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Review Article

MicroRNAs: Micromanagers for the Pathology of Age Related Macular Degeneration

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ABSTRACT

Inflammation, oxidative stress, apoptosis and neovascularization are risky parameters which influence different phases in the pathogenesis of age related macular degeneration (AMD). Beside other mediators, this multitiered and complex event of retinal worsening has been exposed to be orchestrated by small non coding RNA fragments that bind to specific mRNAs and modulate their post transcriptional regulation and gene expression in retina. Several microRNAs (miRNAs) have been revealed which are expressed in retina and influence its functionality. These miRNA fragments play significant role in the development and maintenance of photoreceptors hence, dysregulation of them may augment severe retinal etiopathology. This comprehensive review summarizes the role and relevance of several known miRNAs along with their potential utilities as therapeutic targets in AMD pathogenesis.

Key words: MicroRNA, Age related macular degeneration, inflammation, oxidative stress, angiogenesis.

INTRODUCTION

Age related macular degeneration (AMD) is a complex, neurodegenerative disease of human retina which progressively distorts the central vision due to deterioration of macula. [1] Macula present near the middle of retina consists of high density of photoreceptors, which help in creating central and sharp vision. Clinically, AMD results in two forms- dry AMD and wet AMD. In dry or atrophic macular degeneration, metabolic wastes such as esterified lipids, proteins and triglycerides commonly known as 'drusen' accumulate in subretinal pigment epithelium (RPE). These intransigent lipoproteins (drusen) progressively degenerate RPE and Bruch's membrane hence, contort the central vision. In wet AMD, the clearance of drusen along with oxidative stress causes inflammasome activation and release of growth factors. Consequently, new blood vessels are formed (neovascularization) which usually bleed and form dense macular scars after hemorrhage. [2]

AMD is responsible for vision loss in more than 50 million elderly people in the world and contributes towards 9 percent of total global blindness. [3] AMD has become a serious health concern because of its enormously growing social and economic implications in an aging society worldwide. For this reason, increasing research efforts have been made to understand the molecular mechanisms of AMD to find early diagnosis and treatment for it. Based on the latest evidence, the deregulation of microRNA (miRNA) expression has been evolving as a significant contributor to neurodegeneration by influencing most of the mechanisms

responsible for AMD. [4] Various studies are indicating miRNAs as effective therapeutic targets in the treatment of AMD. [5,6] MicroRNAs are involved in a variety of fundamental cellular processes such as cellular proliferation, development, migration, and apoptosis regulation. [7] These enigmatic fragments are evolutionarily conserved, single-stranded RNA molecules of 19–25 nucleotides long, which do not code for proteins. They recognize sequences in the 3'-untranslated regions (3'-UTR) of target messenger RNAs, and either induce mRNA degradationor inhibit their translation. [8,9]

It has been convincingly proved that miRNAs play imperative role in the pathology of several disease processes such as vasculogenesis, angiogenesis, hypoxia, oxidative stress, and inflammation. [10] Owing to their contributions scientists believe that they can be helpful as therapeutic targets. [11] Although no miRNA has been directly associated with AMD pathology hitherto, but several of them contribute in almost all the critical phases of AMD pathology right from the RPE deterioration to inflammation upto neovascularization and retinal bleeding (Table 1). All known miRNAs and their role and relevance in different phases of AMD pathology has been explored and summarized as follows.

DRUSEN ACCUMULATION AND RPE DEGRADATION

Retinal pigment epithelium (RPE) is the pigmented cell layer, present outside the retina and is firmly attached to the underlying choroid and overlying photoreceptor cells. It maintains normal photoreceptor activity. RPE supplies nutrients, removes waste products from photoreceptor cells and is responsible for visual pigment transport and regeneration. [12] Thus, any damage to the RPE leads to the degeneration of the retina, which may cause visual impairment and blindness. [12] Progressive apoptosis of the RPE in dry AMD results in degeneration of the photoreceptors and the underlying choriocapillaries. [13] In dry AMD patients, it has been revealed that RPE cells have a reduced level of Dicer1 that results in accumulation of *Alu* element transcripts and causes RPE toxicity. [14] Dicer 1 helps in degradation and digestion of *Alu* RNAs whereby, it indirectly protects against the risk of RPE degradation. This indicates that the reduced level of Dicer1 is an important hallmark of the dry AMD. Furthermore, in mice lacking other miRNA processing enzymes such as Drosha (Drosha Ribonuclease III), DGCR8 (DiGeorge syndrome critical region 8) and EIF2C2 (Eukaryotic Translation Initiation Factor2C2), no degeneration of the RPE has been observed which suggests that downregulation of Dicer 1but not of others' contribute in the pathogenesis of AMD. The long double-stranded *Alu* transcripts are constantly produced in the retina. In healthy individuals, these toxic RNAs are processed into shorter, nontoxic products. But in patients with dry AMD, Dicer1 levels are greatly reduced, allowing these long *Alu*RNAs to accumulate and cause RPE degeneration. [14] A recent study by Bhattacharjee and colleagues [15] reveals that increased levels of miRNA-34a might play important role in the pathogenesis of AMD by downregulating the TREM2 (triggering receptor expressed on myeloid cells2) protein, which is a waste sensing transmembrane protein present in the microglial cells of retina. This miRNA plays important role in removing drusen from the retina. The over expression of miR-133a and cyclin D2 has been observed to cause photoreceptor degeneration in mice. [16] It has been explored that miRNA-375-3p downregulation may trigger activation of JAK/STAT pathway and chemokine signalling that can damage photoreceptors. [16] Experiment by Murad *et al.* has revealed that inhibition of miRNA-184 results in the upregulation of EZR (ezrin) gene and causes downregulation of LAMP-1 (Lysosomal-associated membrane protein 1)that affects the phagocytosis in ARPE -19 (human

retinal pigment epithelial cell line) cells in mice and disrupts the RPE homeostasis. [17]

OXIDATIVE STRESS: AN INFLEXIBLE PARAMETER

Prolonged exposure to sunlight along with lifestyle factors such as tobacco smoking and consumption of high glycaemic foods, create a high predisposition of oxidative burden in the retina. This results in progressive and premature apoptosis of the RPE cells and causes degeneration of the photoreceptors and the underlying choriocapillaries. There is increased risk for oxidative stress in the RPE because of its continuous exposure to very high levels of phototoxic blue light and high oxygen tension. [18] Therefore, the RPE has evolved an intrinsic antioxidant defense network that consists of a variety of antioxidant enzymes such as superoxide dismutases, glutathione peroxidases, glutathione S-transferases and catalase. Recently, Haque *et al.* found that miRNA-30b maintains the expression of catalase in human retinal pigment epithelial cell line (ARPE-19). They have reported that this miRNA-30b is upregulated under *in vitro* conditions of oxidative stress to ARPE-19 cells, which in turn inhibit the expression of endogenous catalase both at the transcript and protein levels. [19] In contrast, antioxidant curcumin (diferuloylmethane) that protects RPE cells against oxidative stress, significantly alters the expression of five miRNAs (miRNA-20a, miRNA-126, miRNA-146, miRNA-150, and miRNA-155) that target vascular-endothelial growth factor-A(VEGF-A), platelet-derived growth factor β (PDGFβ), nuclear factor-κB (NF-κB), endothelin-1, and p53 in the ARPE-19 cells. It has been observed that miRNA-30b significantly down regulates after ARPE-19 cells are treated with curcumin. [20] Another finding shows downregulation of miRNA-23a, that regulates retinoic acid-induced neuronal differentiation through the transcription factor Hes-1, which is a target for this miRNA and is required for the differentiation and longevity of neuronal cells. [21] Kutty and colleagues [22] found another important miRNA-9, whose expression is greatly upregulated when ARPE-19 cells are incubated with a retinoic acid derivative that produces oxidative stress conditions *in vitro*.

INFLAMMASOME FUNCTION AND RETINAL INFLAMMATION

Inflammasomes are large multimeric protein conglomerates expressed in myeloid cells that play crucial role in triggering inflammatory process as response of the innate immunity. Depending upon the triggering event, inflammasomes serve as molecular platforms for activation of caspase-1, followed by maturation and secretion of biologically active molecules such as interleukin-1β (IL-1β) and IL-18. The innate immune system involves specific cells and processes that identify and respond to pathogens via pattern recognition receptors (PRRs). These receptors are capable of detecting both pathogen associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs) displayed by either pathogens or dead and degraded cells. [23] The oxidized fatty acids and protein adducts in the RPE cells act as DAMPs that are targeted by PRRs. These receptors consist of membrane-bound Toll-like receptors (TLRs) and cytosolic NOD-like receptors (NLRs) that form large cytoplasmic complexes called inflammasomes. [23] Among other inflammasomes, NLR family pyrin domain containing 3 (NLRP3, also known as NALP3 or cryopyrin) has engrossed much attention as it senses different forms of cell stress earnestly. It has been revealed that miRNA-223 is an important negative post transcriptional regulator of NLRP3 expression. [24] In miR-223 deficient mice, hyperactivation of NLRP3 inflammasome expression is evident which can be linked to dysregulated NLRP3 expression in myeloid chambers. [25] This microRNA suppresses the expression of NLRP3 by

binding to its 3' untranslated region, translating to reduced expression of NLRP3. It has been observed that NLRP3 modulates the toxic expression of proteins present in the drusen and *Alu* RNA in the retina. Furthermore, managing the downstream effector cytokines slows down the retinal damage in AMD. Deficiency of Dicer I ribonuclease type III triggers the accumulation of *Alu* RNA in RPE resulting in retinal degradation. [14]

It has been well known in the clinical arena that AMD pathology involves chronic inflammatory processes. [26] RPE cells coordinate both innate and adaptive immunity as they express complement components. On exposure to the pathogens or rapidly dying cells, the complement system activates and produces numerous membrane-attack complexes, which result in cell lysis, release of chemokines, cytokines and generation of pro-inflammatory molecules. [26] Interestingly, oxidative stress-induced RPE death tends to distort the integrity of RPE and Bruch's membrane, which results in the activation of the complement system followed by chronic inflammation. [27] Inflammatory cells, such as macrophages and microglia cells, have been shown to be involved in the AMD lesions. [28] In these lesions, macrophages tend to express angiogenic growth factors such as VEGF that plays a crucial role in the development of choroidal neovascularization (CNV). Therefore, research including inflammation-related miRNAs in human RPE cells and their response to proinflammatory cytokines could be of great value in understanding the pathogenesis of AMD. Such an investigation has been performed which reveals that miRNA-146a and miRNA-146b, can play a role in inflammatory processes underlying AMD and other retinal degenerative diseases through their ability to negatively regulate the NF-κB pathway in human RPE. [29] The results of this study also highlight that the increased expression of miRNA-155 is evident in RPE cells by activating the JAK/STAT signaling pathway. [22] According to a recent study, NF-κB-regulated miRNAs, miRNA-9, miRNA-125b, miRNA-146a, and miRNA-155 are upregulated in AMD pathology and that miRNA-146a and miRNA-155 target the 3'-UTR of complement factor H (CFH), thus downregulating CFH expression. [30] Deficiency of CFH in turn activates immune-related signaling that drives inflammatory neurodegeneration in the brain and retinal tissue.

HYPOXIA AND VEGF OVEREXPRESSION

Normally, the concentration of oxygen in RPE cells varies from 3 percent to 5 percent; a severe decline below this range is referred to as hypoxia. The pathological response to hypoxia is mediated by hypoxia inducible factors (HIFs). [31] HIFs are the major signaling molecules involved in cell proliferation, cell survival, angiogenesis, iron and glucose metabolism. HIFs are composed of two subunits i.e. α and β subunits. α subunit is regulated by oxygen and β subunit is constitutively expressed in the cells. During optimal oxygen concentration, HIF-1α is hydroxylated by the enzyme proline hydroxylase (PHD) and leads to the degradation of HIF-1α. [32] Oxygen plays a significant role in hydroxylation by serving as a co-factor of proline hydroxylase. But when oxygen concentration declines, hydroxylation does not occur which results in the accumulation of HIF-1α in the cytoplasm of the RPE cells. [32] These aggregated HIF-1α move to the nucleus of these cells, where they act as transcription factors for a central molecule involved in choroidal neovascularization, called vascular endothelial growth factor (VEGF). Increased production of VEGF stimulates the abnormal growth of blood vessels in the choroid. This process is known as angiogenesis. Recent studies have shown that miRNA-31 may target and downregulates the expression of hypoxia-inducible factor-1α (HIF-1α) and PDGF-B, while miRNA-150 targets and downregulate

the expression of PDGF-B and VEGF. [31] Recently, Zhou and coworkers analyzed the miRNA-23~27~24 gene cluster and revealed that the increased expression of miRNA-23 and miRNA-27 is responsible for pathological angiogenesis in a laser-induced CNV mouse Model. [33] These two miRNAs might promote angiogenesis by targeting proteins such as Sprouty2 (SPRY2), Sema6A (Semaphorin 6A), and Sema6D (Semaphorin 6D). [33] In contrast, miRNA-24 has been observed to repress angiogenesis by simultaneously regulating multiple components in the actin related cytoskeleton pathways of endothelial cells (EC). Studies have shown that miRNA-24 inhibits angiogenesis by targeting multiple members downstream of Rho signaling including Pak-4 (Serine/threonine-protein kinase), Limk-2 (LIM domain kinase 2), and Diaph-1 (Protein diaphanous homolog 1) proteins. Similar anti-angiogenic function, via the targeting of Rho signaling in ECs has been found in case of miRNA-21. Here, RhoB silencing through miRNA-21 overexpression impairs EC migration and tubulogenesis, thus providing a possible mechanism by which miRNA-21 can inhibit angiogenesis in course of CNV. [34] In another experiment, researchers have found that miRNA-126 is downregulated in CNV mice and this miRNA-126 targets and increases the levels of VEGF-A, KDR (Kinase Insert Domain Receptor) and SPRED-1 (Sprouty-related, EVH1 domain-containing protein 1). [35]

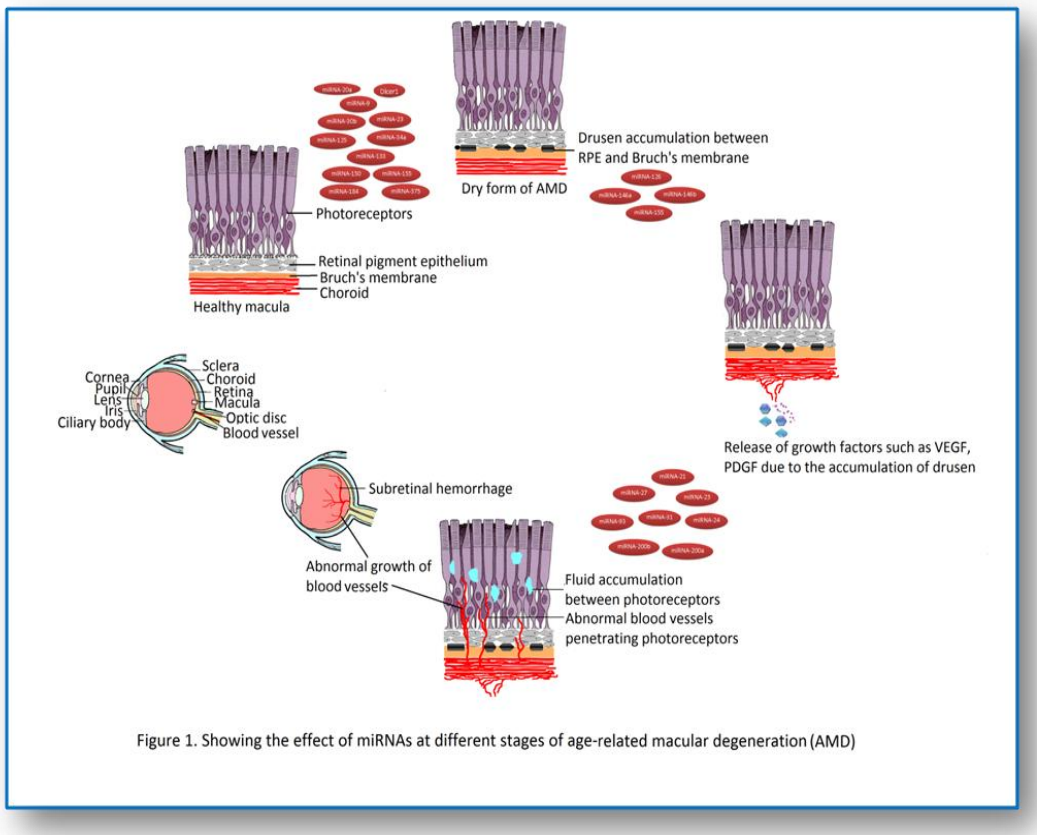

Figure 1. Showing the effect of miRNAs at different stages of age-related macular degeneration (AMD)

CHOROIDAL NEOVASCULARIZATION AND RETINAL HEMORRHAGE

Choroidal neovascularization is a process which involves the abnormal growth of new blood vessels originating from choriocapillaris (capillary layer of choroid membrane). This vascularization may extend upto the photoreceptors layer of retina. These blood vessels tend to penetrate through Bruch's membrane and RPE, which results in the disruption image making ability of retina. [36] The major stimulatory factor involved in developing CNV is vascular endothelial growth factor (VEGF). Besides VEGF, fibrogen growth factor

(FGF), platelet derived growth factor (PDGF) and angiopoietin-1 (Ang-1) also tend to induce neovascularization. [36] These abnormal blood vessels do not possess endothelial tight junctions, which predispose them to spontaneous bleeding. A fibrous component also coexists with these vessels that often contracts and puts additional stress on already fragile vessels. Consequently, it leads to rupture of these vessels in the retina, commonly known as hemorrhage. Recently, Wang *et al.* has analyzed that reduced levels of miRNA-93 is responsible for choroidal neovascularization (CNV) in the mice. In this study, it is found that miRNA-93 appears to play a role in regulating VEGF-A, a known factor involved in CNV. [36] Another study [37] has reported that expression of miRNA-200a-3p and miRNA-200b-3p are significantly reduced in AMD mice eyes. These miRNAs further upregulates zinc finger E-box binding homeobox 1, 2 (ZEB 1, ZEB 2) and vascular endothelial growth factor receptor 1 (VEGFR1) genes that cause pathological ocular angiogenesis. [37] It has also been exposed that another microRNA, miR-133a-3p targets Cyclin D2, which is known to play role in anti-apoptosis, cell cycle arrest and neurogenesis is significantly upregulated in retinal vasculature. [37]

Table 1. Potential role of known micro-RNAs in the pathogenesis of AMD

MicroRNAs	Expression level	Effect	Target	Species/Model/Tissue type	Source
miRNA-30b	Upregulation	Inhibition of catalase expression at the transcript and protein levels	Catalase	Human/in vitro/ARPE-19 under an oxidant environment	19
miRNA-20a, miRNA-126, miRNA-150, miRNA-155	Upregulation	Protection of RPE cells against oxidative stress	VEGF-A, PDGFβ,NF-B, Endothelin, p53	Human/in vitro/ARPE-19 under an oxidant environment	20
miRNA-23a	Downregulation	Protection of RPE cells against oxidative stress	Fas	Human/in vivo/RPE of donor eyes with AMD	21,40
miRNA-9	Upregulation	Importance in maintaining RPE cell function	CEBPA, CEBPB	Human/in vitro/ARPE-19 cells treated with retinoic acid to induce oxidative stress conditions	22,29
miRNA146a, miRNA-146b	Upregulation	Role in inflammatory processes	NF-κB signaling pathway	Human/in vitro/ARPE-19 cells treated with proinflammatory cytokines	29,30
miRNA-155	Upregulation	Role in inflammatory processes	JAK/STAT signaling pathway	Human/in vitro/human RPE cells obtained from adult donor eyes exposed to inflammatory cytokine mix	22,30
miRNA-31, miRNA-150	Downregulation	Dynamic regulation of neovascularization through downregulation of expression of VEGF, HIF and PDGF-B	VEGF, HIF, PDGF-B	Mouse/in vivo/model of ischemia-induced retinal neovascularization	31
miRNA-23, miRNA-27	Upregulation	Induction of sprouting angiogenesis by promoting angiogenic signaling	Sprouty2, Sema6A, Sema6D	Mouse/in vivo/model of ischemia-induced retinal neovascularization	33
miRNA-21, miRNA-24	Downregulation	Inhibition of angiogenesis by targeting multiple members downstream of Rho signaling	Pak-4,Limk-2, Diaph-1	Mouse/in vivo/model of ischemia-induced retinal neovascularization	34
miRNA-126	Downregulation	Regulation of the response of endothelial cells to VEGF	VEGF-A,KDR,SPRED-1	Mouse/in vitro/endothelial cells	35
miRNA-34a	Upregulation	Inhibition of TREM-2 protein	TREM-2	Mouse/in vitro	15
miRNA-93	Downregulation	Responsible for CNV	VEGF-A	Mouse/in vitro/endothelial cells	36
miRNA-125b	Upregulation	Increased levels of oxidative stress and inflammatory neurodegenerative conditions	15-LOX,SYN-2	Mouse/in vitro/endothelial cells	30
miRNA-200a miRNA-200b	Downregulation	Responsible for CNV	ZEB 1, ZEB 2, FLT 1	Mouse/in vitro/endothelial cells	37
miRNA133a-3p	Upregulation	Photoreceptor degeneration	Cyclin D2	Mouse/in vitro	16
miRNA-375-3p	Downregulation	Photoreceptor degeneration	Jak 2	Mouse/in vitro	16
miRNA-184	Downregulation	Affects phagocytosis in human retinal pigment epithelium	LAMP-1,Ezrin	ARPE-19 under an oxidant environment	17
Dicer1	Downregulation	*Alu* transcripts accumulation and RPE toxicity	*Alu* RNAs	Human/in vivo/RPE of humans with GA	14

MICRORNA TARGET IDENTIFICATION

MicroRNAs are the key regulators of gene expression that control the functions of many target genes. Therefore, manipulation of the expression of specific miRNAs which are responsible for causing certain complex diseases, may provide therapeutic solutions to these diseases. By identifying specific targets using computational techniques, miRNAs which are over-expressed can be inhibited and those miRNAs whose expression is very low can be revived in a particular disease. Several computational approaches have recently been developed for the prediction of miRNA targets including miRanda, TargetScan and PicTar. [38] Target sites for miRNA include three categories: - the 5'-dominant canonical site, the 5'- dominant seed region and the 3'-compensatory site. The seed region comprises a stretch of 7 nucleotides which begins from either first or second nucleotide present at the 5' end of a miRNA. Softwares miRanda, TargetScan and PicTar focus on the modulation of the seed region within the miRNAs and allow them to regulate the expression of their corresponding target mRNAs. [38]

This review highlights that the clinical etiology of AMD has a large bearing on the epigenetic signals and it would be highly relevant to suss out knowledge from comprehensive analyses of miRNAs that are dreaded culprits in inflammation, oxidative stress, angiogenesis and other pathways both locally and systemically. Future studies should focus on site specific and phase specific miRNA dysregulation in AMD, for instance miR-146a and miR-155 mediate inflammation and microglial activation in the retina against response to stress, whereas miR-125b and miR-17 regulate apoptosis in response to hypoxia induced stress. Surveillance studies compiling such roles of miRNAs may lead us in the direction of effective diagnosis and unsurpassed therapeutics for AMD.

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