
					• Deletion of miR-155 reduces the expression of Th1- and Th17-polarizing cytokines in DCs. • Upregulation upon TCR stimulation promotes $CD8^+$ T cell effector functions. • Upregulation promotes M1 MΦ phenotype and activity, and MΦ-mediated vascular inflammation. • Upregulation promotes the synthetic VSMC phenotype, VSMC proliferation and migration, and inhibits eNOS production. • Overexpression decreases VSMC viability and induces VSMC apoptosis, in line with medial atrophy in GCA.	
miR-195	miR-195-5p	[11][c]	Down	TAB	• Regulation of VSMC phenotype and intimal hyperplasia. • Regulation of MΦ polarization. • Overexpression inhibits the synthetic VSMC phenotype and pro-inflammatory cytokine production in VSMCs (IL-1β, IL-6, IL-8), and reduces neointimal lesion formation. • Overexpression promotes M2 MΦ phenotype and inhibits pro-inflammatory cytokine production in stimulated M1 MΦ (IL-1β, IL-6, TNF-α). • Under-expression determined in neointimal lesions.	[40,167]
miR-210	miR-210-3p	[12][c]	Up	TAB	• Regulation of T cell differentiation. • Regulation of MΦ polarization. • Regulation of VSMC apoptosis. • Upregulation promotes Th1 and Th17 cell differentiation. • Upregulation in activated monocytes/MΦ promotes M1 MΦ polarization and activity through metabolic reprograming. • Overexpression inhibits VSMC apoptosis.	[62–64,142]
miR-299	miR-299-5p	[10]	Up	TAB	• Regulation of autophagy and apoptosis. • Overexpression inhibits autophagy.	[131]
miR-326	miR-326	[12][c]	Up	TAB	• Regulation of Th17 cell differentiation. • Overexpression promotes Th17 cell differentiation and positively correlates with IL-17 production.	[168]
miR-342	miR-342-5p	[12][c]	Up	TAB	• Regulation of MΦ function. • Regulation of VSMC phenotype. • Overexpression promotes M1 MΦ activity, upregulates miR-155 and induces pro-inflammatory mediator production (NO, IL-6, TNF-α). • Overexpression promotes synthetic VSMC features.	[65,66]
miR-365a	miR-365a-3p	[11][c]	Down	TAB	• Regulation of VSMC proliferation, migration and intimal hyperplasia. • Regulation of IL-17-mediated inflammation and IL-6 production. • Overexpression inhibits VSMC proliferation, migration and neointimal lesion formation. • Overexpression inhibits IL-6 production. • Under-expression determined in neointimal lesions. • Downregulation potentiates IL-17-induced inflammatory response.	[59,89,105,169]
miR-424/503 cluster	miR-424-3p	[28][c]	Up	TAB	• Regulation of VSMC proliferation, migration and intimal hyperplasia.	[170–172]
	miR-424-5p	[11][c], [28][c, e]	Up	TAB	• Regulation of monocyte differentiation. • Regulation of DC phenotype. • Overexpression determined in synthetic VSMCs and neointimal lesions. • Overexpression inhibits synthetic VSMC proliferation, migration and neointimal lesion formation as an adaptive response to vascular injury. • Upregulation promotes monocyte/MΦ differentiation. • Overexpression promotes pro-inflammatory monocyte-derived DC differentiation.	
	miR-503-5p	[28][c, e]	Up	TAB	• Regulation of EC and VSMC function. • Regulation of DC phenotype. • Overexpression and enrichment determined in activated MΦ and MΦ-derived EVs, respectively.	[122,172]

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Table 1 (*continued*)

miRNA	Mature miRNA[a]	Study[b]	Expression[d]	Tissue/ cells	Function[f]	Reference[g]
					• MΦ-derived EVs carrying miR-503-5p inhibit proliferation, migration and angiogenic properties of ECs, and promote VSMC proliferation and migration. • Overexpression determined in pro-inflammatory monocyte-derived DC.	
miR-511	miR-511-5p	[12][c]	Up	TAB	• Regulation of M2 MΦ function. • Overexpression promotes M2 MΦ activity.	[173,174]

GCA, giant cell arteritis; TAB, temporal artery biopsy; PMNC, polymorphonuclear cell; PBMC, peripheral blood mononuclear cell; VSMC, vascular smooth muscle cell; CD, cluster of differentiation; Th, T helper cell; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; MMP, matrix metalloproteinase; CaN, calcineurin; MΦ, macrophage; NFAT, nuclear factor of activated T cells; TLR, Toll-like receptor; ET, endothelin; NLRP3, NLR family pyrin domain containing 3; EC, endothelial cell; Treg, regulatory T cell; cAMP, cyclic adenosine monophosphate; TCR, T-cell receptor; AICD, activation-induced cell death; EV, extracellular vesicle; iNOS, inducible nitric oxide synthase; DC, dendritic cell; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

[a] Name of mature miRNA strand.
[b] Study reporting alteration of miRNA expression in GCA.
[c] Treatment-naïve status of patients with GCA and/or TABs enrolled in the study.
[d] Confirmed altered expression in affected tissue and/or cells from histologically positive patients with GCA, compared to non-GCA controls.
[e] Altered expression only in histologically positive GCA TABs, when compared to histologically negative GCA TABs.
[f] miRNA function and/or miRNA alteration in the context of GCA-related pathophysiology and pathogenesis.
[g] Reference on miRNA function.

pathway in the processes of T cell activation and macrophage function in GCA might be mediated by miRNA dysregulation.

3.1.3. *The CD28-PI3K-AKT-mTORC1-HIF-1α axis*

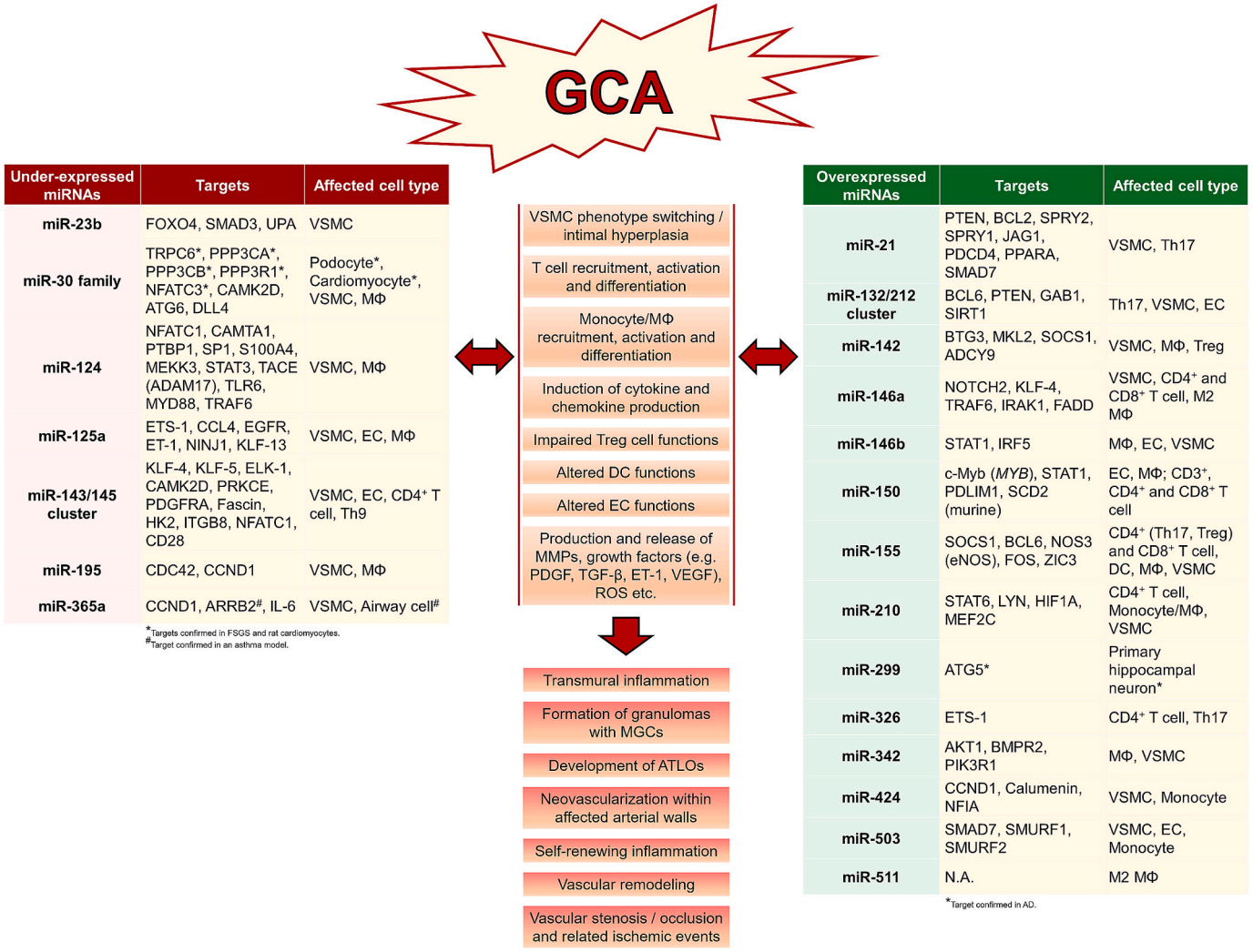
Along with signals delivered by the TCR complex, activation of T cells in GCA lesions is highly dependent on CD28-dependent co-stimulation, where activation of the CD28-PI3K-AKT-mTORC1-HIF-1α axis initiates a metabolic program required for T cell growth, proliferation and differentiation into effector T cells, through maximizing glycolytic flux [6,30]. Sustained activation of mechanistic target of rapamycin complex 1 (mTORC1) is a signature abnormality of circulating and lesional $CD4^+$ T cells from patients with GCA, where mTORC1 promotes glycolysis through upregulation of hypoxia inducible factor 1α (HIF-1α) [4,30]. HIF-1α also positively regulates genes involved in proliferation of both ECs and VSMCs, promoting VSMC recruitment, neoangiogenesis and reduction of vascular integrity [61]. Induction of miR-210 in activated T cells is strongly dependent on TCR-CD28 co-stimulation and miR-210 expression is directly positively regulated by HIF-1α, where miR-210 may target HIF-1α in a negative-feedback loop [62]. miR-210 is abundantly expressed in activated $CD4^+$ T cells, where it induces polarization into the Th1 and Th17 cell lineages in a HIF-1α-dependent manner [62,63], whereas overexpression of miR-210 also inhibits apoptosis of VSMCs in hypoxic conditions [64]. Implication in AKT-dependent signaling has been also determined for miR-342-5p, whose overexpression in VSMCs activated the AKT signaling pathway via downregulation of PIK3R1, which promoted VSMC proliferation, migration and invasion [65], whereas upregulated miR-342-5p directly targeted AKT1 in macrophages and promoted the pro-inflammatory activation of lesional macrophages [66]. Determined overexpression of miR-210 and miR-342-5p in inflamed TABs from patients with GCA (Table 1) therefore suggests to their possible involvement in promotion of pathogenic T cell, macrophage and VSMC functions in GCA through interacting with the CD28-PI3K-AKT-mTORC1-HIF-1α pathway.

3.1.4. *The Ca^{2+}/CaM/CaN/NFAT signaling pathway*

Calcium-mediated CaM/CaN/NFAT signaling pathway is another signal transduction pathway whose activation is crucial for differentiation and pathogenic activity of effector T cells [67,68]. In GCA, DNA methylation profiling revealed hypomethylation of several genes involved in the pathogenic effector T cell responses, including genes encoding for the components of the TCR, for co-stimulatory molecules (i.e. CD28) and for proteins implicated in the CaN/NFAT pathway, specifically PPP3CC, NFATC1 and NFATC2, suggesting to their increased activity in GCA lesions [9]. Moreover, our previous work demonstrated a possible pathogenic role of aberrantly expressed miR-30 family and miR-124 (predicted to target PPP3R1 and NFATC1, respectively) in aberrant T cell-mediated immune responses in GCA, whose under-expression negatively correlated with elevated numbers of $CD3^+$, $CD4^+$, $CD8^+$ and $NFATC1^+$ cells in inflamed TABs from patients with GCA [12]. In line with our study, members of the miR-30 family have been also shown to negatively regulate critical components of the Ca^{2+}/CaN signaling cascade in podocytes [69], whereas miR-124 has been shown to repress NFAT activity in VSMCs by directly targeting NFATC1, thus inhibiting VSMC proliferation and maintaining the differentiated contractile phenotype [70]. In addition, direct targeting of NFATC1 and CD28 by the miR-143/145 cluster in effector $CD4^+$ T cells resulted in inhibition of Th9 and Th17 cell differentiation and proliferation, and decreased production of IL-9 and IL-17 [71,72]. Overall, altered epigenetic regulation of the Ca^{2+}/CaM/CaN/NFAT signaling pathway appears to contribute crucially to GCA pathogenesis, where under-expression of the miR-30 family, miR-143/145 cluster and miR-124 (Table 1) might play a notable role.

3.1.5. *The NOTCH signaling pathway*

Initial loss of self-tolerance and development of autoimmunity in patients with GCA has been closely linked to dysfunction of the NOTCH



Under-expressed miRNAs	Targets	Affected cell type
miR-23b	FOXO4, SMAD3, UPA	VSMC
miR-30 family	TRPC6*, PPP3CA*, PPP3CB*, PPP3R1*, NFATC3*, CAMK2D, ATG6, DLL4	Podocyte*, Cardiomyocyte*, VSMC, MΦ
miR-124	NFATC1, CAMTA1, PTBP1, SP1, S100A4, MEKK3, STAT3, TACE (ADAM17), TLR6, MYD88, TRAF6	VSMC, MΦ
miR-125a	ETS-1, CCL4, EGFR, ET-1, NINJ1, KLF-13	VSMC, EC, MΦ
miR-143/145 cluster	KLF-4, KLF-5, ELK-1, CAMK2D, PRKCE, PDGFRA, Fascin, HK2, ITGB8, NFATC1, CD28	VSMC, EC, $CD4^+$ T cell, Th9
miR-195	CDC42, CCND1	VSMC, MΦ
miR-365a	CCND1, ARRB2#, IL-6	VSMC, Airway cell#

*Targets confirmed in FSGS and rat cardiomyocytes.
#Target confirmed in an asthma model.

Overexpressed miRNAs	Targets	Affected cell type
miR-21	PTEN, BCL2, SPRY2, SPRY1, JAG1, PDCD4, PPARA, SMAD7	VSMC, Th17
miR-132/212 cluster	BCL6, PTEN, GAB1, SIRT1	Th17, VSMC, EC
miR-142	BTG3, MKL2, SOCS1, ADCY9	VSMC, MΦ, Treg
miR-146a	NOTCH2, KLF-4, TRAF6, IRAK1, FADD	VSMC, $CD4^+$ and $CD8^+$ T cell, M2 MΦ
miR-146b	STAT1, IRF5	MΦ, EC, VSMC
miR-150	c-Myb (*MYB*), STAT1, PDLIM1, SCD2 (murine)	EC, MΦ; $CD3^+$, $CD4^+$ and $CD8^+$ T cell
miR-155	SOCS1, BCL6, NOS3 (eNOS), FOS, ZIC3	$CD4^+$ (Th17, Treg) and $CD8^+$ T cell, DC, MΦ, VSMC
miR-210	STAT6, LYN, HIF1A, MEF2C	$CD4^+$ T cell, Monocyte/MΦ, VSMC
miR-299	ATG5*	Primary hippocampal neuron*
miR-326	ETS-1	$CD4^+$ T cell, Th17
miR-342	AKT1, BMPR2, PIK3R1	MΦ, VSMC
miR-424	CCND1, Calumenin, NFIA	VSMC, Monocyte
miR-503	SMAD7, SMURF1, SMURF2	VSMC, EC, Monocyte
miR-511	N.A.	M2 MΦ

*Target confirmed in AD.

Fig. 1. Aberrantly expressed miRNAs in GCA. Putative targets and cells predominantly affected by miRNA alteration in the context of GCA pathogenesis are presented for each miRNA. Recent studies suggest that at least seven under-expressed and 14 overexpressed miRNA families, miRNA clusters and/or individual miRNAs in GCA may interact with genes involved in modulation of the VSMC phenotype and development of intimal hyperplasia, immune cell dysfunction, EC dysfunction and regulation of cytokine, chemokine, MMP and growth factor production. References on miRNA targets and affected cell types are listed in Table 1 for each miRNA. GCA, giant cell arteritis; VSMC, vascular smooth muscle cell; MΦ, macrophage; EC, endothelial cell; CD, cluster of differentiation; Th, T helper cell; Treg, regulatory T cell; DC, dendritic cell; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TGF, transforming growth factor; ET, endothelin; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; MGC, multinucleated giant cell; ATLO, artery tertiary lymphoid organ; FSGS, focal segmental glomerulosclerosis; AD, Alzheimer's disease; N.A., not applicable.

signaling pathway, where hyperactive NOTCH1 signaling contributes to the expansion of $NOTCH1^+$ $CD4^+$ T cells, transmigration of T cells from circulation to the vascular wall and metabolic T cell reprograming [6,73]. In addition to the CD28-PI3K-AKT axis, the Jagged1-NOTCH1 pathway also contributes to high mTORC1 activity in lesional $CD4^+$ T cells, leading to effector Th1 and Th17 cell differentiation [30]. Components of the NOTCH signaling pathway in GCA also facilitate the crosstalk between VSMCs and ECs, regulate VSMC differentiation and plasticity, and allow interaction between T cells, DCs and macrophages [17,20]. Involvement in the NOTCH signaling pathway has been determined for several miRNAs aberrantly expressed in patients with GCA, including the miR-143/145 cluster, miR-146a, miR-21, the miR-30 family and miR-150 (Table 1). As revealed, the Jagged1-NOTCH signaling regulates miR-143/-145 expression in VSMCs, where upregulation of the miR-143/145 cluster is required to induce a differentiated contractile phenotype [74], whereas upregulation of miR-146a and miR-21 accelerated VSMC proliferation via targeting NOTCH2 and Jagged1, respectively [75]. Moreover, overexpression of miR-146a has been shown to inhibit NOTCH1 activity in macrophages, and promoted macrophage polarization into the M2 phenotype [76], and inhibition of several miR-30 family members triggered the DLL4-NOTCH1 signaling and related pro-inflammatory response in macrophages, whereas their overexpression attenuated M1 macrophage activation through a negative regulation of the DLL4-NOTCH signaling pathway [77]. Implication in the NOTCH signaling pathway has been also determined for miR-150, whose overexpression reduced NOTCH3 levels in T cells and had an adverse effect on T cell proliferation and survival [78]. Since NOTCH3 is downregulated in synthetic VSMCs [79], determined upregulation of miR-150 in vascular neointimal lesions [80] also suggests that overexpression of miR-150 in GCA might contribute to pathogenic VSMC phenotypic transition through inhibition of NOTCH3 signaling. Nonetheless, to implicate dysregulated miRNAs in the NOTCH signaling pathway and/or other signal transduction pathways presumably involved in GCA pathogenesis further in-depth assessment in needed.

3.2. Effect of growth factor and cytokine signaling on miRNA alteration in the context of GCA pathogenesis

During the course of inflammatory-driven vessel wall remodeling process in GCA-affected arteries, stimulated macrophages and MGCs located in the media and at the media-intima border, and activated stromal cells (VSMCs, ECs) that acquire pro-inflammatory properties, produce and release large amounts of pro-inflammatory cytokines, tissue-damaging mediators, adhesion molecules and growth factors, primarily PDGF, VEGF, transforming growth factor β (TGF-β) and endothelin-1 (ET-1) [3,16,17]. Overall, studies have shown strong dependence of miRNA expression on PDGF, VEGF, TGF-β and cytokine signaling, indicating to their notable role in instigation of miRNA alteration in patients with GCA.

3.2.1. PDGF signaling

PDGF (both PDGF-AA and PDGF-BB) is widely expressed in inflamed TABs from patients with GCA and produced mainly by lesional macrophages, MGCs and activated VSMCs. As a key mediator of vascular response to injury, PDGF stimulates VSMC phenotypic switch into the synthetic state (myofibroblast-like phenotype), VSMC proliferation and migration towards the intimal layer, where synthetic VSMCs synthesize and deposit extracellular matrix proteins, collectively resulting in intimal hyperplasia [3,5,16,81]. PDGF is also a potent regulator of miRNA expression, predominantly of those miRNAs whose regulatory activity dictates the phenotypic modulation of VSMCs. As such, the miR-143/145 cluster, miR-30a, miR-124, miR-125a-5p and miR-365, with determined under-expression in inflamed TABs from patients with GCA (Table 1), have been previously shown to be responsive to PDGF signaling, displaying PDGF-dependent downregulation directly related to the synthetic proliferative and migratory VSMC phenotype. In contrast, their stable expression displayed strict commitment to the contractile VSMC phenotype in physiologically normal conditions, and their overexpression has been even shown to restore the contractile VSMC phenotype from the synthetic state and/or attenuate the extent of intimal hyperplasia in injured vessels [82–89]. Noteworthy, miR-143 and miR-145 belong to the miR-143/145 cluster and are among the most under-expressed miRNAs in GCA [10–12,28]. Upregulation of the miR-143/145 cluster is crucial for the maintenance of the differentiated contractile VSMC phenotype through targeting a network of transcription factors comprising KLF-4, KLF-5, myocardin and ELK-1, whereas its downregulation results in VSMC phenotypic transition to the synthetic proliferative and migratory phenotype [82,84]. Vascular stress-induced elevated PDGF levels have been shown to inhibit miR-143/145 in VSMCs, resulting in the formation of podosomes, dynamic short-lived actin-rich membrane protrusions involved in cell migration, which facilitated VSMC migratory and invasive capacity [83]. In addition, downregulation of the miR-143/145 cluster has been determined in arterial neointimal lesions, while their overexpression decreased neointimal lesion formation [90].

Overexpression of several miRNAs whose PDGF-dependent upregulation positively associates with the development of the synthetic VSMC phenotype has also been determined in GCA, including miR-142-5p, miR-146b and miR-150 (Table 1). Overall, these miRNAs were all upregulated in VSMCs following PDGF-BB stimulation, and involved in pathways promoting cell proliferation and migration [91–94]. Interestingly, miR-142-5p expression levels positively associated with expression of MMP-2 and MMP-9 in PDGF-BB-stimulated VSMCs [91], while another study revealed that miR-23b negatively regulates MMP-9 production in TNF-α-stimulated VSMCs [95]. Consistent with their determined expression in GCA (Table 1), dysregulated miR-142-5p and miR-23b might mediate tissue destruction through enhancement of MMP-2 and MMP-9 production, since both MMPs are involved in arterial wall remodeling in GCA [4,16].

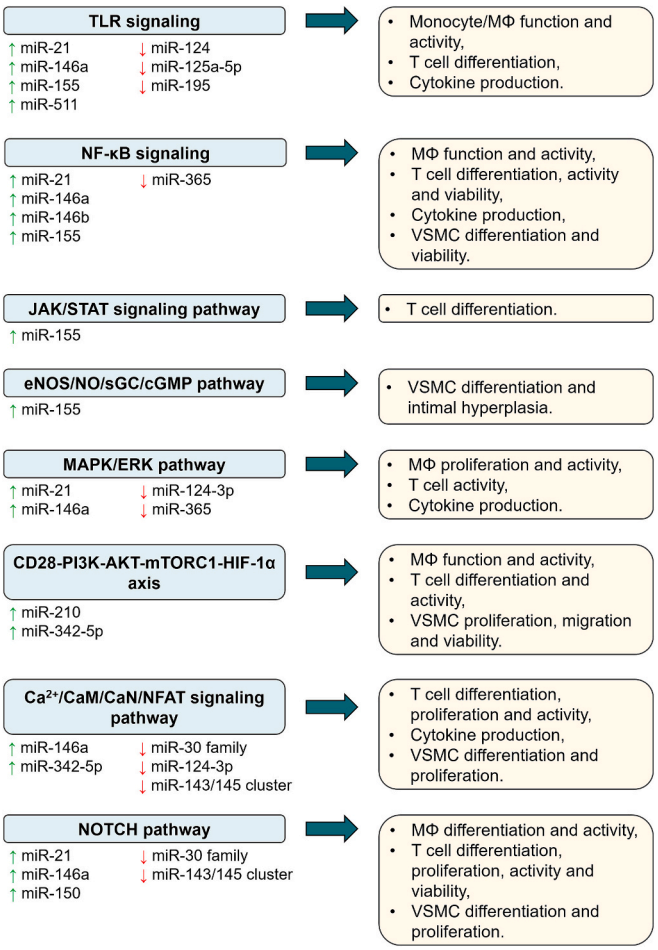


Fig. 2. Implication of aberrantly expressed miRNAs in signaling pathways presumably involved in the pathogenesis of GCA. miRNAs with determined altered expression in inflamed temporal arteries of patients with GCA, which have been shown to either modulate, interact or be under the transcriptional regulation of each presented signaling pathway, are displayed. Influence of each signal transduction pathway on vasculitis-inducing immune and nonimmune cells is presented in yellow rounded rectangles. Green and red arrows indicate miRNAs that have been identified as overexpressed and under-expressed in patients with GCA, respectively.
MΦ, macrophage; VSMC, vascular smooth muscle cell; TLR, Toll-like receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; JAK, Janus kinase; STAT, signal transducer and activator of transcription; eNOS, endothelial nitric oxide synthase; NO, nitric oxide, sGC, soluble guanylyl cyclase; cGMP, cyclic guanosine monophosphate; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; CD, cluster of differentiation; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; HIF-1α, hypoxia-inducible factor 1-alpha; CaM, calmodulin; CaN, calcineurin; NFAT, nuclear factor of activated T cells; NOTCH, neurogenic locus notch homolog protein.

3.2.2. VEGF signaling

VEGF is abundant in sera of patients with GCA [4,6]. Although the exact cellular source of circulating VEGF has not been determined yet, it has been revealed that lesional macrophages and MGCs possess the ability to produce VEGF, which drives the neoangiogenesis process within the GCA-affected vessel wall and promotes the local inflammatory response [4,6,16]. Importantly, VEGF also upregulates Jagged1 (a NOTCH1 ligand) in ECs of the *vasa vasorum*, which stimulates the NOTCH1 receptor expressed on infiltrating $CD4^+$ T cells, facilitating T cell transmigration into the arterial wall and directing their differentiation into effector Th1 and Th17 cell lineages through metabolic reprograming. Hyperactivity of the VEGF-NOTCH1-Jagged1 signaling

pathway is thus regarded as a key step in the initial phase of GCA development [4,6]. Overall, information on VEGF-dependent regulation of miRNAs aberrantly expressed in GCA is currently limited. Nonetheless, VEGF and miRNAs putatively implicated in the NOTCH signaling pathway in GCA (please refer to section 3.1.5) might interrelate, where the miR-143/145 cluster, miR-146a, miR-21, the miR-30 family and miR-150 could be subjected to the regulatory influence of VEGF signaling and/or vice versa. Notably, it has been revealed that miR-150 is upregulated and enriched in PDGF-BB-stimulated VSMCs, and secreted via extracellular vesicles (EVs). EV-mediated transfer of miR-150 from activated VSMCs to ECs increased VEGF-A production and secretion in recipient ECs, and enhanced their migration through activation of the VEGF-A/VEGFR/PI3K/AKT signaling pathway [94]. This suggest that overexpressed miR-150 in patients with GCA (Table 1) might mediate the crosstalk between VSMCs and ECs through activation of the PDGF-miR-150-VEGF axis, which might be involved in neovascularization within the affected vessel walls and might also contribute to the hyperactivity of the VEGF-NOTCH1-Jagged1 signaling, by inducing Jagged1 expression in ECs.

3.2.3. TGF-β signaling

Overexpression of TGF-β has been determined predominantly in GCA-affected arteries with transmural inflammation, where TGF-β is expressed mainly by activated macrophages and pro-inflammatory synthetic VSMCs, and is involved in vessel wall remodeling, VSMC phenotype switching and extracellular matrix production [16,96]. Although the canonical TGF-β signaling helps to induce and sustain the contractile VSMC phenotype, in the context of vascular injury, TGF-β stimulates VSMC proliferation, production and secretion of extracellular matrix proteins, and development of intimal hyperplasia, linked to the activation of the non-canonical TGF-β signaling via the MAPK signaling pathway [23]. Therefore, function of TGF-β appears to depend largely on the pathological context of vascular injury, and it is not surprising that TGF-β signaling may promote overexpression of miRNAs that positively associate with both, the contractile and/or the synthetic VSMC phenotype, including miRNAs with altered expression in GCA. As such, TGF-β-mediated upregulation of miR-21, miR-142-3p and the miR-143/145 cluster resulted in activation of contractile genes in VSMCs, induction and maintenance of the contractile VSMC phenotype and inhibition of the VSMC migration capacity [97–99]. Moreover, TGF-β also induces upregulation of the miR-143/145 cluster in VSMCs and facilitates the transfer of miR-143/-145 to ECs, thereby reducing EC proliferation and contributing to vessel stabilization [100]. These pro-contractile properties of TGF-β-induced miR-21, miR-142-3p, miR-143 and miR-145 appear to be in line with the canonical TGF-β signaling in VSMCs, and do not seem to fit in the context of GCA pathogenesis, and vary from settings that resemble GCA pathophysiology (Table 1).

In addition, TGF-β in combination with specific GCA-related pro-inflammatory cytokines (i.e. IL-6, IL-21 and IL-23) directs T cell polarization into the effector Th17 cell lineage [20,101], and enhances expression of those aberrantly expressed miRNAs in GCA, whose upregulation has been related to promoting Th17 cell differentiation and activity. As revealed, TGF-β and IL-6 collectively upregulate the miR-132/212 cluster under Th17-polarizing conditions, where miR-132/-212 positively regulate Th17 differentiation and promote IL-17 production [102]. Similarly, TGF-β in combination with IL-23 upregulates miR-210 in $CD4^+$ T cells in a HIF-1α-dependent manner, where overexpressed miR-210 subsequently induces Th17 and Th1 cell differentiation [63] (additionally described in section 3.1.3). Accordingly, TGF-β-dependent overexpression of the miR-132/212 cluster and miR-210 might be implicated in the pathogenesis of GCA (Table 1).

Notably, TGF-β can also induce ET-1, a potent vasoactive peptide, which is upregulated in GCA lesions and predominantly expressed by infiltrating mononuclear cells and activated VSMCs [103]. In GCA, ET-1 contributes to the development of intimal hyperplasia by increasing VSMC migration and facilitating the outgrowth of synthetic VSMCs from the media towards the intima [103]. Expression of ET-1 is at least partially under the regulatory influence of miR-125a-5p and miR-125b-5p, which have been shown to negatively regulate ET-1 expression in ECs [104]. In line with enriched ET-1 levels in GCA lesions [103], determined under-expression of miR-125a-5p in inflamed TABs from patients with GCA (Table 1) suggests that aberrant expression of miR-125a might contribute to the enhanced activation of the ET-1 pathway in GCA.

3.2.4. Cytokine signaling

Responsiveness of miRNA expression to cytokine signaling has been well studied, and cytokines involved in GCA pathogenesis have been shown to modulate several miRNAs whose expression is altered in patients with GCA. As such, pro-inflammatory cytokines, including TNF-α, IFN-γ, IL-1β and IL-6, have been shown to induce expression of miRNAs whose alteration associates with activity of cells involved in the inflammatory-driven vessel wall remodeling process in affected arteries of patients with GCA. Specifically, TNF-α upregulates miR-155-5p expression in VSMCs in a NF-κB-dependent manner, where miR-155-5p impairs the contractile VSMC phenotype and NO-mediated vasorelaxation [53]. Similarly, IFN-γ-induced overexpression of miR-155 in macrophages enhances the production of CCL2 and M1-type markers (i.e. NOS2 (iNOS) and TNF-α), which promotes the development of the M1-like macrophage phenotype, pro-inflammatory macrophage activity and potentiates vascular inflammation [51]. Notably, IFNs (IFN-β and IFN-γ) require TNF-α autocrine/paracrine signaling to upregulate miR-155 expression in macrophages, where miR-155 represents a component of the primary macrophage response to different type of inflammatory stimuli [35], highlighting the importance of the TNF-α-IFN-γ-miR-155 axis, which may drive the maladaptive immune response in inflamed arterial walls of patients with GCA. In addition, a recent study revealed that IFN-γ and IL-1β directly positively regulate miR-146a and miR-146b expression in an in vitro cell model of GCA, where upregulated miR-146a and miR-146b increased ICAM-1 expression and soluble ICAM-1 production [48], which is in line with overexpression of ICAM-1 on activated *vasa vasorum* ECs in GCA lesions [3,16,19]. Moreover, upregulation of miR-146b-5p has been also shown to be IL-6-dependent [47].

In contrast and in concordance with their expression in GCA, TNF-α has been shown to downregulate miR-23b in VSMCs, resulting in phenotypic switching and increased migration of TNF-α-stimulated VSMCs [95], whereas IL-17 inhibits the expression of miR-365a-3p, which is regarded as a negative regulator of IL-17-initiated inflammation [105]. Overall, induction of miR-142-5p and miR-146b has been also shown to be dependent on Th2 cytokines [106–108], although these cytokines are not recognized as drivers of GCA-related vascular pathophysiology.

3.3. miRNA cooperation in the context of GCA pathogenesis

Regulatory networks involving miRNAs show a high degree of complexity, where an individual biological process can be regulated by multiple miRNAs that act synergistically [13,109]. In line, functional cooperation between several miRNAs that are aberrantly expressed in GCA has been linked to processes closely resembling GCA pathophysiology. Such miRNA cooperation has been determined for miR-143 and miR-145, essential for the maintenance of the contractile VSMC phenotype, promotion of VSMC differentiation from other cell types, including fibroblasts and multipotent neural crest stem cells [82], and negative regulation of multiple regulatory factors of actin dynamics [83,110]. In addition, induction of miR-143/-145 cooperatively inhibits Th9 cell differentiation, proliferation and IL-9 production [71], which relates alteration of these miR-143/-145 functions to their determined under-expression in inflamed arteries of patients with GCA (Table 1). Functional miRNA cooperation in regulation of VSMC proliferation has also been determined for miR-21 and miR-146a, where upregulated co-

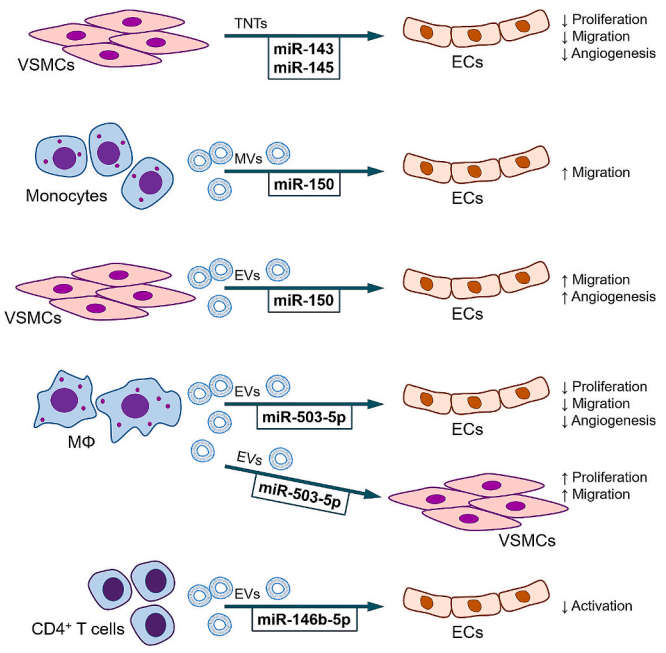


Fig. 3. Inter-cellular miRNA transfer in GCA. Altered GCA-related arterial tissue miRNAs involved in inter-cellular crosstalk between cells recognized as drivers of GCA disease process are presented. Overall, miRNAs can be transferred between cells by either EV-mediated transfer, or by diverse highly organized cell-to-cell connective structures formed between adjacent donor and acceptor cells.

VSMC, vascular smooth muscle cell; MΦ, macrophage; EC, endothelial cell; CD, cluster of differentiation; TNT, tunneling nanotube; MV, microvesicle; EV, extracellular vesicle.

expression of miR-21 and miR-146a synergistically promoted VSMC proliferation through induction of the G_1 phase cell cycle progression, resulting in an increased percentage of cells in the S and G_2/M phases [75]. Moreover, upregulation of miR-146a and miR-146b increased ICAM-1 expression and production in primary cell cultures from TABs of patients with GCA and affected viability of in vitro primary cell models [48], whereas the crosstalk between miR-30a-3p and the miR-132/212 cluster resulted in an impaired endothelial function [111]. In regards to macrophage polarization, synergistic role of miR-142-5p upregulation and miR-130a-3p downregulation has been shown to promote polarization and pro-fibrogenic activity of M2-like macrophages in chronic inflammation, by altering SOCS1 and PPARG expression, respectively [106]. Although expression of miR-130a-3p has not been validated yet in GCA, its under-expression in inflamed TABs from treatment-naïve patients has been confirmed by miRNA expression profiling experiments [11]. Finally, multiple miRNAs that are overexpressed in GCA, including miR-155, miR-424 and miR-503, have been shown to induce cell cycle arrest and partial cell differentiation through combinatorial cooperative regulation in conjunction with various transcription factors in monocytes [112].

The incidence of GCA increases with age, which suggests that the aging process may influence GCA development. Age at GCA onset has a significant impact on clinical manifestations in elderly patients, and a synergy between immunosenescence, T cell aging, age-related vascular wall remodeling and chronic low-grade inflammation associated with aging (i.e. inflammaging) may have a role in increasing the risk of GCA development with age [3,7,16,56]. Age-dependent immune dysfunction associated with GCA pathogenesis is also interlinked with epigenetics [3,16], including miRNA dysregulation. It has been revealed that age-related overexpression of miR-21 promotes effector T cell differentiation from memory T cells in older individuals, by sustaining activation of the MAPK and AKT-mTORC signaling pathways [113]. In addition, upregulation of miR-150 in aged macrophages promotes macrophage-mediated inflammation and pathological angiogenesis by targeting SCD2 in a VEGF-independent manner, directing macrophages towards an aged, disease-promoting and proangiogenic phenotype [114]. Overall, miR-150 is abundantly expressed in monocytes and has a critical role in T and B cell development, maturation and differentiation [78,115,116]. Moreover, miR-150 regulates differentiation and effector functions of $CD8^+$ T cells, promotes EC migration, affects macrophage polarization, and regulates VSMC proliferation, migration and intimal hyperplasia [94,116–119], indicating to a pleiotropic function of miR-150 in vascular pathophysiology. In particular, miR-150 deficiency reduces pro-inflammatory macrophage responses, decreases macrophage infiltration and results in decreased production of several pro-inflammatory mediators, including TNF-α, IL-1β, IL-6 and iNOS, suggesting miR-150 is an important pro-inflammatory miRNA [118], whose effects on vascular pathology and intimal hyperplasia are largely dependent on its effects in macrophages [118,119]. Although a direct cooperation between the function of miR-21 and miR-150 in elderly patients has not been determined yet, both miRNAs might be involved in inflammaging and age-related vascular alterations in GCA, according to their determined overexpression in patients with GCA (Table 1).

Noteworthy, importance of miRNA-dependent regulation of other miRNAs has been highlighted in macrophages, where upregulation of miR-342-5p directly suppressed the AKT1-mediated inhibition of miR-155, which resulted in a subsequent upregulation of miR-155 and miR-155-dependent induction of iNOS, and promotion of pro-inflammatory macrophage activity [66]. This indicates that miR-342-5p and miR-155 form a functional miRNA pair, whose selective upregulation positively regulates the pro-inflammatory activation of lesional macrophages [66], which might also apply for GCA.

3.4. *Aberrantly expressed miRNAs involved in inter-cellular crosstalk*

Inter-cellular communication coordinates activity between cells through signals that enable one cell to influence the behavior of another. Inter-cellular exchange of miRNAs has been shown to influence or direct the fate of target recipient cells by triggering their differentiation or dedifferentiation, activation, proliferation and migration, or affecting their viability. Cell-to-cell miRNA transfer between immune and/or nonimmune cells can also promote pathogenic activity of stimulated cells in promoting inflammation and development of autoimmunity. Modes of miRNA transfer between cells vary and may involve either EV-mediated transfer, where EVs secreted by a donor cell are accepted by an acceptor cell, or involve diverse highly organized cell-to-cell connective structures formed between adjacent donor and acceptor cells [120,121]. Overall, several miRNAs that are aberrantly expressed in patients with GCA, comprising miR-143, miR-145, miR-146b-5p, miR-150 and miR-503-5p (Table 1), have been involved in inter-cellular crosstalk between cells that are recognized as drivers of GCA disease process, including monocytes, macrophages, T cells, VSMCs and ECs (Fig. 3). Notably, transfer of these miRNAs has been shown to affect mostly EC and VSMC functions, which could be related to the pathophysiology of GCA.

In line, upregulation of the miR-143/145 cluster in differentiated contractile VSMCs triggers a direct cell-to-cell transfer of miR-143 and miR-145 from VSMCs to neighboring ECs through specialized membrane protrusions known as tunneling nanotubes. Passage of miR-143/-145 reduced proliferation and migration of recipient ECs and reduced their capacity to form vessel-like structures, thereby contributing to the stabilization of the endothelium [100]. Determined under-expression of the miR-143/145 cluster in inflamed TABs of patients with GCA (Table 1) could therefore influence vessel stabilization properties of the VSMC-to-EC transfer of miR-143/-145, and promote aberrant EC functions responsible for neovascularization within GCA-affected vessel walls.

In response to various inflammatory stimuli, monocytes express high

levels of miR-150, selectively package miR-150 into microvesicles (MVs), and actively secrete these miR-150-enriched MVs into the circulation. Secreted monocyte-derived MVs containing miR-150 have the ability to be effectively delivered to recipient ECs, where transferred exogenous miR-150 functions as an endogenous miRNA and strongly enhances EC migration via miR-150-dependent downregulation of c-Myb (*MYB*) [116]. Similarly, EV-mediated transfer of miR-150 from VSMCs to ECs also results in promotion of recipient EC migration and angiogenesis [94] (also refer to section 3.2.2).

In addition, enrichment of miR-503-5p in macrophage-derived EVs and their inter-cellular transfer from macrophages to recipient ECs and VSMCs inhibited proliferation, migration and angiogenic properties of ECs, and promoted proliferation and migration of VSMCs, at least partly through downregulation of SMURF1, SMURF2 and SMAD7 [122]. It has been also revealed that miR-146b-5p, produced by stimulated $CD4^+$ T cells, can be packaged into EVs and actively secreted into the circulation. Following their release, EVs protect their miRNA cargo against RNase degradation and effectively transfer miR-146b-5p to ECs, thereby reducing endothelial activation and decreasing the endothelial inflammatory response [123]. Nonetheless, these functions of EV-transferred miR-146b-5p differ from the regulatory role of upregulated miR-146b determined in an in vitro cell model of GCA, where miR-146a and miR-146b were unable to block inflammation associated with activation of the NF-κB signaling pathway [48], highlighting the importance of utilizing relevant disease-specific models in elucidation of miRNA function in distinct disease settings, including GCA.

3.5. *Effect of glucocorticoid treatment on altered miRNA expression in the context of GCA*

To prevent irreversible ischemic complications, including visual disturbances, visual loss and/or ischemic stroke, rapid therapeutic intervention is needed in patients with a strong suspicion of GCA [2,4,5]. Glucocorticoids (GCs) remain the standard therapy of choice due to their highly effective untargeted immunosuppression, particularly in suppressing the extravascular component of GCA, by diminishing the acute phase response, constitutional symptoms and abnormal laboratory parameters in treated patients [4]. Nevertheless, GCs have been proven as relatively insufficient in treating the vascular component of GCA, where IL-17-producing Th17 cells and IL-21-producing $CD4^+$ T cells have been reported to be highly sensitive to high-dose GC therapy and essentially disappear after treatment, whereas IFN-γ-producing Th1 cells have proven to be resistant to GC therapy. Persistence of Th1 cells in arterial lesions of patients with GCA is thus regarded to contribute to the development and sustaining of chronic smoldering vascular inflammation, explaining the occurrence of relapse in about half of patients when GCs are tapered [4,16,124,125]. Treatment with GCs has been also shown to influence miRNA biology and modulate miRNA expression in various disease settings [126–128], whereas GC therapy appears to smother miRNA alteration in treated patients. As such, pronounced effect of GC treatment on miRNA alteration might be revealed when comparing miRNA expression status in inflamed TABs between treatment-naïve patients receiving therapy following a TAB [11] and patients receiving GC therapy prior a TAB [10], where significantly more aberrantly expressed miRNAs were identified in patients with GCA that were treatment-naïve prior to a TAB procedure [11]. Noteworthy, determined overexpression of miR-299-5p in inflamed TABs of prednisone- or methylprednisolone-treated patients [10] indicates that miR-299-5p might be induced by GC therapy, since expression of this miRNA appeared as unchanged in treatment-naïve patients [11].

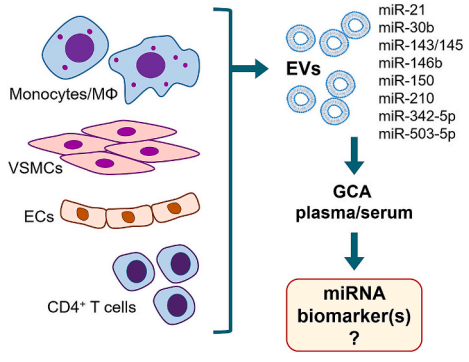


Fig. 4. EV-derived miRNAs in GCA. Altered GCA-related arterial tissue miRNAs that might be released from various cellular sources into the bloodstream via EV-mediated transfer and utilized as putative diagnostic and prognostic biomarkers of GCA are presented.
GCA, giant cell arteritis; miRNA, microRNA; MΦ, macrophage; VSMC, vascular smooth muscle cell; EC, endothelial cell; CD, cluster of differentiation; EV, extracellular vesicle.

There is currently limited data on miR-299 function in vasculitides, including GCA. According to target prediction analysis, miR-299-5p putatively targets AGTR1 and CDKN1A [10], whose upregulation has been shown to activate the switch from the contractile to the synthetic VSMC phenotype in murine models and cultured VSMCs, promoting VSMC migration and development of intimal hyperplasia [129,130]. However, validation experiments and previous reports on AGTR1 and CDKN1A protein expression levels in GCA suggested that these two genes are not effectively targeted by miR-299-5p in inflamed TABs of patients with GCA [10]. It has been shown that miR-299-5p inhibits autophagy via targeting ATG5 and acts as a negative regulator of apoptosis in hippocampal neurons [131]. In line with GCA pathophysiology, PDGF-BB signaling induces a distinct form of autophagy in VSMCs, essential for attaining the synthetic VSMC phenotype and promoting VSMC proliferation, migration and extracellular matrix production [132,133]. Specific activation of autophagy has been also determined outside of adventitial nerves in the vessel wall of inflamed temporal arteries of patients with GCA [134], whereas enhanced activation of autophagy also promotes the formation of a multinucleated syncytium [135], which might associate with MGC formation in GCA lesions. Since GCs have been shown to suppress different types of autophagy [136,137] and inhibit VSMC proliferation [138], treatment of patients with GCA with GCs might at least partly inhibit autophagy in arterial lesions via induction of miR-299, upregulation of which could contribute to GC-mediated immunosuppression and suppression of intimal hyperplasia. Nonetheless, further studies are needed to elucidate the interrelation between miRNA dysregulation and outcomes of pharmacological treatment in GCA.

4. Altered plasma and serum miRNA profiles in GCA

There is currently a significant lack of information on dysregulated miRNA status in blood plasma and serum of patients with GCA. Overall, comprehensive correlation analyses revealed that altered miRNA profiles in affected arterial tissues associate well with diagnostic ultrasonographic examination parameters (including the presence of the "halo sign" and luminal stenosis in temporal arteries), TAB-based histopathological parameters, distinct cellular composition of inflammatory infiltrates and several clinical characteristics of patients with GCA [10,12,29]. Evaluated diagnostic performance and differential expression between subgroups of patients with cranial involvement and non-GCA controls also suggests that dysregulated arterial miRNAs could be utilized as putative diagnostic and prognostic biomarkers of GCA [10–12,28,29]. By extrapolating data on miRNA alteration determined in inflamed TABs of treatment-naïve patients (Table 1), we may speculate that altered expression of arterial tissue miRNAs could be also detected in the circulation of patients with GCA. This may be especially in the case of those miRNAs that were identified as overexpressed, due to their possible release from arterial lesions into the blood stream, most likely via EV-mediated transport, a feature determined for several

aberrantly expressed miRNAs in GCA, including miR-146b-5p, miR-150 and miR-503-5p (please refer to section 3.4). In addition, dysregulated circulating levels of several other GCA-related miRNAs have been determined in biological fluids such as blood serum and plasma, including miR-21, miR-143, miR-145, miR-30b-5p, miR-342-5p and miR-210 [139–142], indicating to their potential to serve as non-invasive GCA biomarkers (Fig. 4). Since extracellular/circulating miRNAs can be released from various types of donor cells via EVs, apoptotic bodies and/or protein-miRNA complexes [143,144], the precise mechanism of potential selective miRNA secretion from GCA arterial lesions still needs to be determined. These data would represent valuable insight on whether miRNA release in GCA is an active process or whether miRNAs are spontaneously released from apoptotic lesional cells. Identification of circulating miRNAs and the extent of their selective and/or spontaneous secretion in patients with GCA, together with information on their cellular sources could eventually become applicable in determining the extent of lesional cell activation and lesional cellular inflammatory infiltrate composition, based on specific circulating miRNA "fingerprints". As alterations in circulating miRNA levels might become detectable before perceivable intimal thickening, vessel lumen occlusion and clinical manifestations in patients with GCA, their detection could enable a relatively rapid recognition of GCA clinical onset. Thus, these miRNAs could serve as non-invasive biomarkers for predicting relapses, considerably improving the management of GCA, which remains problematic due to the lack of reliable disease biomarkers capturing vessel wall inflammation [4].

5. Conclusion and future perspectives

Over the past decade, there has been a gradually increasing compelling evidence that miRNA alteration importantly contributes to the shaping of the inflammatory milieu and inflammatory-driven vessel wall remodeling process in affected arteries of patients with GCA. Nevertheless, several crucial challenges remain. While expression profiles of aberrantly expressed miRNAs in inflamed arterial tissue tend to associate well with GCA-related histopathology and pathophysiology, it remains unknown to what extent do dysregulated miRNAs actively participate in GCA pathogenesis. It is also unknown whether the magnitude of miRNA alteration in GCA lesions occurs due to the enhanced activation of signal transduction pathways linked to the GCA disease process or due to the presence of an increased number of infiltrating immune cells and/or activated vascular tissue-resident stromal cells, which overexpress or fail to express specific miRNAs. These issues could be eventually overcome by employing functional studies utilizing appropriate in vitro, ex vivo and in vivo disease models that are currently lacking for GCA [145], which hinders a comprehensive exploration of the impact of miRNA dysregulation on GCA pathogenesis. Moreover, there is a shortage of studies exploring the interrelation between miRNA dysregulation and manifestations of vascular aging in patients with GCA, including age-related vascular wall remodeling, immunosenescence and inflammaging, all of which may increase the risk of GCA development with age [3,7,16,56]. Overall, current assessment of miRNA function in GCA still mostly relies on "observational" studies performed on TABs, where identified aberrantly expressed miRNAs have been implicated in GCA pathogenesis based on extrapolation of their previously determined functions in vitro or in loss- or gain-of-function studies employing animal models. Such extrapolation of miRNA function remains challenging, since the majority of in vitro studies usually focus on an individual cell type, rather than taking into account the overall population of effector cells responsible for specific disease pathology, which may generate significant discrepancies in obtained results between in vitro and in vivo settings. Furthermore, no specific animal (mouse) models for GCA have been developed yet [145,146]. Nevertheless, primary cell cultures obtained from TABs along with ex vivo TAB sections [147,148] have been recently successfully utilized to assess the aberrant regulatory activity of miR-146a and miR-146b upregulation in GCA [48], indicating to a progressive advance in functional assessment of dysregulated miRNAs in GCA. Progress in the field may become even more profound through utilization of high-throughput technologies, including RNA sequencing (RNA-Seq), spatial transcriptomics, bioinformatics and artificial intelligence, whose employment would undoubtedly accelerate biomarker discovery and identify novel disease-relevant pathways and molecular systems in GCA, including those involving dysregulated miRNAs. Overall, these molecular systems may include the ubiquitin–proteasome system and RISC, which were both recognized as putative targets of aberrantly expressed miRNAs in GCA [11]. In addition, dysregulation of other ncRNAs, including long ncRNAs (lncRNAs) and circular RNAs (circRNAs) that can act as miRNAs sponges [109], may eventually become identified and linked to GCA pathogenesis, shedding light on the currently concealed interrelationship between various epigenetic regulatory mechanisms and processes affected by their dysregulation.

There are several factors that currently limit the use of miRNAs as prognostic and/or diagnostic tools in clinical settings. In general, validation and implementation of miRNA biomarkers has been mostly unsuccessful due to the lack of protocol standardization in the pre-analytical phase, comprising sample collection, storage and processing, extraction protocols and efficient quality control, varying on the sample type (e.g. tissue, serum, plasma and EVs). On the other hand, absence of consensus on endogenous controls and methodology used for data normalization represents the main post-analytical challenge. Altogether, inconsistency of these procedures between laboratories strongly affects the obtained results, leading even to contradictory findings [149]. Nevertheless, absolute quantification of miRNA expression by utilization of digital PCR (dPCR) holds a significant potential to count individual miRNA copy numbers at limiting dilutions without bias, particularly in body fluids such as blood plasma or serum [149]. Absolute quantification of miRNA dysregulation in patients with GCA might therefore provide stringent cut-offs of tissue and circulating miRNA biomarker levels, enabling an effective differentiation between patients with distinct patterns of arterial involvement, identification of patients with relapsing disease course and classification of patients based on their vascular and extravascular disease component. Finally, comparison of miRNA alteration between GCA, GCA mimickers and other vasculitides that affect medium and large vessels might reveal shared molecular pathogenic determinants together with fundamental differences in disease effector pathways involving miRNAs across these vascular pathologies. For instance, apparent absence of dysregulated miR-221/222 and miR-17∼92 clusters in inflamed TABs of treatment-naïve patients with GCA [11], previously identified as key miRNA mediators in facilitation of the VSMC phenotypic transition into the synthetic state and development of intimal hyperplasia [150,151], implies to crucial molecular specificities of GCA compared to other pathologies characterized by similar vascular alterations. Taken together, insight into dysregulated miRNA-mediated regulatory processes holds great potential for a more productive management of GCA, allowing to a more personalized diagnostic, prognostic and therapeutic approaches.

Funding

This work was supported by the Slovenian Research and Innovation Agency (ARIS) [research core funding No. P3–0054].

Declaration of competing interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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