Non-coding RNA Research 8 (2023) 426–450

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Non-coding RNA-mediated epigenetic alterations in Grave's ophthalmopathy: A scoping systematic review

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ARTICLE INFO

Keywords:
Epigenetics
Graves' ophthalmopathy (GO)
Non-coding RNA (ncRNA)

ABSTRACT

Background: It is becoming more and more apparent that Grave's Ophthalmopathy (GO) pathogenesis may be aided by epigenetic processes such as DNA methylation modifications, histone tail covalent modifications, and non-coding RNA (ncRNA)-based epigenetic processes. In the present study, we aimed to focus more on the miRNAs rather than lncRNAs due to lack of investigations on these non-coding RNAs and their role in GO's pathogenesis.

Methods: A six-stage methodology framework and the PRISMA recommendation were used to conduct this scoping review. A comprehensive search was conducted across seven databases to discover relevant papers published until February 2022. The data extraction separately, and quantitative and qualitative analyses were conducted.

Results: A total of 20 articles were found to meet inclusion criteria. According to the results, ncRNA were involved in the regulation of inflammation (miR-146a, LPAL2/miR-1287–5p axis, LINC01820:13/hsa miR-27b-3p axis, and ENST00000499452/hsa-miR-27a-3p axis), regulation of T cell functions (miR-146a/miR-183/miR-96), regulation of glycosaminoglycan aggregation and fibrosis (miR-146a/miR-21), glucocorticoid sensitivity (miR-224–5p), lipid accumulation and adipogenesis (miR-27a/miR-27b/miR-130a), oxidative stress and angiogenesis (miR-199a), and orbital fibroblast proliferation (miR-21/miR-146a/miR-155). Eleven miRNAs (miR-146a/miR-224–5p/miR-Let7d-5p/miR-96–5p/miR-301a-3p/miR-21–5p) were also indicated to have the capacity to be used as biomarkers.

Conclusions: Regardless of the fact that there is significant documentation of ncRNA-mediated epigenetic dysfunction in GO, additional study is needed to thoroughly comprehend the epigenetic connections concerned in disease pathogenesis, paving the way for novel diagnostic and prognostic tools for epigenetic therapies among the patients.

1. Introduction

1.1. Graves' ophthalmopathy

Graves' Ophthalmopathy (GO) is an organ-specific autoimmune disorder. It is referred to as thyroid-associated ophthalmopathy, Graves' orbitopathy, or thyroid eye disease. At first, the condition was documented during the 19th century [1]. It happens in about 25% of persons suffering from Graves' disease (GD) as an extrathyroidal symptom [2]. The signs and indicators may include exposure keratopathy [3], retraction of the eyelid, proptosis, double vision, periorbital edema, as well as optic neuropathy [4]. GO is a condition associated with increased production of inflammatory cytokines in the connective tissue of the

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https://doi.org/10.1016/j.ncrna.2023.04.001
Received 15 December 2022; Received in revised form 25 March 2023; Accepted 27 April 2023
Available online 16 May 2023
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Abbreviations

AGO	Argonaute
AMPK	AMP-activated protein kinase
ANGLE1	Angle of entrainment 1
cAMP	Cyclic AMP
ceRNA	Competing endogenous RNA
CD14	Cluster of differentiation 14
CD4+T	T helper
CpG	Cytosine-phosphate-guanine
CXC12	C-X-C motif chemokine 12
CXCL1	C-X-C Motif Chemokine Ligand 1
DGCR8	DiGeorgeCritical Region 8
DNMT1	DNA Methyltransferase 1
DNMT3A	DNA methyltransferase 3 alpha
DNMT3B	DNA methyltransferase 3 beta
DRD4	Dopamine receptor D4
EGFR	Epidermal growth factor receptor
EGR-1	Early growth response 1
ENCODE	Encyclopedia of DNA Elements
FPR2	Formyl peptide receptor 2
FT3	Free triiodothyronine
FT4	Free thyroxine
GD	Graves' disease
GENCODE	Project Consortium
GO	Graves' ophthalmopathy
GPCR	G-protein coupled receptor
GSK-3β	Glycogen synthase kinase-3β
H3K4	Histone H3 at lysine 4
H3K9	H3 lysine 9
H4K20	H3 lysine 20
H3K27	H3 lysine 27
H3K36	H3 lysine 36
H3K79	H3 lysine 79
HA	Hyaluronic acid
HIF-1	Hypoxia-inducible factor 1
ICAM-1	Intercellular adhesion molecule-1
IL-1 α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-16	Interleukin-16
IL-17	Interleukin-17
lncRNAs	Long non-coding RNAs
LPAL2	Lipoprotein(A) Like 2
LYAR	Ly-1 antibody reactive
MALAT1	Metastasis associated in lung adenocarcinoma transcript 1
MBP	Myelin basic protein
MeSH	Medical Subject Headings
MIAT	Myocardial infarction associated transcript
miRNAs	MicroRNAs
ncRNA	Non-coding RNA
NEAT1	Nuclear enriched abundant transcript 1
NF-κB	Nuclear factor κB
NOX4	NADPH Oxidase 4
OFs	Orbital fibroblasts'
OIP5-AS	Opa-interacting protein5 antisense RNA 1
PI3K	Phosphatidylinositol-3-kinase
pre-miRNAs	Precursor miRNAs
R–CHOP	Rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone
PDCD4	Programmed cell death 4
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol 3-kinases
PPARγ	Peroxisome proliferator-activated receptor-gamma
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PRKCε	Protein kinase C epsilon
PTEN	Phosphatase and tensin homolog
PVT1	Plasmacytoma variant translocation 1 gene
RISC	RNA-induced silencing complex
RNase	Ribonuclease
RNPol II	RNA Polymerase II
Smad4	Mothers against decapentaplegichomolog 46
ST8SIA4	Alpha-*N*-acetyl-neuraminide alpha-2,8-sialyltransferase 4
STAT4	Signal transducer and activator of transcription 4
TGF	Transforming growth factor
TGF-β	Transforming growth factor beta
Th1	T-helper 1
Th2	T-helper 2
Thy1–	No Thy1
Thy1+	Thy1 surface expression
TRAb	Thyrotropin receptor autoantibody
TRAF6	TNF receptor associated factor 6
TRBP	TAR-RNA binding protein
TSH	Thyroid-stimulating hormone
TSHR	Thyrotropin receptor
TSHR-Abs	Thyroid-stimulating hormone receptor-antibodies
VEGF-A	Vascular endothelial growth factor A
XIST	X-inactivespecific transcript
ZNRF3	Zinc and ring finger 3

orbit, increased orbital volume from a glycosaminoglycan overproduction, as well as increased adipogenesis [5,6]. Despite unknown exact pathophysiology, growing evidence suggests that GO results from autoimmune responses where sensitive T cells and autoantibodies respond to certain antigens [such as thyrotropin receptor (TSHR), insulin-like development factor-1 receptor, thyroglobulin, calsequestrin, and collagen XIII] lead to edema and fibrosis by promoting the orbital fibroblasts' (OFs) activation and proliferation [7–10]. Because of the lack of understanding of pathophysiology, treatment options differ, including glucocorticoids, surgery, and immunosuppressive medicine [4]. Many variables, which include environmental, immunological, and genetic factors, contribute to GO development [8], enabling etiology and therapy to be examined from various viewpoints. Particular attention has been paid to the role of epigenetics in GO and non-coding RNAs (ncRNAs) in relation to GO pathogenesis, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs).

1.2. Chromatin-based epigenetic mechanisms

A chromatin-based epigenetic control of gene expression affects both the protein level (post-translational histone changes) and the DNA level (DNA methylation) (Fig. 1). Post-translational changes in particular amino acids in histone tails impact gene expression and construction of chromatin [11]. Histones may undergo a variety of post-translational changes, including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation [12], with lysine acetylation and methylation being the most well-studied. As a result of the acetylation of positively charged lysine, histone acetyltransferases weaken the electrostatic relations between histones and negatively charged DNA, allowing for better access to the chromatin construction [13]. In particular, histone methyltransferases control the methylation of lysine residues in histone tails, either monomethylation, dimethylation, or trimethylation. Transcriptional activity has the ability to either be

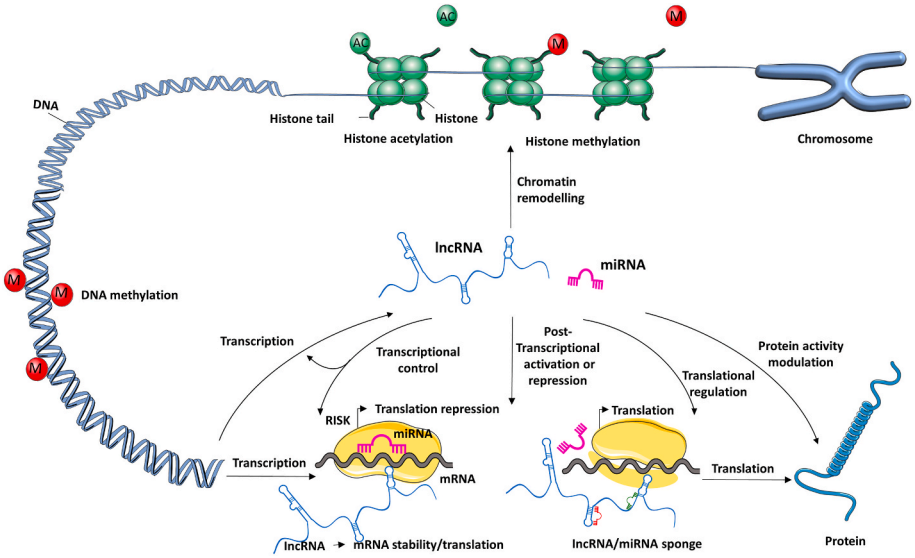

Fig. 1. Chromatin- and non-coding RNA-based epigenetic mechanisms. Chromatin modifications, such as chromatin accessibility, DNA methylation, and histone tail modifications, as well as non-coding RNAs (microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) expression are regulatory mechanisms that contribute to the establishment of a repressive or active state. This figure was created using the vector image bank of Servier Medical Art (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

induced or inhibited by these changes [12]. The transcriptional function has been related to increased acetylation levels and trimethylation of histone H3 at lysine 4 (H3K4), H3 lysine 36 (H3K36), and H3 lysine 79 (H3K79), while transcriptional repression is associated with reduced amounts of acetylation and methylation of H3 lysine 9 (H3K9), H3 lysine 27 (H3K27), and H3 lysine 20 (H4K20) [12,14,15]. Additional enzymes that operate as writers and erasers have been discovered as a consequence of these histone changes [16]. Histone alterations in GO have not been fully explored; however, histone changes in GD have been examined and may give some insight into how histone changes impact GO etiology. It is unclear if these alterations occur in GO, as well as whether there are any additional histone changes [17].

DNA methylation is a process by which DNA is modified, and gene expression is controlled. During this procedure, DNA methyltransferases transfer a methyl group from *S*-adenyl methionine to cytosine at the fifth carbon position to create 5Mc [18]. DNA methylation happens most often at cytosine-phosphate-guanine (CpG) dinucleotides, sometimes known as CpG islands, although it may impact non-CpG regions as well [19,20]. Non-CpG DNA methylation is usually seen in embryonic stem cells and lost in adult tissues [21]. DNA methylation is found in roughly 70% of CpG dinucleotides found in heterochromatin and a substantial number of gene promoters, based on research [20]. Three enzymes are in charge of DNA methylation and the genomic methylation structures maintenance (DNA Methyltransferase 1 (DNMT1), DNA methyltransferase 3 alpha (DNMT3A), and DNA methyltransferase 3 beta (DNMT3B). The DNMT1 regulates replication and copy of the methylation pattern from parental to recent DNA, while the DNMT3A and DNMT3B genes affect intact DNA, resulting in unique methylation patterns [18]. DNMT3B plays a role in the integrity of mRNA transcription initiation and may prevent abnormal transcription starts [22]. DNA methylation silences gene production in 5′ promoters and controls cell context-specific alternate promoters in gene structures [23]. Current findings suggest that numerous genes in GO are abnormally methylated. For example, lower levels are found in dopamine receptor D4 (DRD4) and BOLL, and higher levels in cluster of differentiation 14 (CD14), myelin basic protein (MBP), angle of entrainment 1 (ANGLE1) and Ly-1 antibody reactive (LYAR) [17].

MicroRNAs (miRNAs), a family of short non-coding RNAs that control gene expression at the post-transcriptional level [24,25]and play crucial roles in regulating a broad range of biological processes, are an emerging class of epigenetic regulators [26,27]. The “epi-miRNAs” subclass of miRNAs, which targets epigenetic regulators like DNA methyltransferases (DNMTs), HDACs, or polycomb repressor complex components, has demonstrated to contribute to the epigenetic cellular landscape and represents novel tools to reverse aberrant epigenetic alterations found in various disorders [28]. Additionally, the majority of nuclear lncRNAs have been shown to act as histone modifiers that, to date, can epigenetically control the transcriptome. These lncRNAs—referred to as Epi-lncRNAs in this context—define a new paradigm of epigenetic control involved in human development and diseases [29].

1.3. RNA-based epigenetic mechanisms

Since the first known process of chromatin-dependent epigenetic control was discovered, the realm of ncRNAs has been investigated increasingly. Two of the most functionally relevant groups of ncRNAs are lncRNAs and miRNAs [30,31]. These work primarily at the post-transcriptional phase of gene expression in various biological mechanisms, creating a unique control mechanism for genome regulation [32] (Fig. 1).

MiRNAs are single-stranded RNAs commonly preserved across the evolutionary tree, although their precise quantity is even unknown due to the constant discovery of unique miRNAs [25,33,34]. According to the most recent version of the miRbase collection (http://www.mirbase.org), a repository for miRNA sequences, there were 271 species. A total of 1978 mature miRNAs were identified in *Mus musculus* (derived from 1234 precursors), whereas 2654 mature miRNAs (derived from 1917 precursors) were identified in *Homo sapiens* [32]. RNA polymerase II transcribes endogenous transcripts into lengthy dsRNA precursor transcripts known as primary-miRNA, which are then capped and polyadenylated to produce miRNAs [35–37]. Ribonuclease (RNase) III Drosha-DiGeorge Critical Region 8 (DGCR8)/Pasha nuclear complex processes miRNA precursors into smaller hairpin-shaped precursor miRNAs (pre-miRNAs) with a length of 60–100 nucleotides. In the nuclear pore, the exportin5-RanGTP pathway transports the pre-miRNA to the cytoplasm [38,39]. Using the Dicer enzyme, the unstructured miRNAs are cleaved into miRNA-miRNA* duplexes, with miRNA as the antisense (or guide/mature) strand and miRNA* as the sense (or passenger) strand. The mature strand of miRNA is put into the RNA-induced silencing complex (RISC), which consists of the Argonaute (AGO) protein, Dicer, as well as the dsRNA binding protein (TAR-RNA binding protein (TRBP) in humans). During miRNA strand loading into RISC, just a single strand binds to AGO and becomes the guide strand; the non-guided strand is cut [36,40]. The guide strand then directs the RISC compound to a target RNA with a nucleotide ordering that complements

miRNA (short nucleotide sequences at nucleotides 2–8 on the 5′ ending of miRNA normally attach to the 3′ UTR of their target RNAs). Upon binding, the mRNA is degraded, or its translation is abolished [41,42]. Around 85% of miRNA-mediated regulation in mammals is thought to be mediated by mRNA degradation [43].

LncRNAs are considered unusual epigenetic agents that may influence gene expression at particular loci. LncRNAs are a broad and varied family of transcripts transcribed and processed identically to mRNAs and generally have a length greater than 200 nucleotides. Most lncRNAs are transcribed by RNA Polymerase II (RNPol II) and go through the same splicing, polyadenylation, and 5′ capping processes as other RNAs. However, they have a modest level of expression, a smaller number of exons, and more specificity in tissues compared to mRNAs [44,45]. The processes that are responsible for the dysregulation of miRNAs have been the subject of an increasing amount of study recently. In addition to being controlled by the epigenetic machinery, microRNAs have the ability to impact the expressions of components of the epigenetic machinery by targeting enzymes linked with epigenetics. This may have a knock-on effect on the expression of other epigenetic machinery components. Epigenetic enzymes that are controlled epigenetically by microRNAs are referred to as *epi*-miRNAs. Examples of epigenetic enzymes include DNMTs, TETs, HDACs, and EZH. In recent years, there has been a growing awareness of the major role that microRNAs play in the control of epigenetic expression, which includes DNA methylation, RNA modification, and histone modification. DNMTs and TETs are the primary regulators of DNA methylation and demethylation, respectively. miRNAs have the ability to modulate the expression level of DNA methylation by exerting an influence on the expression of enzymes associated to DNA methylation. This has the effect of altering the methylation profile of the whole genome. For example, miR-29b is a member of the miR-29 family. This family of miRNAs targets DNMTs and TETs, and as a result, they have an effect on DNA methylation. In addition to DNA methyltransferases, microRNAs also have the ability to influence the modification of histones. During the process of human spermatogenesis, histone modifications such as H3K4me1, H3K27me3, H3K27ac, H3K9ac, H3K4me3, and H2AZ are controlled by microRNAs. These alterations were discovered by analysis using bioinformatics software. In particular, miR-34a controls HDAC1 expression in foam cells by binding to the 30 untranslated region (UTR) of the HDAC1 mRNA. The buildup of abnormal lipids in the foam cell was ultimately caused by overexpression of miR-34a, which, in turn, suppressed the expression of HDAC1 and elevated the acetylation levels of H3K9ac. The lncRNAs may be transcribed from promoter regions or be interleaved, intergenic regions, overlapping or antisense to annotated protein-coding genes [46]. Even though the initial genome-wide lncRNA transcript expression profile was published in 2011 [47], just a tiny percentage of it has been investigated molecularly. The Encyclopedia of DNA Elements (ENCODE) Project Consortium (GENCODE release 29) estimates that the individual genome has 16,066 lncRNA genes that encode over 29,000 different lncRNA transcripts. There are 13,002 lncRNA genes in the mouse genome (GENCODE release 20), which encode roughly 18,000 lncRNA transcripts [32]. The bulk of lncRNAs (70%) are poorly preserved between species, and just some lncRNAs, such as X-inactive specific transcript (XIST), plasmacytoma variant translocation 1 *gene (*PVT1), myocardial infarction associated transcript (MIAT), nuclear enriched abundant transcript 1 (NEAT1), metastasis associated in lung adenocarcinoma transcript 1 (MALAT1), as well as Opa-interacting *protein* 5 antisense RNA 1 (OIP5-AS), demonstrate substantial sequence conservation among species [48]. Nonetheless, lncRNA genes have greater overall sequence conservation than haphazardly chosen genomic areas [48]. LncRNAs have a wide range of functions, including chromatin change, nuclear domain organization, transcriptional management, RNA splicing, translation regulation, and protein activity modulation [49]. LncRNAs may influence the expression of one or several genes generally. The lncRNA regulates the expression of many protein-coding genes by direct or indirect processes, and these genes are likely dispersed across the genome. Therefore, examining the co-expression of lncRNA and mRNA across several biologic samples might reveal the probable targets of a specific lncRNA [32]. Furthermore, lncRNAs may act as miRNA sponges and compete for binding of miRNAs to their transcripts and therefore favorably influencing the expression of their targets [50,51].

Multiple investigations have recently shown a link between miRNAs, lncRNAs, as well as GO [17]. Each of these processes controls gene expression independently of changing the main DNA sequence; as a result, the changes are known as epigenetic alterations.

1.4. Aims of the study

In this scoping review, we aimed to highlight possible targets and processes by reviewing currently published literature and to discuss in detail the important roles of miRNAs as well as lncRNAs in the pathogenesis of GO. It should be pointed out that due to limited number of investigations on lncRNAs, our main focus is on the studies of miRNAs and GO's pathogenesis.

2. Methods

The structure of the current scoping review was proposed by Arksey and O'Malley (2005) [52] then revised and improved by Levac et al. (2010) [53]. This process comprises five unique steps: [1] identifying the research question [2], identifying relevant studies [3], study selection [4], charting the data, and [5] collating, summarizing, and reporting results. As an optional sixth stage, consultation was not employed in our research. In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist was very beneficial in conducting this review [54].

2.1. Identifying the research question

This study was based on five areas: [1] changes in expression profiles of miRNAs and lncRNAs [2], the effect of the abnormal expression of miRNAs and lncRNAs on GO onset and progression [3], miRNA-lncRNA interactions [4], miRNAs and lncRNAs molecular mechanisms, and [5] their corresponding potentials as possible biomarkers and also therapeutic targets for GO diagnosis and treatment. In order to achieve this goal, we tried to respond to the following query: What is precisely known about epigenetic changes mediated by ncRNAs in GO?

2.2. Identifying relevant studies

A limited preliminary search in PubMed and Embase was conducted. Afterward, the keywords in the titles and abstracts, besides the index terms used in the publications, were evaluated. A secondary search was carried out in PubMed, Embase, Scopus, Web of Science, and Cochrane databases (based on particular search tips for every database) with no limitations, using the keywords **Medical Subject Headings** (MeSH), or Emtree terms identified from the initial search; Fig. 2 shows the search strategies for PubMed and Embase. Furthermore, searches were conducted in 2 Gy literature databases (i.e., difficult to find or unpublished): Google Scholar and ProQuest. The last search was undertaken on February 17, 2022. In addition, we looked through the references of related literature as well as review papers for additional resources.

2.3. Selecting studies

On the one hand, in terms of inclusion criteria [1], the papers specifically discussing the changes in miRNAs and lncRNAs expression in GO and [2] published in English were included in this study. On the other hand, exclusion criteria were defined as [1] non-original research [2], papers with inadequate data, and [3] the ones authored in

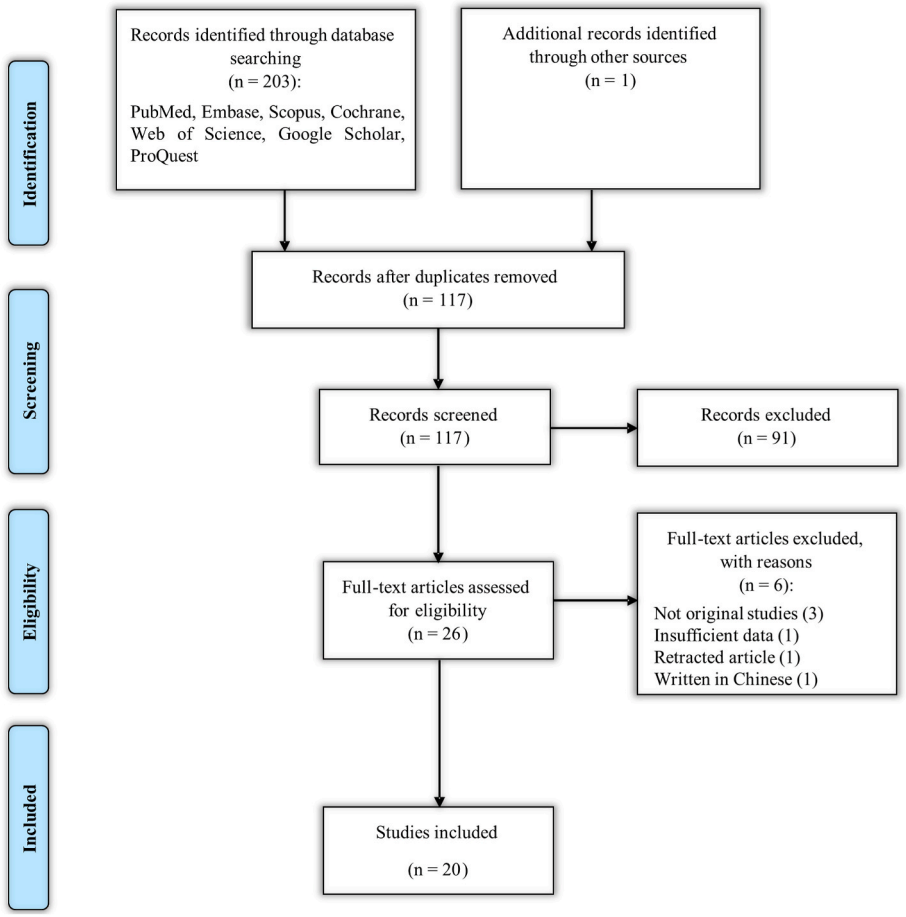

Fig. 2. Search strategy flow chart based on the PRISMA flow diagram.

non-English. The titles and abstracts of papers were separately evaluated for eligibility using the aforementioned criteria by two reviewers. The remaining papers' full texts were reviewed, and those that met the eligibility were included in the final data analyses. Further, any conflicts were resolved by discussion or, if necessary, with the assistance of a third reviewer.

2.4. Charting the data

Independently, two reviewers extracted data and then put them into charts (pre-designed), using Microsoft Excel software, presenting details about the first author, year of publication, origin, type of study, cell line (s), human samples, number of patients, methods, expression levels, and key findings.

2.5. Collating, summarizing, and reporting the results

Quantitative and qualitative analyses were carried out. In terms of quantitative investigations, a descriptive numerical overview of the properties of the included papers was presented. Regarding the latter one, we gave a narrative review of current data responding to our previously specified research question, with an emphasis on the significance of results in the larger context as recommended by Levac et al. [53].

3. Results

3.1. Search results

The flow chart in Fig. 2 depicts the various stages involved in identifying eligible studies. There were 203 articles detected from various sources, of which 86 were duplicates. A total of 91 items were excluded due to their irrelevance. The remaining 26 full texts were assessed, and six further articles were removed because three were not original studies [55–57], one lacked sufficient data [58], one was retracted [59], and another was in Chinese [58]. Finally, a total of 20 eligible articles remained [60–79].

3.2. Study characteristics

Table 1 summarizes the features of the selected studies. The papers were published between 2014 and 2022. The majority of the research was conducted in China. Fig. 3a depicts the origin's comprehensive details. Case-control and cell culture design was utilized in nine studies [63–66,68,69,71,75,79], the case-control design was used in seven studies [60,61,72,74,76–78], cell culture design was used in three studies [62,67,73], and case-control, cell culture, and animal model design were utilized in one research [70] (Fig. 3b). Different cell lines, animal models, and human samples were utilized. In Eighteen investigations, 275 patients with GO have been documented. Seventeen of the included papers used bioinformatics and diverse experimental methodologies to assess miRNAs, and three studies examined lncRNAs or lncRNA-miRNA interaction. Table 1 summarizes the observed ncRNA expression levels and their related potential mechanisms of action in GO pathogenesis. Among the ncRNAs implicated in inflammatory regulation was miR-146a [80,81], LPAL2/miR-1287–5p axis, LINC01820:13/has-miR-27b-3p axis, and ENST00000499452/hsa-miR-27a-3p axis (Fig. 4a). MiR-146a, miR-183, and miR-96 were all implicated in T cell function regulation (Fig. 4b). Glycosaminoglycan aggregation and fibrosis were regulated by miR-146a and miR-21 (Fig. 4c). According to one research, miR-224–5p was linked

Table 1
Characteristics of studies included in the scoping review.

First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
Wei et al.	2014	China	Case-control	NA	NA	Serum and plasma	57 subjects (15 GD without ophthalmopathy, 14 active GO, 13 inactive GO, and 15 healthy control)	qRT-PCR and ELISA	miR-146a	NA	Downregulation	Throughout GD, inactive-GO, and active-GO groups, serum IL-17 concentrations were considerably greater than those of control. An elevated concentration of IL-17 was found in the active GO group compared to the inactive GO and GD groups. MiR-146a in the active-GO and inactive-GO groups were dramatically downregulated compared to the control group. miR-146a levels were considerably lower in the active-GO group compared to the inactive-GO group. Among GO patients, serum concentrations of IL-17 and miR-146a were both shown to be strongly linked with the presence of CAS. The expression of miR-146a in the bloodstream was negatively correlated with the concentration of IL-17. These results suggest that miR-146a and IL-17 concentrations in the bloodstream may serve as biomarkers for active GO and may serve a critical role in the development of the disease.
Tong et al.	2015	China	Case-control and cell culture	Orbital fibroblasts	NA	Orbital tissues	36 subjects (26 GO and 10 control)	Real-time PCR, western blot, transfection of miRNAs and siRNA, TGF-β1 treatment, cell proliferation, cell apoptosis, and measurement of collagen content	miR-21	NA	Upregulation	When comparing donors with and without GO, the expression of miR-21 throughout orbital fibroblasts from GO was greater. Additionally, throughout GO orbital fibroblasts, it was discovered that miR-21 increased proliferation,

(*continued on next page*)

Table 1 (*continued*)

First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												reduced apoptosis, and stimulated differentiation. Furthermore, it was demonstrated that TGF-β1 promoted the transcription of miR-21 in a time- and dose-dependent mechanism. The mRNA expression of collagen I and total collagen synthesis triggered by TGF-β1 were also increased by miR-21. The TGF-β1/Smad mechanism was also stimulated by miR-21, which increased phosphorylated Smad3. Orbital muscle fibrosis and miR-21 expression are predicted to be closely linked in this study. This suggests a new therapeutic target for GO.
Shen et al.	2015	China	Case-control and cell culture	Ocular fibroblasts and 293T cells	NA	Serum	35 patients (14 responsive, 4 partial responsive, and 17 resistant to glucocorticoid therapy)	MiScript PCR array, real-time PCR, DNA constructs, luciferase assay, and western blot	hsa-miR-155–5p, hsa-miR-224–5p, hsa-miR-21–5p, hsa-miR-26b-5p, hsa-miR-192–5p, hsa-miR-100–5p, hsa-miR-26a-5p, hsa-miR-222–3p, hsa-miR-15a-5p	NA	hsa-miR-155–5p, hsa-miR-224–5p, hsa-miR-21–5p, hsa-miR-26b-5p, hsa-miR-192–5p, hsa-miR-100–5p, hsa-miR-26a-5p, hsa-miR-222–3p (upregulation), hsa-miR-15a-5p (downregulation)	Arrays of miScript PCR revealed variations in nine miRNAs between participants who were responsive and those who were unresponsive. MiR-224–5p serum levels were significantly lower throughout resistant patients after verification of the top two miRNAs in all 35 participants. Transrepression of the NF-κB reporter by dexamethasone was restored by upregulation of miR-224–5p, which may have been achieved by targeting GSK-3β to enhance glucocorticoid receptor levels. In vitro upregulation of miR-224–5p renewed glucocorticoid responsiveness in a resistant cell model in

(*continued on next page*)

Table 1 (*continued*)

First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												this study, which illustrated that baseline serum level of miR-224–5p was linked with this responsiveness.
Jang et al.	2016	Korea	Case-control and cell culture	Orbital fibroblasts	NA	Orbital adipose/ connective tissue	36 subjects (19 GO and 17 age- and sex-matched control)	Microarray analysis, quantitative real-time PCR, transfection, ELISA, and western blotting	hsa-miR-155–5p, hsa-miR-106b-5p, hsa-miR-126–3p, hsa-miR-130a-3p, hsa-miR-143–3p, hsa-miR-195–5p, hsa-miR-146a-5p, hsa-miR-15a-5p, hsa-miR-16–5p, hsa-miR-452–5p, hsa-miR-130b-3p, hsa-miR-146b-5p, hsa-miR-106a-5p, hsa-miR-17–5p, hsa-miR-184, hsa-miR-198, hsa-miR-4443, hsa-miR-25–3p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-363–3p, hsa-miR-148b-3p, hsa-miR-432–5p, hsa-miR-4324, hsa-miR-27b-5p, hsa-miR-29b-1-5p, hsa-miR-30e-3p, hsa-miR-584–5p, hsa-miR-224–5p, hsa-miR-34a-5p, hsa-miR-3197, hsa-miR-1972, hsa-miR-3131, hsa-miR-3064–5p, hsa-miR-711, hsa-miR-4769–5p, hsa-miR-4484, hsa-miR-451a, hsa-miR-3195, hsa-miR-4423–3p, hsa-miR-331–3p, hsa-miR-378h, hsa-miR-371b-5p, hsa-miR-572, hsa-miR-602	NA	hsa-miR-155–5p, hsa-miR-106b-5p, hsa-miR-126–3p, hsa-miR-130a-3p, hsa-miR-143–3p, hsa-miR-195–5p, hsa-miR-146a-5p, hsa-miR-15a-5p, hsa-miR-16–5p, hsa-miR-452–5p, hsa-miR-130b-3p, hsa-miR-146b-5p, hsa-miR-106a-5p, hsa-miR-17–5p, hsa-miR-184, hsa-miR-198, hsa-miR-4443, hsa-miR-25–3p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-363–3p, hsa-miR-148b-3p, hsa-miR-432–5p, hsa-miR-4324, hsa-miR-27b-5p, hsa-miR-29b-1-5p, hsa-miR-30e-3p, hsa-miR-584–5p, hsa-miR-224–5p, hsa-miR-34a-5p, hsa-miR-3197, hsa-miR-1972, hsa-miR-3131, hsa-miR-3064–5p, hsa-miR-711, hsa-miR-4769–5p, hsa-miR-4484, hsa-miR-451a (upregulation), hsa-miR-3195, hsa-miR-4423–3p, hsa-miR-331–3p, hsa-miR-378h, hsa-miR-371b-5p, hsa-miR-572, hsa-miR-602 (downregulation)	When comparing GO patients to healthy controls, microarray analysis in orbital connective tissue from GO individuals revealed that expression of 38 miRNAs was increased, and seven miRNAs were decreased. MiR-146a, one of the overexpressed miRNAs, was found to be dramatically higher in GO orbital adipose tissue compared to non-GO. A time and concentration-dependent upregulation in miR-146a was observed as a result of IL-1β. NF-κB, JNK-1/2, and PI3K inhibitors significantly reduced IL-1β-induced increases in miR-146a transcription. MiR-146a mimics, but not miR-146a inhibitors, further reduced IL-1β-induced IL-6 protein synthesis. Among orbital fibroblasts, miR-146a may be involved in the control of the inflammatory response and the pathophysiology of GO.
Lee et al.	2016	Korea	Cell culture	Orbital fibroblasts	NA	NA	4 GO patients	Cell proliferation assay, transfection, western blot, and qRT-PCR	miR-21	NA	Upregulation	Proliferation is increased in human orbital fibroblasts by PDGF-BB, which suppresses PDCD4 transcription by

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Table 1 (*continued*)

First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												upregulating miR-21. According to these findings, PDGF-BB seems to drive cell proliferation via miR-21-mediated PDCD4 downregulation, which culminates in the establishment of GO.
Hu et al.	2017	China	Case-control and cell culture	$CD4^+$ T cells	NA	Peripheral venous blood	12 subjects (6 GO and 6 age- and sex-matched control)	Cell transfection, qRT-PCR, miRNA target prediction, plasmid construction, double luciferase reporter assay, and western blot	miR-146a	NA	Downregulation	When GO patients were in the active phase, the transcription of miR-146a was shown to be decreased in their $CD4^+$ T cells. Additionally, it was discovered that miR-146a could target NUMB in $CD4^+$ T cells from individuals with GO. The ocular inflammatory response in active GO is exacerbated by the downregulation of miR-146a in $CD4^+$ T cell types through NUMB targeting.
Yang et al.	2017	China	Case-control and cell culture	$CD4^+$ T cells and Jurkat cells	NA	PBMCs	40 subjects (20 GO and 20 age- and sex-matched control)	Cell transfection, cell cycle and apoptosis determination, qRT-PCR, and cytokine assays	miR-146a	NA	Downregulation	GO patients had decreased levels of miR-146a in their PBMCs and T cells. Th1 differentiation and multiplication of T-lymphocytes were suppressed by miR-146a. Findings from this study demonstrated the importance of dysregulated miR-146a in the pathogenesis of GO by showing that it was a potent inhibitor of human Th1 differentiation and T cell multiplication.
Jang et al.	2018	Korea	Case-control and cell culture	Orbital fibroblast	NA	Orbital adipose/ connective tissue	12 patients (9 patients with GO and 3 patients with non-GO)	Transfection, qrt-pcr, and western blotting	miR-146a	NA	Upregulation	Time and concentration-dependent increases in miR-146a transcription were seen in orbital fibroblasts from individuals with GO, as shown by TGF-β treatment. TGF-β

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												induced fibronectin, collagen Iα, and α-smooth muscle actin protein synthesis is further reduced by miR-146a mimics. MiR-146a mimics reduced Smad4 and TRAF6 proteins considerably relative to controls. They rose dramatically in comparison to control when miR-146a production was inhibited. During the generation of TGF-β induced fibrotic markers, miR-146a acts as a negative modulator. Hence, the modulation of fibrosis in orbital fibroblasts from individuals experiencing GO may be influenced by miR-146a.
Zhang et al.	2018	United Kingdom	Case-control	NA	NA	Plasma	46 subjects (19 GO, 14 GD, and 13 healthy control)	microRNA sequencing and bioinformatics	Novel:19_15038, Novel:hsa-miR-22–3p, Novel:hsa-miR-27a-3p, Novel:4_29251, Novel:hsa-miR-182–5p, Novel:hsa-miR-1266–3p, Novel:hsa-miR-6748–3p, Novel:hsa-miR-8069, hsa-mir-320b-1, hsa-mir-320b-2, hsa-mir-497, Novel:hsa-miR-4254, hsa-mir-10b, Novel:7_36289, Novel:1_16536, Novel:hsa-miR-612, Novel:12_6007, hsa-mir-371a, Novel: hsa-miR-4731–3p, Novel:hsa-miR-4512, hsa-mir-99a, hsa-mir-10a, hsa-mir-215, hsa-mir-141, hsa-mir-320c-2, hsa-mir-6131, hsa-mir-885	NA	Novel:19_15038, Novel:hsa-miR-27a-3p, Novel:4_29251, Novel:hsa-miR-182–5p, Novel:hsa-miR-1266–3p, Novel: hsa-miR-6748–3p, hsa-mir-320b-1, hsa-mir-320b-2, hsa-mir-497, Novel:hsa-miR-4254, hsa-mir-10b, Novel:7_36289, Novel:1_16536, Novel:hsa-miR-612, Novel:12_6007, Novel:hsa-miR-4731–3p, hsa-mir-99a, hsa-mir-10a, hsa-mir-215, hsa-mir-320c-2, hsa-mir-6131, hsa-mir-885 (upregulation), Novel:hsa-miR-22–3p, Novel:hsa-miR-8069, hsa-mir-371a, Novel:hsa-miR-4512, hsa-mir-141 (downregulation)	Differential expression of 27 miRNAs was found among GD, GO, and controls (12 identified and 15 new). Novel:19 15038 and Novel:hsa-miR-27a-3p were the top recognized and innovative miRNAs that were upregulated in GO, whereas Novel:hsa-miR-22–3p was downregulated during GO. Novel:19 15038, Novel:hsa-miR-182–5p, Novel:hsa-miR-22–3p, Novel:hsa-miR-27a-3p, and Novel:hsa-miR-6748–3p are among the five miRNAs discovered using a predictive models. Hippo signaling, bacterial penetration of epithelial cells, and mRNA monitoring are associated metabolic

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												processes discovered by functional analysis.
Martínez-Hernández et al.	2018	Spain	Case-control	NA	NA	Serum	34 subjects (12 GD with GO and 22 healthy control)	miRNA NGS and qRT-PCR	miR-Let7d-5p, miR-96–5p, and miR-301a-3p	NA	miR-Let7d-5p (downregulation), miR-96–5p, and miR-301a-3p (upregulation)	It has been shown that miR-Let7d-5p, miR-96–5p, and miR-301a-3p expression is linked to more severe illness symptoms such as active ophthalmopathy. According to the results of this study, three serum miRNAs have been shown to be associated with a poorer clinical description in GO patients.
Jang et al.	2019	Korea	Case-control and cell culture	Orbital fibroblast	NA	Orbital adipose tissue	21 subjects (13 GO and 8 non-GO)	Cell transfection, qRT-PCR, western blotting, and Oil Red O staining	miR-27a and miR-27b	NA	Downregulation	The miR-27a and miR-27b concentrations in orbital fat tissues decreased much more in GO individuals than in non-GO participants. When adipogenic differentiation was induced in orbital fibroblasts, the transcription of miR-27a and miR-27b was at its greatest on day 0 and steadily decreased after that. A reduction in PPARγ, C/EBPα, and C/EBPβ transcription as well as compared to negative controls a decline in Oil Red O-stained lipid droplets were seen in GO orbital fibroblasts transfected with miR-27a and miR-27b mimics. MiR-27a and miR-27b were shown to prevent adipogenesis in orbital fibroblasts from GO participants, based on these findings.
Thiel et al.	2019	Germany	Case-control, animal study, and cell culture	Murine $CD8^+$ and $CD4^+CD25^-$ T cells, and human $CD4^+$ and $CD8^+$ T cells	TCR-HA/Thy.1.1 transgenic mice	Peripheral blood	NR	Transduction, antagomiR treatment, proliferation, flow cytometry, luciferase assay, qRT-PCR, and adoptive transfer	miR-183 and miR-96	NA	Upregulation	After being activated in vitro, the levels of miR-183 and miR-96 in the $CD4^+$ T cells of individuals with GO and in human and mouse T cells were found to be

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												elevated. It was discovered that miR-183 and miR-96 target EGR-1 utilizing Luciferase-based binding analyses. Retroviral gene transfer increased the phosphorylation of Akt and lowered the levels of EGR-1 and PTEN in murine $CD4^+$ T cells overexpressing miR-183 and miR-96. The treatment of murine $CD4^+$ T cells with particular antagomiRs, on the other hand, resulted in increased EGR-1 and PTEN transcription, as well as a reduction in proliferative capacity when the cells were stimulated in vitro. AntagomiR-treated T cells prevented the initiation of diabetes, but a selective transfer of miR-183/96 overexpressing antigen-specific T cells into INS-HA/Rag2KO mice increased the progression of the autoimmune state of this disease. Using these outcomes, it was shown that the capacity of T cell stimulation could be controlled by miR-183 and miR-96. This means that the advancement and severity of T cell-based autoimmune diseases can be controlled by these two RNAs.
Woeller et al.	2019	United States	Cell culture	Primary human orbital fibroblast	NA	NA	NA	Cell proliferation assay, gene expression knockdown using siRNA, introduction of miRNA mimics, qRT-PCR, western blot	miR-146a and miR-155	NA	Upregulation	TSHR signaling increases multiplication of GO orbital fibroblasts directly via PI3K/Akt signaling and indirectly via upregulation of miR-

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												146a and miR-155. By inhibiting the expression of target genes (ZNRF3 and PTEN) that typically inhibit cell multiplication, miR-146a and miR-155 promote the proliferation of GO orbital fibroblasts. The fibroproliferative pathogenesis seen in GO may be explained in part by the transcription of miR-146a and miR-155 regulated by TSHR.
Al-Heety and Al-Hadithi	2020	Iraq	Case-control	NA	NA	Peripheral blood	80 subjects (30 patients with orbitopathy, 10 patients without orbitopathy, and 40 age-matched controls)	ELISA and qRT-PCR	miR-21–5p	NA	Upregulation	When comparing patients with and without orbitopathy, there is a substantial difference in the level of circulatory miR-21–5p transcription. A correlation between concentrations of TSH, FT3, FT4, and TSHR-Abs and miR-21–5p was shown to be statistically significant. All patient groups showed an increase in the expression of miR-21–5p, which indicates that it may be used to diagnose GO and its development to orbitopathy and that miR-21–5p is an essential biological target for treatment.
Liu et al.	2020	China	Case-control and cell culture	Orbital fibroblasts	NA	Orbital connective tissue	10 subjects (6 patients with inactive GO and 4 non-GO patients)	Immunohistochemistry, qRT-PCR, ELISA	miR-146a	NA	NR	In GO orbital fibroblasts, upregulation of miR-146a decreased while suppressing miR-146a enhanced the synthesis of hyaluronic acid and collagen I. To summarize, in GO orbital fibroblasts in vitro, miR146a inhibited the production of hyaluronic acid and

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												collagen I, triggering glycosaminoglycan accumulation and collagen sedimentation in GO.
Hammond et al.	2021	United States	Cell culture	Thy1+ and Thy1- orbital fibroblasts	NA	NA	12 subjects (8 GO patients and 4 non-GO patients)	Real-time quantitative PCR, luciferase reporter assays, transfection, AdipoRed assay, western blot, fluorescent staining, and gene expression knockdown using small interfering RNA	miR-130a	NA	Upregulation	MiR-130a concentrations rise in GO whenever Thy1- orbital fibroblasts aggregate, resulting in a reduction in AMPK function. An increase in orbital fatty tissue is caused by reduced AMPK activation, which encourages lipid storage in fibroblasts.
Wu et al.	2021	China	Case-control	NA	NA	Orbital adipose/ connective tissues	16 subjects (8 GO patients and 8 normal control)	RNA sequencing, bioinformatics, and qRT-PCR	NA	With the cut-off thresholds of $p < 0.05$ and $\log2\|\text{fold change}\| > 1$, there were 809 differentially expressed lncRNAs	374 up-regulated and 435 down-regulated	There were 809 lncRNAs and 607 mRNAs found to be differentially expressed. It was shown that orbital adipose/ connective tissue lncRNAs might govern extracellular matrix reformation using co-expression network evaluation. It was also possible to identify the lncRNAs' target genes, including those involved in lipid metabolism and cytokine-cytokine-receptor interactions. In the orbital adipose/ connective tissue of GO, these findings may offer possible regulatory pathways for lncRNAs.
Yue et al.	2021	China	Case-control	NA	NA	Orbital adipose/ connective tissues	10 subjects (5 GO patients and 5 control)	Microarray sequencing, bioinformatics, and qPCR	NA	242 lncRNAs were differentially expressed between the GO group and the normal group according to the criteria of an $FC > 2$ and $p < 0.05$.	97 up-regulated and 145 down-regulated	CeRNA networks have been developed using the 361 mRNA and 242 lncRNA differently expressed among GO patients relative to healthy controls. The qPCR findings revealed that between GO and control participants, four mRNAs (THBS2, CHRM3, CXCL1, and FPR2) and two lncRNAs

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												(LINC01820:13, ENST00000499452) were differentially expressed. The LINC01820:13-hsa-miR-27b-3p-FPR2 and the ENST00000499452-hsa-miR-27b-3p-CXCL1 ceRNA were found as two key ceRNA axes, influencing the GO patient's autoimmune response and inflammatory processes.
Wang et al.	2021	China	Case-control and cell culture	Orbital fibroblasts	NA	Orbital tissues	24 subjects (12 GO and 12 control)	Cell transfection, PCR-based analyses, immunoblotting, immunofluorescence assay, 5-ethoxy 2-deoxyuridine assays, colony-formation assays, ELISA, microarray profiling, luciferase reporter assay, radioimmunoprecipitation assays and RNA pull down assays, and immunohistochemical staining	miR-1287–5p	LPAL2	LPAL2 (upregulation), miR-1287–5p (downregulation)	Cell adhesion signaling components differently expressed throughout GO organs, such as ICAM-1, ICAM-4, vascular cell adhesion molecule, and CD44, were all elevated in damaged orbital organs, according to bioinformatics results. Between the two sets of analysis, 55 lncRNAs were statistically different between GO and non-GO specimens in terms of expression. A favorable correlation was found between the lncRNAs DNM3OS, PRRT3-AS1, and LPAL2, as well as the four main signaling components of focal adhesions. Within the GO orbital organs, the lncRNA LPAL2 showed the greatest upregulation. The transcription of ICAM-1, ICAM-4, and LPAL2 in the GO orbital fibroblasts was dramatically enhanced after activation with TGF-β1. TGF-β1-induced elevations in cell adhesion factor concentrations and stimulation of orbital fibroblasts were

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First author	Year of publication	Origin	Type of study	Cell line(s)	Animal model	Human samples	Number of patients	Methods	miRNA	lncRNA	Expression level	Key findings
												reduced when LPAL2 was knocked down in these cells.
												GO and healthy ocular organs were subjected to microarray analysis in order to discover miRNAs that were differentially expressed. MiR-1287–5p was found to be significantly downregulated in disordered orbital specimens. LPAL2 controlled EGFR/Akt signaling by targeting miR-1287–5p, which was directly linked to the EGFR 3′ untranslated sequence and LPAL2.
Craps et al.	2022	Belgium	Case-control	NA	NA	Orbital adipose tissues	20 subjects (16 GO patients and 4 control)	microRNA reverse transcription, qRT-PCR, western blot, immunohistochemistry, and in situ hybridization	miR-199a	NA	Downregulation	VEGF-A overexpression and HIF-1 stabilization were shown to be associated with increased NOX4 levels in GO orbital fats. Intriguingly, miR-199a-3p/-5p was found to be downregulated in GO orbital fats. According to the findings, a transcription factor identified to inhibit miR-199a production, STAT-3, was shown to be activated in GO orbital fats. One of the most critical players in GO was NOX4/HIF-1/VEGF-A. GD thyroids and GO orbital fats are both thought to be driven by the same activator, miR-199a, which is regulated by the transcription factor STAT-3.

Abbreviations.

Akt, protein kinase B; CAS, clinical activity score; ELISA, enzyme-linked immunosorbent assay; GD, Grave's disease; GO, Grave's ophthalmopathy; NA, not available; NGS, next generation sequencing; NR, not reported; PBMCs, peripheral blood mononuclear cells; qRT-PCR, quantitative reverse transcription PCR; qPCR, quantitative PCR; thyroid-stimulating hormone receptor, TSHR.

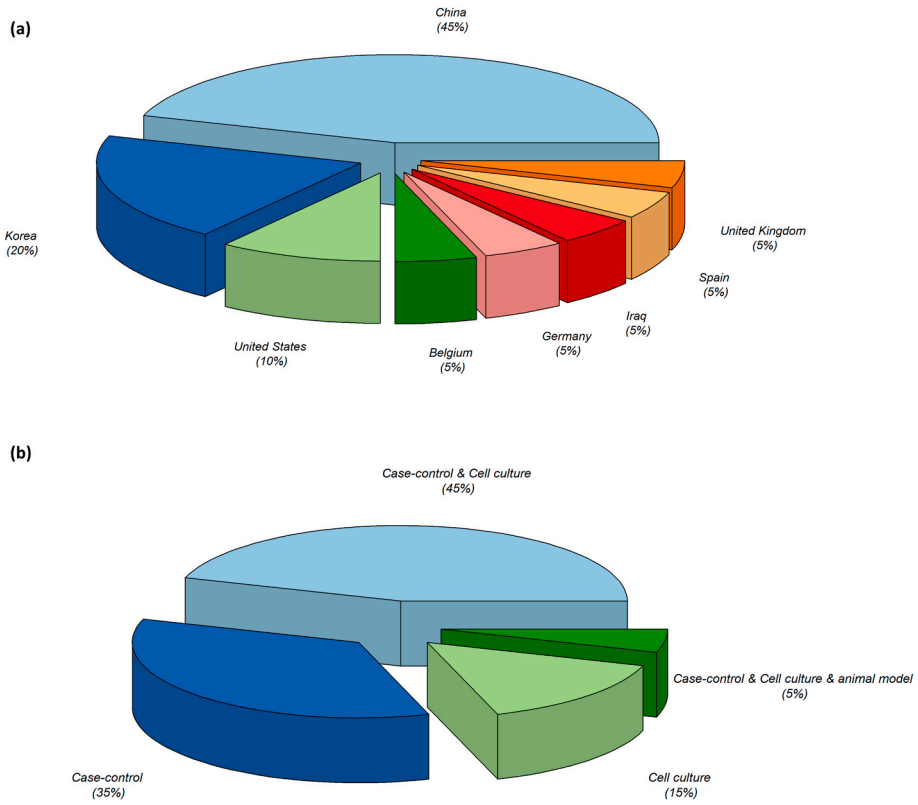

Fig. 3. Details of **(a)** origin and **(b)** study design of included articles.

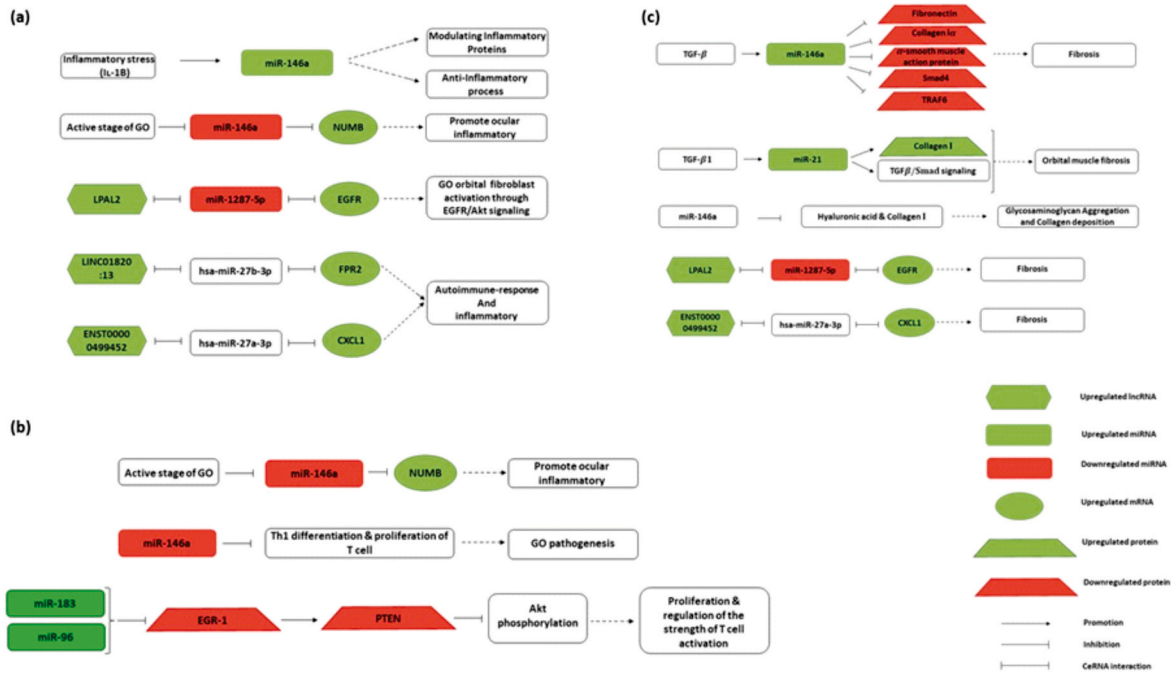

Fig. 4. Role of non-coding RNAs (ncRNAs) in Graves' ophthalmopathy pathogenesis. NcRNAs expression pattern and their corresponding mechanisms in **(a)** inflammatory process, **(b)** regulation of T cell functions, and **(c)** glycosaminoglycan aggregation and fibrosis.

to glucocorticoid sensitivity in GO (Fig. 5a). MiR-27a, miR-27b, and miR-130a were described as ncRNAs associated with lipid accumulation and adipogenesis (Fig. 5b). Another dysregulated miRNA in GO was miR-199a, which led to oxidative stress and angiogenesis (Fig. 5c). Additionally, miR-21, miR-146a, and miR-155 were implicated in the proliferation of OFs (Fig. 5d). Additionally, five research evaluated the potential utility of miR-146a, miR-224–5p, Novel:19_15038, Novel: hsa-miR-182–5p, Novel:hsa-miR-22–3p, Novel:hsa-miR-27a-3p, Novel: hsa-miR-6748–3p, miR-Let7d-5p, miR-96–5p, and miR-301a-3p, and miR-21–5p as biomarkers.

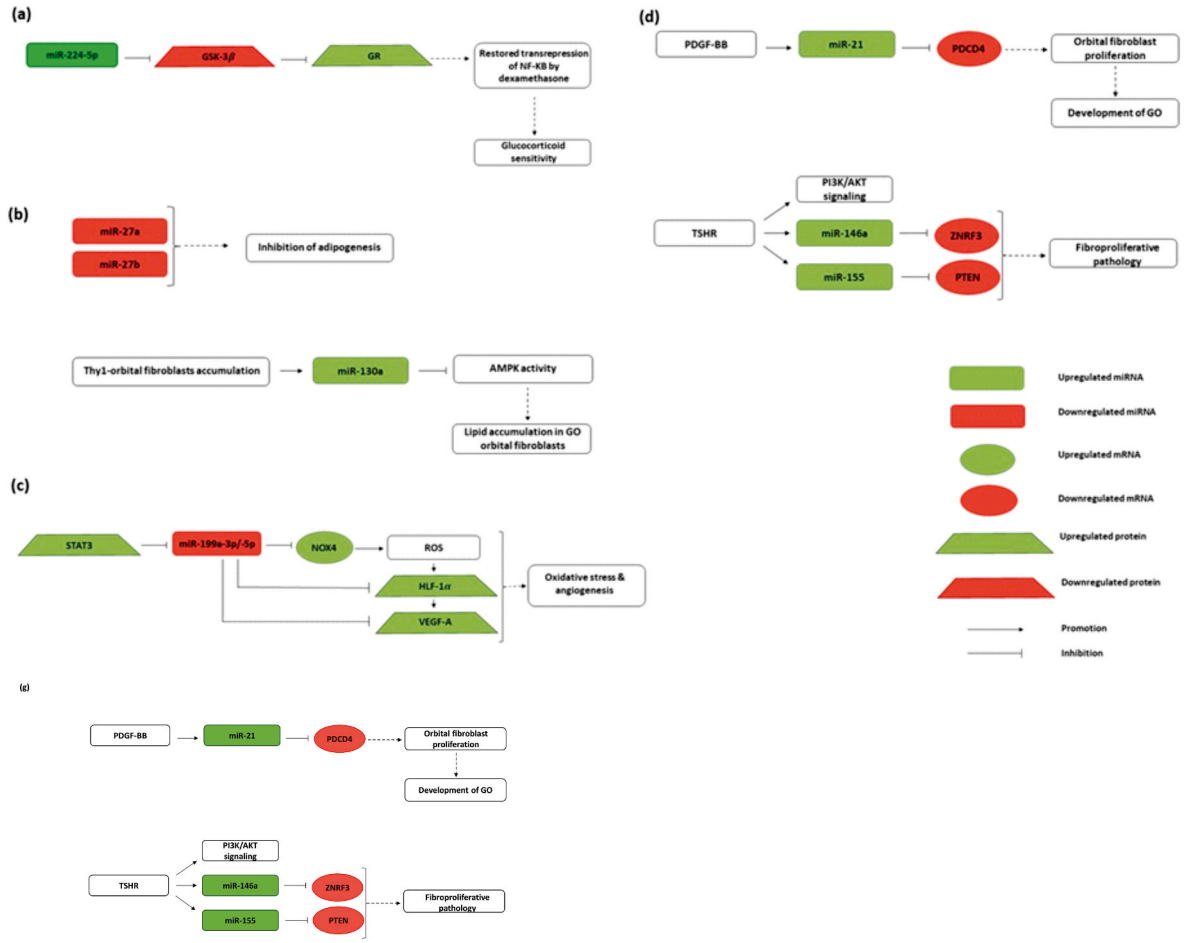

Fig. 5. Role of non-coding RNAs (ncRNAs) in Graves' ophthalmopathy pathogenesis. NcRNAs expression pattern and their corresponding mechanisms in **(a)** glucocorticoid insensitivity, **(b)** lipid accumulation and adipogenesis, **(c)** oxidative stress and angiogenesis, and **(d)** proliferation of fibroblasts.

4. Discussion

As an autoimmune disease, GO has not been thoroughly recognized, particularly in terms of its pathophysiology, which is unknown yet. Epigenetics is hypothesized to engage in the prevalence, development, and consequence of GO. Based on the findings, ncRNAs have contributory roles in GO through a variety of ways, including etiology, clinical characteristics, as well as therapeutic outcomes. These results are addressed in more detail below. It is worth mentioning that focusing on miRNAs was our priority because of limited number of studies investigating on lncRNAs in the pathogenesis of GO.

4.1. Role of lncRNAs, miRNAs, and their interactions in the inflammatory process

MiR-146a likely might contribute to GO development via influencing the expression of inflammatory proteins (like intercellular adhesion molecule-1 (ICAM-1) and interleukin-6 (IL-6)) as well as cellular activities in OFs [64]. Among inflammatory autoimmune diseases, miR-146 is rather considered a well-recognized miRNA [82,83]. Inflammatory stress factors, like interleukin-1 beta (IL-1β), lead to the upregulation of miR-146a. The findings demonstrate that miR-146a has a favorable influence on anti-inflammatory processes in GO [64]. Another research on GO individuals throughout the active phase discovered that the expression level of miR-146a faced downregulation in T helper (CD4+T) cells [63]. Moreover, miR-146a may target NUMB, and the reduced miR-146a within CD4+T cells induces ocular inflammation via affecting NUMB in active GO [63]. MiR-146a has been implicated in the pathophysiology of various autoimmune diseases, including Sjögren's syndrome [84], rheumatoid arthritis [85,86], osteoarthritis [87], and systemic lupus erythematosus [88]. NUMB is a protein containing a tyrosine-binding domain that is attached to the cell membrane [89]. In living organisms, this protein is considered one of the essential cell fate determinants. NUMB also has a wide distribution in mature tissues, where it plays a vital role in balancing various key physiological processes, including differentiation/proliferation, tissue regeneration, cell migration, apoptosis control, and other processes [89].

Salmena et al. (2011) hypothesized a novel mechanism for RNA interactions, termed competing endogenous RNA (ceRNA) [90]. This theory proposes that cross-talk between RNAs, coding and ncRNAs (like circRNAs, lncRNAs, and pseudogenes), via miRNA complementary sequences known as miRNA response elements, causes a massive regulatory network across the transcriptome. According to the ceRNA theory, assuming two RNA transcripts control each other through a ceRNA-mediated pathway, the expressions of the two RNA transcripts might be negatively connected with the target miRNAs levels and positively linked with each other [90]. The lncRNA-associated ceRNA axes have been implicated in various diseases, such as Alzheimer's disease [91,92], cancer [93], autism spectrum disorder [94], schizophrenia [94,95], myasthenia gravis [96], and autoimmune diseases [91,97–99]. Based on the findings, the lncRNA LPAL2/miR-1287–5p/epidermal growth factor receptor (EGFR) ceRNA axis controls the activation of OFs derived from GO patients via cell adhesion factors [71]. The activation of OFs, which are the primary target cells in GO, is critical to the pathophysiology of the disease [100,101]. OFs release cytokines like interleukin-1 alpha (IL-1 α), IL-1β, and IL-6 [102] as well as strong

monocyte chemoattractants like IL-8, RANTES (regulated on activation, normal T cell expressed, and secreted), and interleukin-16 (IL-16) [103,104] following activation by growth factors, inflammatory mediators, and stimulatory autoantibodies directed against thyrotropin. This results in increased chemotaxis of lymphocytes through the orbit and a dysregulated inflammatory response [105–107]. It was shown that Lipoprotein(A) Like 2 (LPAL2) sponged miR-1287–5p to raise the amounts of adhesion molecules, hence improving the activation of OFs in GO via miR-1287–5p downstream EGFR/protein kinase B (Akt) signaling [71]. MiR-1287–5p has been linked to the development of numerous malignancies. MiR-1287–5p enhances the proliferation and invasion of non–small cell lung cancer cells by targeting G antigen 1 [71]. MiR-1287–5p might decrease colorectal cancer proliferative and migratory activities by targeting Y-box binding protein 1 [108]. Notably, transforming growth factor (TGF)α-/EGFR interaction apparently promotes Phosphatidylinositol-3-kinase (PI3K)/Akt signaling, which then promotes nuclear factor κB (NF-κB), resulting in ICAM-1 production and stimulation of human osteogenic sarcoma cells' ability to migrate [109]. Changes in the lncRNAs and/or miRNAs expression have recently been found to impact the translation and stability of genes playing roles in the fibroblast activation process in the kidney [110], liver [111], lung [110,112], and heart [113,114]. Other ceRNA axes proposed to engage in inflammation and autoimmune response were LINC01820:13/has-miR-27b-3p/formyl peptide receptor 2 (FPR2) and the ENST00000499452/hsa-miR-27a-3p/C-X-C Motif Chemokine Ligand 1 (CXCL1) [76]. Depending on the regulatory activity of FPR2 and miR-27b, as well as the ceRNA's action mechanism, it was hypothesized that LINC01820:13 decreases miR-27b′s inhibitory effect on FPR2 by binding to the RISC of miR-27b (in a competitive manner), thereby upregulating FPR2 expression and leading to inflammation and autoimmune responses in patients with GO [76]. Also, ENST00000499452 competitively suppresses miR-27a via the same mechanism, hence reducing its inhibitory impact on CXCL1 and boosting the immunological and inflammatory responses in the patients [76]. CXCL1 may activate angiotensin II, causing cardiac hypertrophy, inflammation, and fibrosis. CXCL1 can control the activation process of fibroblasts and upregulation of pro-inflammatory factors in head and neck squamous cell carcinoma tissues [115,116]. FPR2 is essential in inflammatory disorders and regulating host immunity, and activating its corresponding signaling pathway can result in an imbalance in host immune responses and inflammation. FPR2 is implicated in a number of disorders, including bacterial infections, inflammation, cancer, asthma, and Alzheimer's disease [117,118]. The precise involvement of these RNAs in GO pathophysiology and the presence of an obvious targeting effect between LINC01820:13, hsa-miR-27b-3p, and FPR2 and between ENST00000499452, hsa-miR-27b-3p, and CXCL1 remain unknown.

RNA sequencing was used in a study to identify the lncRNAs and mRNAs profiles in the orbital adipose or connective tissue in GO [74]. There were 607 differential mRNAs and 809 differential lncRNAs detected, with 52 genes shown to be strongly connected to the extracellular matrix. According to a co-expression network study, lncRNAs may influence the remodeling process of the extracellular matrix in orbital adipose/connective tissue in GO. Furthermore, the lncRNAs target genes implicated in the cytokine-cytokine receptor interaction were uncovered [74]. Gene co-expression networks could be employed to link unknown genes to biological processes, to give priority to potential disease genes, or to identify transcriptional regulatory programs [119]. Thanks to recent breakthroughs in transcriptomics and next-generation sequencing, co-expression networks built from RNA sequencing may now extrapolate roles and disease connections for non-coding genes and splice variants. While gene co-expression networks often give no data on causality, new approaches for differential co-expression analysis allow finding regulatory genes driving distinct diseases [119].

4.2. Role of miRNAs in the regulation of T cell functions

The findings regarded miR-146a as a potent inhibitor for T-helper 1 (Th1) differentiation and cellular proliferation in CD4+T cells, and its dysregulation contributed to GO pathogenesis [75]. Furthermore, as previously stated, miR-146a might target NUMB; in CD4+T cells, reduced levels of miR-146a enhances ocular inflammation in the active status of GO through targeting NUMB [63]. CD4+T cells participate in proliferative and immunological responses, both of which are critical in GO incidence and progression [5,120]. Currently, it is thought that the immunological responses to GO are mostly driven by CD4+T cells, with an imbalance present between Helper T cells, Regulatory cell, four CD4+T cells, and associated cytokines [120–122]. The Th1/T-helper 2 (Th2) response may be important in autoimmune diseases development [123]. Previous research found that miR-146a inhibited Th1 cell development in human T cells through protein kinase C epsilon (PRKCε) targeting. As a component of a functional complex consisting of PRKCε and signal transducer and activator of transcription 4 (STAT4), this molecule regulates Th1 cell development in human $CD4^+$ T cells [124]. In human lung alveolar epithelial cells, miR-146a upregulation has been shown to decrease inflammatory chemokines production [125], indicating that miR-146a may potentially play a pivotal role in $CD4^+$ T cell migration.

The other two miRNAs involved in autoimmune reactions by modulating activation of T cells are miR-183 and miR-96 [70]. The $CD4^+$ T cells from GO subjects and activated T cells from humans and mice showed increased expression levels of miR-183 and miR-96 [70]. Results obtained from the functional evaluation of the T cells, which overexpress both miR-183 and miR-96, or those treated with respective antagomiRs, demonstrated that the two miRNAs are implicated in the control of the intensity of T cell activation and proliferation. The miRNAs play this regulatory role through targeting the transcription factor early growth response 1 (EGR-1), which respectively downregulates the phosphatase and tensin homolog (PTEN), leading to enhanced Akt phosphorylation [70]. Qin and coworkers discovered the overexpression of miR-183 in GD individuals' tissue samples [126]. Furthermore, miR-96 has been shown to be increased in blood samples from individuals with the autoimmune thyroid disorders Hashimoto thyroiditis and GD [127]. Surprisingly, splenic T cells from three separate lupus animal models displayed higher levels of miR-183 and miR-96 [128], indicating that these miRNAs are important in T cell-mediated autoimmunity. By attaching to a consensus EGR-1 binding domain in the PTEN promoter, EGR-1 was found to transactivate the negative regulator PTEN [129]. Furthermore, PTEN is a lipid phosphatase protein that directly inhibits PI3K signaling and negatively controls the Akt signaling pathway [130].

4.3. Role of lncRNAs, miRNAs, and their interactions in glycosaminoglycan aggregation and fibrosis

MiR-146a has been linked to the aggregation of glycosaminoglycan and the deposition of collagen. An In-vitro study revealed that miR-146a inhibits hyaluronic acid (HA) and collagen I release in OFs in GO, which might also alter glycosaminoglycan's aggregation and collagen deposition in GO [68]. OFs have been shown to generate substantial quantities of collagen I and HA during GO development [131]. HA is the main element of glycosaminoglycan and, following production, stays anchored to the cell surface via attaching to hyaluronan synthase or other surface receptors, whereas some HA is degraded by hyaluronidase and secreted in the extracellular matrix [132]. Because of the hydrophilicity of HA, its aggregation has been shown to enhance orbital tissues growth [133]. Collagen I is thought to be a fibrosis marker [66]. It has been shown that fibrocytes expressing CD34 and CXC4 generate collagen I and infiltrate tissues after stimulation by numerous chemokines, such as C-X-C motif chemokine 12 (CXC12) [106], potentially leading to orbital fibrosis. The primary element of glycosaminoglycan

aggregation is HA. Due to its remarkable hydrophilic nature may bind to a considerable quantity of water, causing abnormal eyelid tissue and extraocular muscle interstitial edema [5]. Increased HA synthesis and collagen deposition have been shown to enhance the amount of orbital tissue in GO, intensifying the signs of eyeball protrusion [134]. In addition, a prior study found that miR-146a inhibited collagen I expression and was linked to transforming growth factor beta (TGF-β)-mediated fibrosis [66].

Based on another research, miR-146a was found to be important in fibrosis regulation in OFs in GO patients [66]. Fibrosis is regarded as a pathological condition induced by an excess of the extracellular matrix, particularly collagen, which is a primary component of the extracellular matrix, resulting in increased proliferation, hardness, or scars in different tissues [135]. Fibrosis in GO can build up around the extraocular muscles, resulting in a deposition of the extracellular matrix and also fat in the periorbital area, which leads to eye protrusion [107]. MiR-146a negatively regulates TGF-β-induced fibrotic markers (α-smooth muscle actin protein, fibronectin, and collagen Iα, TNF receptor associated factor 6 (TRAF6), and Mothers against decapentaplegic homolog 4 (Smad4)) [66]. A low amount of research has looked at the link between fibrosis and miR-146a; Sonkoly et al. [136] found that miR-146a was highly expressed in psoriatic skin lesions – known as fibrosing skin disease-relative to normal skin. Furthermore, Morishita et al. [137] revealed that miR-146a prevented renal fibrosis by inhibiting the Smad4-TGF-1 and TRAF6-NF-κB signaling pathways.

In contrast to miR-146a, miR-21 has been demonstrated in GO to induce fibrosis in OFs [79]. MiR-21 is a small multifaceted RNA active in various physiological systems [138]. MiR-21 has piqued the interest of scientists in various fields, including development, stem cell biology, cancer, and aging, and is now one of the most investigated miRNAs. MiR-21 is found in high concentrations in cancer cells as well as other types of lesions. It functions as a diagnostic/prognostic marker, besides being a possible therapeutic target in various disorders [138]. TGF-β1 enhanced the expression of miR-21 in a time and dose-dependent fashion, according to Tong et al. [79]; miR-21 boosted the expression of collagen I mRNA and overall collagen synthesis caused by TGF-β1. Furthermore, miR-21 stimulated the TGF-β1/Smad signaling pathway by increasing the phosphorylation of Smad3. These findings show a relationship between orbital muscle fibrosis and miR-21, as well as offering a new treatment target for GO. Various reports have shown that miR-21 promotes tumor proliferation [139] and invasion [140] while impeding apoptosis [141]. Aside from that, growing data show that miR-21 plays a crucial role in fibrosis in different illnesses. For instance, in lung fibrosis, miR-21 facilitates fibrogenic activity of pulmonary fibroblasts [142], enhances renal fibrosis [143], speeds atrial fibrosis, and boosts structurally atrial myocardium remodeling [144]. Considerable remodeling occurs as a result of pulmonary artery stenosis, resulting in decreased right ventricular performance. Antagomir-21 therapy lowers myocardial fibrosis and enhances right ventricular functions. Further, miR-21 induces myocardial fibrosis and decreases right ventricular functions; inhibiting miR-21 with a particular antagonist may provide a potential treatment alternative in right heart hypertrophy [145].

As previously stated, the LPAL2/miR-1287–5p/EGFR ceRNA axis modulates TGF-β1-induced alterations in cell adhesion factors and activation of OFs, influencing fibrosis in the GO pathogenesis [71]. Considering inflammation is considered one of the most significant causes of fibrosis throughout reparative processes, activation of OFs is the key process linked to fibrosis throughout the GO mechanism [71]. LPAL2 has been shown to specifically target miR-1287–5p, which is a downregulated miRNA in orbital tissues of GO cases. In opposed to LPAL2 knockdown, miR-1287–5p suppression boosted TGF-β1-induced OF hyperproliferation and raised adhesion molecules and collagen I protein expression [71]. Epigenetic studies have recently demonstrated that changes in the expression levels of lncRNAs and/or miRNAs can impact the stability and translation of genes implicated in the activation of fibroblast and fibrosis in the lung [110,112], kidney [110], liver [111], and heart [113,114].

Regarding the regulatory roles of CXCL1 and miR-27a as well as ceRNA mechanism, Yue et al. suggested that ENST00000499452 competitively inhibits miR-27a, thereby reducing its inhibitory impact on CXCL1 and boosting the immune response, inflammatory reaction, and even fibrosis in OF in GO individuals [76]. CXCL1 may be involved in cardiac hypertrophy, fibrosis, and inflammation by activating angiotensin II. Moreover, CXCL1 can control fibroblast activation and the up-regulation of pro-inflammatory factors in head and neck squamous cell carcinoma tissues [115,116].

As previously indicated, Wu et al. [74] found that 809 distinct lncRNAs may influence extracellular matrix remodeling in GO orbital adipose/connective tissue by their co-expression network investigation. The extracellular matrix's formatting and dynamics may significantly impact cell physiological operation, and a changed extracellular matrix exists as both a result and a cause of fibrosis [146]. As a result, further research into the molecular pathways involving the extracellular matrix in GO patients' ocular fat tissues is required.

4.4. Role of miRNAs glucocorticoid insensitivity

During induced glucocorticoid resistance, miR-224–5p overexpression reformed dexamethasone-mediated transrepression of the NF-κB reporter, perhaps by targeting glycogen synthase kinase-3β (GSK-3β) to enhance glucocorticoid receptor protein levels [69]. In active moderate to intense patients, intravenous glucocorticoid injection is presently the first-line treatment option [147,148]. NF-κB activation has previously been displayed to upregulate miR-224–5p expression [149]. Lately, serum miR-224–5p levels were considerably raised following infliximab treatment for some diseases [150] like Crohn's disease [151] and served as one of the rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and prednisone (R–CHOP) therapy reaction indicators in diffuse big B cell lymphoma [152].

4.5. Role of miRNAs in lipid accumulation and adipogenesis

MiR-130a has been implicated in the remodeling of GO orbital tissue, particularly in terms of excessive lipid deposition and adipogenesis [62]. The activation and differentiation of fibroblasts in orbit cause the significant orbital tissue remodeling seen in GO [107,153,154]. OFs are diverse cells that may proliferate and develop into myofibroblasts and adipocytes, which contribute to scarring and excessive fat tissue accumulation, respectively. When stimulated, fibroblasts with high levels of Thy1 surface expression (Thy1+) generate myofibroblasts more easily, whereas fibroblasts with little or no Thy1 (Thy1–) create adipocytes [155–157]. T cells that generate prostaglandins, such as 15-deoxy-$\Delta^{12,14}$- prostaglandin J2, an endogenous ligand of peroxisome proliferator-activated receptor (PPAR), a transcription factor that promotes adipogenesis and fat accumulation, may activate OFs [107,158]. MiR-130a is found in a range of cell types and affects cellular processes via a number of distinct targets [159]. MiR-130a may target two AMP-activated protein kinase (AMPK) subunit genes, resulting in decreased AMPK expression and activity. Thy1– OFs are primed for lipid accumulation and the adipogenic pathway, according to these findings. AMPK regulation of lipogenic gene activity and fatty acid synthesis is released when miR-130a targets and inhibits AMPK function [62]. There is also evidence that miR-130a has a role in obesity. Obese persons have higher levels of miR-130a [160,161], and circulating miR-130a increases as body mass index rises [162]. Furthermore, miR-130a has been found to inhibit adipogenesis in human adipose-derived stromal cells by targeting and suppressing peroxisome proliferator-activated receptor--gamma (PPARγ) expression [163].

Furthermore, miR-27a and miR-27b decreased adipogenesis in GO patients' OFs [65]. MiR-27 is one of many miRNAs that have been linked to cholesterol and fatty acid metabolism [164]. During adipocyte

development, the miR-27 gene family has been demonstrated to be downregulated. By targeting PPARγ, miR-27a and miR-27b impede adipocyte development [165,166]. Similar findings were reported by Kim et al. [166] in research utilizing mouse 3T3-L1 cells and Karbiener et al. [165] in studies employing human multipotent adipose-derived stem cells.

4.6. Role of miRNAs in oxidative stress and angiogenesis

In orbital adipose tissues, downregulation of miR-199a was shown to be a driver of the NADPH Oxidase 4 (NOX4)/hypoxia-inducible factor 1 (HIF-1)/vascular endothelial growth factor A (VEGF-A) pathway [61]. The oxidative stress and hypervascularization of GO orbital fat are both elevated [61,167]. A transcription factor known to negatively influence miR-199a production, STAT-3, was shown to be activated in GO orbital fats. In addition, the NOX4/HIF-1/VEGF-A signaling pathway has been identified as a key player in GO. The regulation of miR-199a by STAT-3 has been postulated as a common driver of these processes in GO orbital fats [61]. The miR-199a family, which includes the mature forms miR-199a-3p and -5p, has recently been discovered to play a role in a complex regulatory network in endothelial cells that regulates nitric oxide, reactive oxygen, species, and angiogenesis [168]. In brown adipocytes, overexpression of miR-199a-3p reduced lipid deposition and adipogenic gene expression [169], but upregulation of miR-199a-5p reduced lipid accumulation in porcine preadipocytes [170]. MiR-199a-3p and -5p have been hypothesized as tumor suppressors in papillary tumors and follicular carcinoma, respectively, in the thyroid [171,172].

4.7. Role of miRNAs in the proliferation of fibroblasts

In human OFs, platelet-derived growth factor (PDGF)-BB was reported to promote proliferation by inhibiting programmed cell death 4 (PDCD4) expression via overexpression of miR-21 [67]. Cytokine production, hyaluronan production, and cell proliferation are all critical effector actions of activated OFs in GO [67]. The miR-21-mediated down-regulation of PDCD4 by PDGF-BB increases cell proliferation, resulting in the formation of GO [67]. PDGF is a dimeric protein that promotes the proliferation and survival of myofibroblasts, which is important in tissue healing and fibrotic disorders [173]. Furthermore, PDGF-A and PDGF-B chains have been shown to be elevated in orbital tissues from GO patients [133,174]. In terms of stimulating OFs to proliferate and generate IL-6 and hyaluronan, PDGF-BB is the most effective of the three PDGF isoforms, whereas PDGF-AA is the least potent [174]. As a result, PDGF isoforms containing the PDGF-B chain may have a role in GO orbital tissue growth. A variety of anticancer therapies have been developed using PDCD4, a well-known tumor suppressor [175]. The PI3K-Akt-mammalian target of rapamycin (mTOR)-dependent proteasome-mediated degradation and/or by miR-21-mediated-inhibition of PDCD4 translation down-regulates the expression of the PDCD4 protein expression [176–180]. PDCD4 has been identified as a substantial, functionally important target of miR-21 [176,179]. Treatment with lipopolysaccharide (LPS) reduces PDCD4 expression in RAW264.7 cells, and transfection with antisense oligonucleotides to miR-21 or targeted protection of the miR-21 site in Pdcd4 mRNA inhibits LPS-reduced PDCD4 expression, implying that LPS reduces PDCD4 expression by inducing miR-21 [176].

OFs from GO patients proliferate substantially more than non-GO OFs in response to thyroid-stimulating hormone (TSH) in another investigation [73]. TSH-induced proliferation needed the PI3K/Akt signaling cascade and was reliant on thyroid TSHR expression [73]. In GD and GO, TSHR is the primary autoantigen [181,182]. TSHR is expressed by OFs from both normal and GO patients, in addition to being expressed on thymocytes [5]. As a result, TSHR autoantibody-OF interactions may be responsible for several aspects of GO pathology. TSHR is a G-protein coupled receptor (GPCR) that activates the PI3K/Akt signaling pathway and produces cyclic AMP (cAMP) [183]. TSH, the natural ligand of TSHR, is used to activate it. Stimulatory autoantibodies that attach to the TSHR increase TSHR signaling in GO. While TSH and stimulatory antibodies both activate TSHR signaling pathways, the pharmacodynamics of activating antibodies cause the receptor to be activated for a longer period of time [184]. In GO OFs, TSHR signaling increases proliferation both directly via PI3K/Akt signaling and indirectly through the activation of miR-146a and miR-155. MiR-146a and miR-155 promote the proliferation of GO OFs by inhibiting the expression of target genes (Zinc and ring finger 3 (ZNRF3) and PTEN) that typically inhibit cell proliferation. Part of the fibroproliferative pathology seen in GO might be explained by the TSHR-dependent production of miR-146a and miR-155 [73]. In psoriasis, increased expression of miR-155 increases proliferation and apoptosis [185]. Furthermore, in mice, miR-155 overexpression in hematopoietic stem cells produces myeloproliferative illness [186]. In follicular thyroid cancer cells, miR-146a may disrupt the expression of the phosphatidylinositol 3-kinases (PI3K) inhibitor alpha-*N*-acetyl-neuraminide alpha-2, 8-sialyltransferase 4 (ST8SIA4), enhancing their proliferation rate [187].

4.8. MiRNAs as biomarkers for GO

Apart from their function in etiology, miRNAs also have a role in the clinical manifestations of GO and the prediction of treatment outcomes. Serum IL-17 levels of GD, inactive-GO, and active-GO groups were all significantly higher than that of the control. The IL-17 level in the active-GO group was considerably greater than in the inactive-GO and GD groups. MiR-146a expression was considerably lower in the active-GO and inactive-GO groups than in the control group. MiR-146a levels in the active-GO group were considerably lower than in the inactive-GO group. In GO patients, serum levels of IL-17 and miR-146a were also substantially linked with clinical activity score. There was a strong negative connection between blood interleukin-17 (IL-17) levels and circulating miR-146a expression. These results suggest that circulating levels of miR-146a and IL-17 might be useful biomarkers for active GO, as well as playing a role in the disease's development [72]. For active moderate-to-severe GO cases, intravenous glucocorticoid injection is presently the first-line treatment [147,148]. Individual patient responses vary widely, with roughly 75–80% of patients responding well, 6.5% morbidity, and 0.6% fatality [188,189]. The most serious adverse effects, such as severe cardiovascular and liver failure, are often caused by underlying conditions or therapy. As a result, carefully selecting patients and providing personalized therapy based on glucocorticoid outcome prediction is challenging [69]. Patients who were insensitive to glucocorticoids exhibited decreased expression of miR-224–5p and increased thyrotropin receptor autoantibody (TRAb) in serum, according to Shen et al. [69]. With a positive predictive value of 91.37% and a negative predictive value of 69.56%, the combination of miR-224–5p at baseline and TRAb functions as an independent factor associated with the outcome of glucocorticoid treatment. For the discovery of blood biomarkers associated with GO from a miRNA sequencing experiment, researchers used a method that combined predictive and inferential statistics. A total of 5 robust circulating miRNAs have been identified (Novel:19_15038, Novel:hsa-miR-182–5p, Novel:hsa-miR-22–3p, Novel:hsa-miR-27a-3p, Novel:hsa-miR-6748–3p), potentially able to discriminate between healthy controls, GD and GO patients [77]. The expression of miR-Let7d-5p, miR-96–5p, and miR-301a-3p in individuals with GD was linked to greater severity of illness, including active ophthalmopathy, according to one research [127]. The present findings identify three serum miRNAs that may be associated with a poorer clinical outcome in GD patients. Furthermore, Al-Heety and Al-Hadithi [60] found that circulating miR-21–5p expression is significantly higher in individuals with orbitopathy than in patients without orbitopathy. According to the findings, the levels of TSH, Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone

receptor-antibodies (TSHR-Abs) are all positively linked with miR-21–5p. Finally, the increased expression of miR-21–5p in all patient groups suggests that miR-21–5p may aid in the diagnosis of GD and its progression to orbitopathy. The discovered blood biomarkers might be a useful tool for physicians to employ for early GD diagnosis and prognosis, including the possibility of developing orbitopathy, and represent a step forward in the direction of technology-driven precision medicine [190]. There is adequate evidence to recommend circulating extracellular miRNAs as essential participants and/or prospective biomarkers for a number of disorders. These miRNAs may be obtained either from plasma or serum. The capacity to recover sufficient RNA for analysis to profile a large number of miRNAs is now being improved by research that are currently being conducted. Yet, there is still a lack of consistency and uniformity in this subject; as a result, efforts are required to develop common practices. In addition, before developing research to investigate circulating miRNAs, there are a number of crucial considerations that need to be made. The circulating miRNA profiles obtained from plasma or serum are still open to the possibility of major technical development as this area continues to develop. There is a possibility of obtaining an extracellular miRNA signature by collecting bodily fluids using methods that do not need invasive surgery. In point of fact, the information that is gained via the process of extracting extracellular RNAs from plasma or serum may be generalized to other bodily fluids, such as saliva or urine. Without a doubt, the accumulation of this knowledge will result in the production of diagnostic tests that use bio-fluids that are simple to evaluate. So, when future experimental and clinical studies begin filling in the gaps in our knowledge, the power of exploiting not just extracellular miRNAs, but potentially also other RNA species, will considerably increase our understanding of illnesses and may lead to novel and intriguing therapeutics. Up to now, different isolation methods of miRNAs have been exploited including Chloroform-based extraction, Silica-based miRNA recovery methods, Exiqon miRCURY™RNA Isolation kit, and mir Premier® microRNA Isolation Kit. These methods are among mostly-used techniques in extracting these small ncRNAs from the bio-liquids [191,192].

5. Conclusion

Pathogenesis of GO is closely linked to the modifications of ncRNAs, especially miRNAs. LncRNAs and miRNAs have the potential to be diagnostic markers for GO. Moreover, due to their key role in the regulation of inflammation, regulation of T cell functions, regulation of glycosaminoglycan aggregation and fibrosis, glucocorticoid sensitivity, lipid accumulation and adipogenesis, oxidative stress and angiogenesis, and proliferation, these ncRNAs, especially miRNAs may be potentially novel candidates for therapeutic targets in the future studies. Nonetheless, the precise functions of most lncRNAs and miRNAs and the fundamental processes remain unknown, necessitating more research. Apart from their involvement in GO pathogenesis, miRNAs also are involved in the clinical manifestations of the disease. Ultimately, we suggest that lncRNAs may be interesting candidates for future investigations, as the number of studies is limited and their precise role in the pathogenesis of GO is not completely revealed.

Ethics approval and consent to participate

None.

Consent for publication

All authors are agreed.

Funding

None.

Authors' contributions

Dr. Kourosh Shahraki designed the study and wrote the first draft of manuscript. Dr. Vida Ilkhani Pak, Dr. Amin Najafi, Dr. Kianoush Shahraki, Dr. Paria Ghasemi Boroumand searched, collected and analyzed data and interpreted results. Roghayeh Sheervalilou revised the final version of manuscript.

All authors read and approved the final manuscript.

Declaration of competing interest

"The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article".

Acknowledgements

None.

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