Bottos *et al. International Journal of Retina and Vitreous* (2025) 11:110
https://doi.org/10.1186/s40942-025-00736-8

International Journal of Retina
and Vitreous

REVIEW **Open Access**

RNA dysfunction in age-related macular degeneration: the role of U1 snRNP complex and neurodegenerative diseases

Juliana M. Bottos[1,2*], Ericks S. Soares[2], Camila G. M. Zimmer[2], Vanessa V. C. Sinatti[2], Caio B. Q. S. Leal[2] and Juliana M. F. Sallum[1]

Abstract

Background Age-related macular degeneration (AMD), a leading cause of vision loss in elderly individuals, is a multifactorial disease driven by genetic, environmental, and cellular aging processes. Emerging evidence highlights the critical role of ribonucleic acid (RNA) splicing dysfunction in AMD pathogenesis, with a focus on the U1 small nuclear ribonucleoprotein (U1 snRNP) complex, a key spliceosome component. U1 snRNPs ensure the fidelity of RNA cotranscription and pre-mRNA splicing initiation, and their dysfunction has been implicated in neurodegenerative disorders and other age-related diseases.

Main body This narrative review explores the impact of U1 snRNP dysregulation on retinal cells, focusing on its role in transcriptomic instability, impaired protein homeostasis, cellular stress, impaired autophagy, and inflammation, which are important features of AMD pathogenesis. Finally, we propose that targeting U1 snRNP dysfunction could provide a novel therapeutic approach to slow, prevent, or restore retinal degeneration, offering insights into broader implications for age-related diseases.

Short conclusion Understanding the molecular mechanisms underlying U1 snRNP dynamics in retinal health and degeneration is essential for developing innovative and effective treatments for AMD, which may provide ways to delay or reverse the effects of aging and associated diseases.

Keywords Age-related macular degeneration, RNA splicing, U1 snRNP, Spliceosome, Neurodegenerative diseases, Aging, Cotranscription, Long genes

---

*Correspondence:
Juliana M. Bottos
jubottos@gmail.com
[1]Department of Ophthalmology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil
[2]Aptah Bio Inc, MBC BioLabs, 930 Brittan Avenue, San Carlos 94070, USA

Background

Age-related macular degeneration (AMD) is a progressive neurodegenerative disease influenced by multiple factors, including aging, genetics, and environmental conditions [1]. It is the leading cause of irreversible central vision loss in elderly individuals, and its prevalence is expected to increase significantly owing to the aging population and increasing life expectancy. In 2020, 196 million people were affected by AMD worldwide, and this number is projected to reach 288 million by 2040 [2]. AMD manifests in two primary forms: dry (nonexudative) and wet (exudative) AMD. The dry form, accounting for approximately 90% of all cases, is characterized by the gradual accumulation of drusen beneath the retina, leading to atrophy of the retinal pigment epithelium (RPE) and loss of photoreceptors (PR), which results in a slow, progressive decline in central vision. Conversely, wet AMD, although less common, is more severe and characterized by abnormal growth of choroidal blood vessels (choroidal neovascularization) beneath the retina. These fragile vessels leak blood and fluid, causing rapid retinal damage, scarring, and substantial vision loss [3, 4].

The treatment options for AMD vary by form. Wet AMD is often managed with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors to suppress abnormal blood vessel growth, or in combination with angiopoietin-2, to enhance vascular stability [5]. However, treatment for dry AMD is limited to strategies that slow the progression of AMD through lifestyle modifications, intravitreal complement modulation, and vitamin supplementation [6–9]. The primary therapeutic strategies for dry AMD that are currently under investigation include the following:

- complement pathway inhibitors
- drugs that target oxidative stress
- beta-amyloid antibodies
- neuroprotective small molecules
- visual cycle modulators
- stem cell therapies
- and anti-inflammatory agents [10]

However, the development of these treatments faces significant challenges, including an incomplete understanding of AMD pathogenesis, the complexity of delivering drugs to the retina, limited preclinical models, and the need for innovative clinical trial approaches and novel endpoints [6–10].

Addressing the complex pathophysiology of AMD will likely require multitargeted approaches rather than focusing on a single aspect. The increasing understanding of RNA mechanisms and their role in neurodegenerative diseases has spurred the development of biomarkers and innovative therapeutic strategies [11].

This article is a narrative, integrative review that synthesizes current evidence from molecular biology, retinal degeneration, and neuroscience to construct a novel theoretical framework regarding the role of RNA splicing dysfunction in AMD, with a particular focus on the U1 snRNP complex. Relevant studies were identified through a comprehensive search of peer-reviewed literature using databases such as PubMed and Web of Science. Keywords included "age-related macular degeneration," "RNA splicing," "U1 snRNP," "spliceosome," "neurodegenerative diseases," "aging," "cotranscription," and "long genes." Articles were selected based on their conceptual relevance, methodological rigor, and contribution to understanding molecular mechanisms of neurodegeneration. This synthesis aims to construct a cohesive pathogenic framework that supports future therapeutic strategies targeting the dysfunction of the U1 snRNP complex in AMD and related disorders.

The RNA biology

When Sydney Brenner first reported the discovery of messenger RNA (mRNA) in 1961, it was considered merely a molecule that acted as a bridge between deoxyribonucleic acid (DNA) and proteins to transfer genetic information [12]. Currently, at least 15 distinct types of RNA molecules reveal unique features of the RNA landscape [13].

The human transcriptome is the complete set of RNA molecules transcribed from the human genome. It represents all the RNA content in a particular cell, tissue, or organism at a specific time, reflecting the genes actively expressed under certain conditions.

The transcriptome can generally be separated into two categories: coding RNA, which is represented by mRNAs and accounts for 4% of the total RNA, and noncoding RNA (ncRNA), which accounts for the remaining 96% [14]. ncRNAs are further separated into housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs) [15]. Regulatory ncRNAs include small noncoding RNAs (fewer than 200 nucleotides in length) and long noncoding RNAs (more than 200 nucleotides) [16]. Table 1 presents an overview of the categories of coding and ncRNAs and their primary functions.

RNA splicing

RNA splicing was first described by Richard J. Roberts and Phillip A. Sharp in 1977 [17–20]. They independently discovered that, in contrast to simpler bacterial genes, complex genes in eukaryotic cells are divided into segments known as coding regions (exons) and noncoding regions (introns). During transcription, both gene

Table 1 Primary categories of coding and noncoding RNAs

RNA Class	Description	Molecular Function
CODING RNA		
mRNA	Messenger RNA	Template for protein synthesis
NON-CODING RNA		
Housekeeping ncRNA		
tRNA	Transfer RNA	Delivers amino acids to the ribosome for protein assembly
rRNA	Ribosomal RNA	Component of ribosomal subunits, catalyzes peptide bond formation
snoRNA	Small nucleolar RNA	Guides chemical modifications of rRNA, tRNA, and snRNA
snRNA	Small nuclear RNA	Component of the spliceosome, catalyzes pre-mRNA splicing
Regulatory ncRNA		
Long noncoding RNA (> 200 nt)		
ceRNA	Competing endogenous RNA	Regulates gene expression by competing for miRNA binding
circRNA	Circular RNA	miRNA decoys, transcription regulators, interference with splicing
lincRNA	Long intergenic noncoding RNA	DNA–chromatin complex scaffolds
NATs/OS	Natural antisense transcripts/opposite strand	Transcriptional regulation in cis or trans
Small noncoding RNA (< 200 nt)		
miRNA	microRNA	Posttranscriptional silencing, translational repression
piRNA	PIWI-interacting RNA	Silences transposons, regulates epigenetic modifications in germline cells

Abbreviations: *mRNA: messenger RNA, ncRNA: noncoding RNA, tRNA: transfer RNA, rRNA: ribosomal RNA, snoRNA: small nucleolar RNA, snRNA: small nuclear RNA, ceRNA: competing endogenous RNA, circRNA: circular RNA, lincRNA: long intergenic noncoding RNA, NATs/OS: natural antisense transcripts/opposite strand RNA, miRNA: microRNA, piRNA: PIWI-interacting RNA*

regions are transcribed into precursor mRNAs (pre-mRNAs). RNA splicing involves the removal of introns and the joining of exons from pre-mRNAs to create mature mRNAs. The mRNA is then exported to the cytoplasm and translated into a protein [21] (Fig. 1). The discovery of this process has transformed the understanding of gene expression and structure. This groundbreaking discovery earned Roberts and Sharp the 1993 Nobel Prize in Physiology or Medicine [17, 20].

The spliceosomal machinery

Splicing is accomplished by a large macromolecular complex (~3 MDa) known as the spliceosome. This intricate macromolecular machine comprises five snRNPs—U1, U2, U4, U5, and U6—and numerous proteins with a dynamic structure and composition [22, 23]. Over 170 proteins are associated with the core splicing machinery at various stages of the splicing process [23], with each step being precisely regulated to support cellular homeostasis and maintain cellular fitness [24]. These processes are accompanied by extensive remodeling of the snRNPs within the spliceosome, conferring accuracy and adaptability to the splicing machinery [22].

The spliceosome acts as a molecular scissor, removing intronic regions from pre-mRNAs. It recognizes the intron−exon boundaries of genes, which are defined by the 5′ splice donor, 3′ splice acceptor, and branch sites [25]. Spliceosome activity can be regulated by multiple splicing activators and repressor proteins, called regulatory splicing factors (SFs), which bind to enhancer and silencer elements in pre-mRNAs [26].

U1 snRNP complex

The U1 snRNP complex is a key component of the spliceosome and is the most abundant ribonucleoprotein (RNP) complex in human cells. Each cell is thought to contain approximately one million copies of this complex [27], which is formed by a U1 small nuclear RNA (snRNA), seven Sm proteins, and U1-A, U1-C, and U1-70K snRNPs, which work together as functional units in pre-mRNA splicing [28].

The U1 snRNP complex is required for pre-mRNA splicing initiation and gene regulation, participating in 5′ splice site recognition, spliceosome assembly, splicing fidelity, alternative splicing (AS) modulation, and 3′ untranslated region (UTR) processing through cotranscriptional mechanisms (detailed in subsequent sections) [27]. In addition to its role in splicing, U1 snRNP interacts with RNA polymerase II (RNA Pol II), coordinating transcription dynamics and mRNA stability [29]. This functional coupling promotes efficient cotranscriptional splicing, prevents exon misprocessing, and contributes to the accuracy of gene expression. U1 snRNPs integrate splicing and cotranscriptional regulation to preserve transcriptome integrity, with a prominent function in maintaining the expression of long genes [29].

U1 snRNP is the first small nuclear RNP to bind pre-mRNA, recognizing the 5′ splice site, which marks the exon–intron boundary, to initiate spliceosome assembly. This interaction guides the recruitment of additional snRNPs, including U2, and stabilizes the early spliceosomal complex, ensuring accurate splice site selection and efficient pre-mRNA splicing [30, 31] (Fig. 2).

Dysfunction of the U1 snRNP complex disrupts these tightly regulated processes, leading to widespread gene expression abnormalities. In splicing, its impairment results in intron retention, exon skipping, and the activation of incorrect or cryptic splice sites, generating aberrant mRNA isoforms. These defective transcripts can produce nonfunctional, truncated, or toxic proteins associated with genetic disorders, cancer, and neurodegenerative diseases [32]. Additionally, U1 snRNP dysfunction affects its interaction with RNA Pol II, leading to premature transcription termination, defective mRNA maturation, and instability, particularly in long genes [29]. This

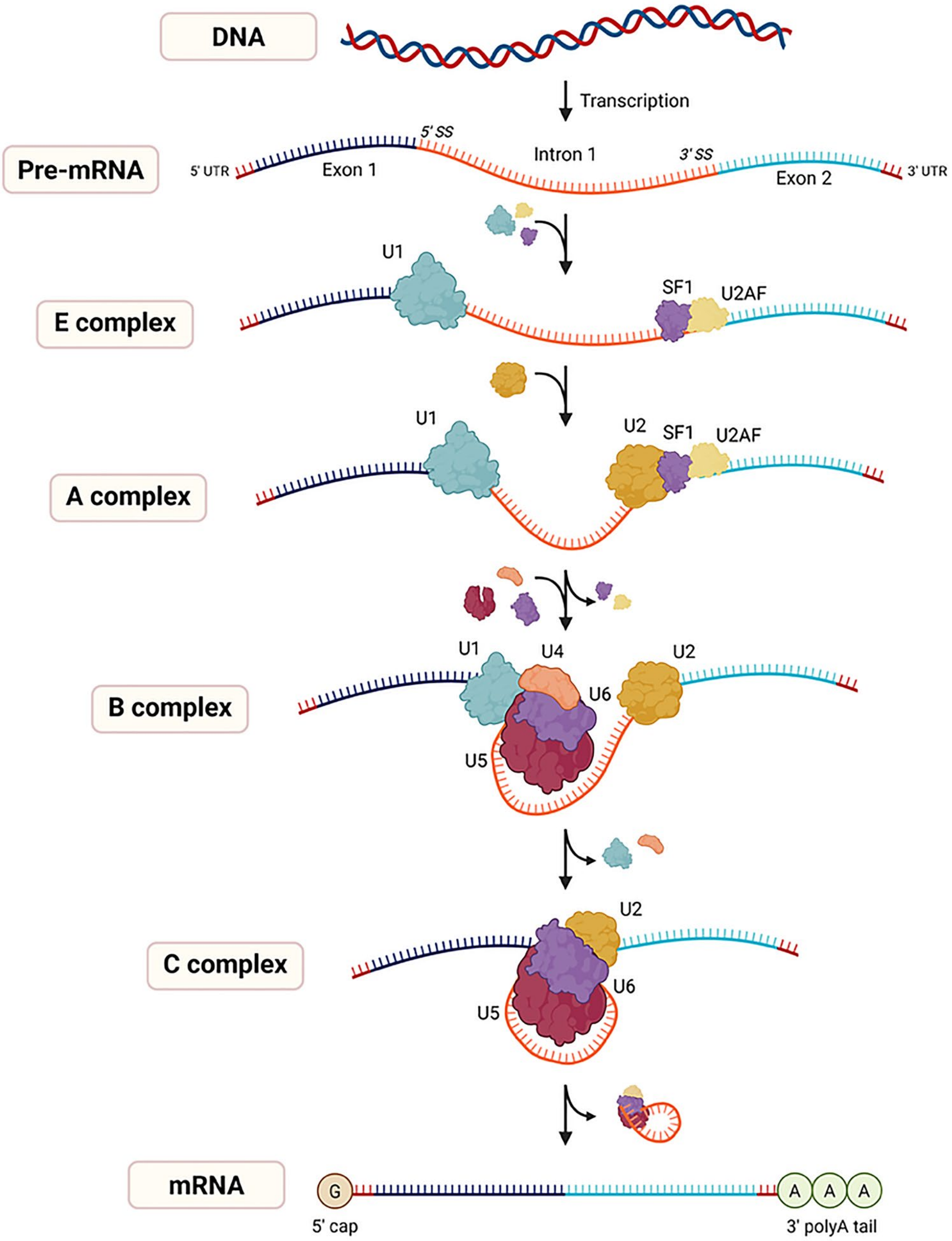

Fig. 1 RNA splicing is a tightly regulated process in which the spliceosome, a dynamic snRNPs complex (U1, U2, U4, U5, and U6) and associated proteins, recognizes specific splice sites in pre-mRNAs, to remove introns and join exons, producing mature mRNAs. This mechanism ensures accurate and flexible RNA processing, contributing to transcriptome diversity. UTR: untranslated region. *created with*BioRender.com

dysregulation not only alters protein diversity but also contributes to cellular stress, impaired homeostasis, and disease progression [32, 33].

Alternative splicing

AS is a mechanism that generates multiple mRNA isoforms from a single pre-mRNA, thereby increasing proteome diversity. [34] This process contrasts with constitutive (regular) splicing, a default mechanism in which all introns are removed, and exons are joined together in a fixed, sequential manner to produce a single, specific mRNA transcript. This transcript encodes one specific protein product, as the same combination of exons is consistently retained [35].

In contrast, AS is a tightly regulated process in which the spliceosome selectively includes or excludes specific exons, creating multiple mRNA isoforms from the same pre-mRNA. This mechanism enables the generation of diverse protein isoforms, thereby expanding the proteome to produce cell-specific protein combinations that define the functional properties of different cell types [34].

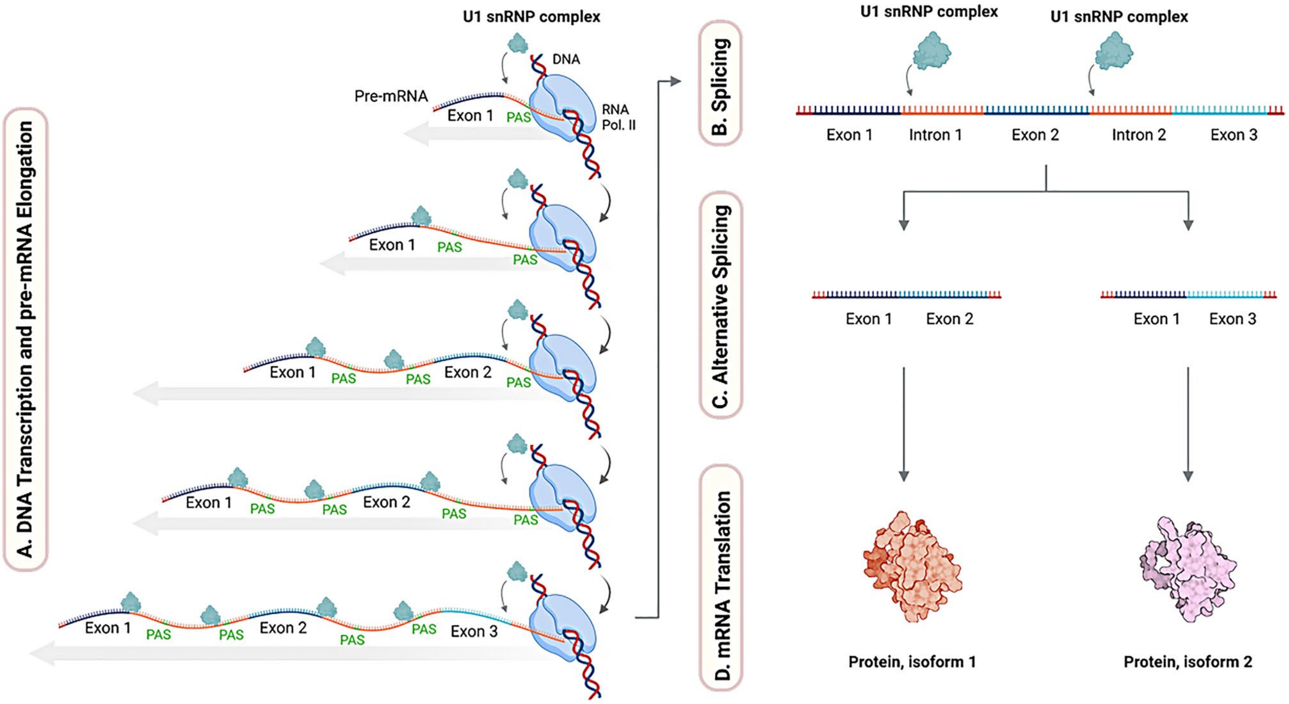

Fig. 2 This figure illustrates the dual functions of U1 snRNPs in cotranscription and RNA splicing. This coupling is essential for gene expression and stability, especially in long genes. **A**. DNA transcription and pre-mRNA elongation—U1 snRnps interact with RNA polymerase II, coordinating transcription and mRNA stability, promoting cotranscriptional splicing, and preventing exon misprocessing. **B**. Splicing—U1 snRNP also binds to the 5′ splice site of pre-mRNA to initiate spliceosome assembly, ensuring the accuracy of splicing. **C**. Alternative splicing—a regulated process in which the spliceosome selectively includes or excludes specific exons, generating multiple mRNA isoforms from the same pre-mRNA. **D**. mRNA translation—the mechanism of alternative splicing increases proteomic diversity, allowing cell-specific protein expression and functional specialization by the generation of different protein isoforms. *created with*BioRender.com

The generation of unique mRNA isoforms through AS, coupled with the cotranscriptional function of U1 snRNPs to ensure stability, mainly in long genes, enables higher eukaryotes to achieve proteomic complexity without a proportional increase in gene number, highlighting the evolutionary importance of U1 snRNPs across species [36–39].

Although all cells require the function of the spliceosome, neural brain and retina cells are remarkably vulnerable to splicing perturbations owing to their complex cellular functions, which require specific splice isoforms. AS is relevant in specialized cells, where it supports neurogenesis, migration, and synaptic function [26, 34, 40, 41]. While AS enhances genetic plasticity, it also increases the risk of splicing errors, leading to functional disruptions [42]. As a result, numerous neurodegenerative diseases are linked to splicing defects [21, 43, 44].

Transcriptome analyses have revealed unprecedented levels of AS in retinal PR cells, suggesting a link between AS and light perception [11, 45–47]. The unique noncoding transcripts and isoforms in these cells highlight AS as a key factor in the transcriptional complexity of retinal gene expression, making the retina an ideal model for RNA biology research [11, 47–51].

U1 snRNP cotranscription and premature polyadenylation

Polyadenylation (PA) is a two-step process that involves the cleavage of pre-mRNAs, usually at the 3’ UTR, and the addition of a polyadenosine (polyA) tail, which is fundamental for mRNA stability, nuclear export, and efficient translation. Premature PAs, where the polyA tail is added before complete transcript processing, can lead to the formation of truncated mRNAs and nonfunctional or harmful proteins [52].

The U1 snRNP complex suppresses premature cleavage and PA of pre-mRNAs by masking cryptic PA sites, ensuring transcript integrity [31, 32]. This U1 snRNP cotranscriptional process is essential for the full-length transcription of genes, particularly those with long introns, which are more susceptible to premature PA [27, 53, 54]. Both alternative splicing and U1 cotranscriptional processes are considered key drivers of evolutionary complexity [55], as they significantly impact the cellular regulatory landscape, protein diversity, and organismal complexity [56].

Longer genes generate more splice variants with distinct functions [57], which require regulatory mechanisms to prevent premature cleavage. U1 snRNP protects these transcripts, ensuring full-length mRNA production. Loss of this protection can lead to dysfunctional, shortened transcripts [58]. This phenomenon is observed in various diseases. A moderate reduction in U1 snRNP levels leads to shorter transcripts, a pattern observed in stem cells and activated immune cells [59]. While this process supports normal cellular function, it may also increase protein production, which can activate oncogenes in cancer cells [52, 60]. In contrast, during development and differentiation, especially in specialized cells such as neurons in the brain and retina, longer mRNA transcripts are produced [52, 60–62]. The vulnerability of neurons to disturbances in U1 snRNP homeostasis may explain the prevalence of these defects in neurodegenerative disorders [24](Fig. 3).

Epitranscriptome

Epigenetics refers to heritable changes in gene expression that do not involve alterations in the DNA sequence and are often mediated by mechanisms such as DNA methylation, histone modification, and chromatin remodeling [63]. In parallel, the term epitranscriptome refers to chemical modifications of RNA that regulate its metabolism without changing the RNA nucleotide sequence [64]. To date, over 150 different epitranscriptome modifications have been described for RNA, positioning the epitranscriptome as a key regulator of the transcriptional landscape, given that these modifications can disrupt RNA stability, splicing, and translation [11, 64–68].

Retinal cells, particularly RPE and PR cells, are highly susceptible to these epitranscriptomic changes, especially the N6-methyladenosine (m6A) modification [69]. As a neural tissue that is directly exposed to sunlight throughout life, with no turnover, high metabolic demand, and limited regenerative capacity, the retina faces cumulative damage from photooxidative stress. These chronic

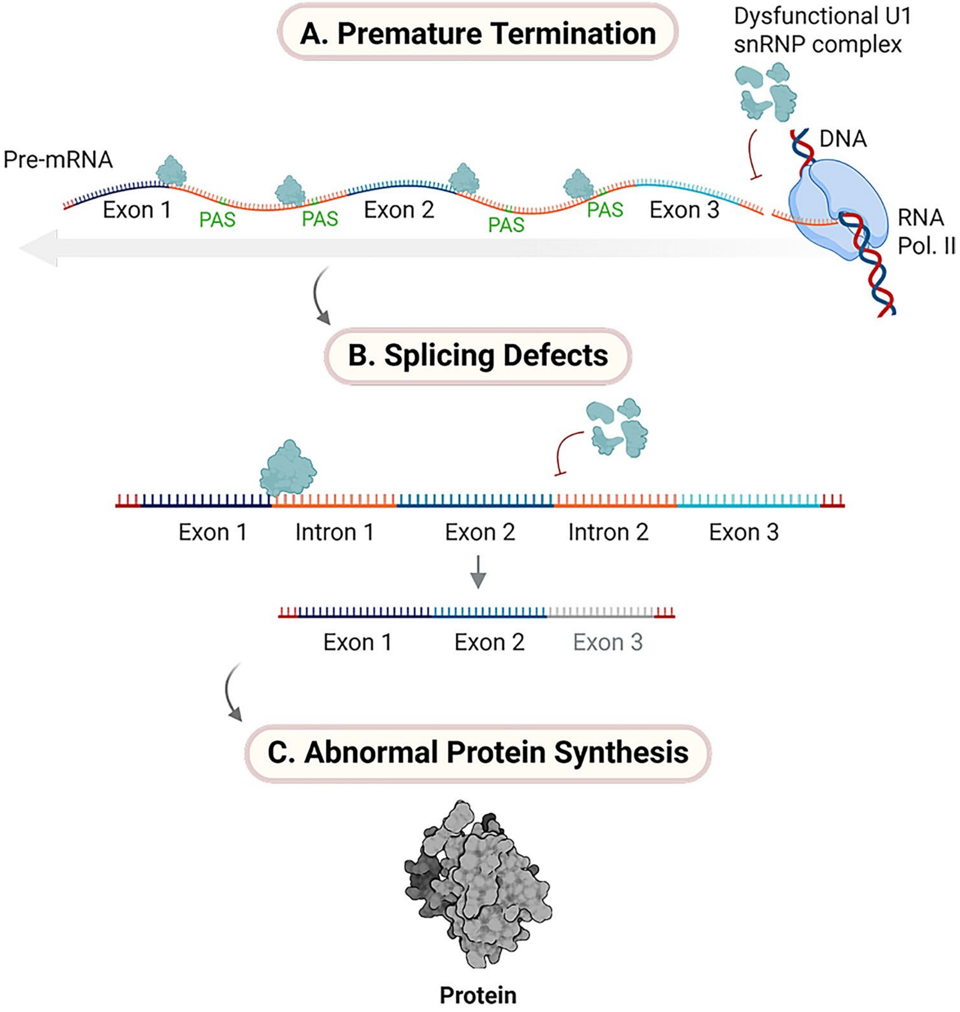

Fig. 3 **A**. Premature termination. disruption of the cotranscriptional function of U1 snRNPs impairs their ability to suppress premature polyadenylation, leading to early cleavage of pre-mRNA transcripts. **B**. Splicing defects. this results in truncated, nonfunctional, or harmful mRNAs, particularly long genes with multiple splice variants. **C**. Abnormal protein synthesis. the loss of transcript integrity contributes to dysregulated protein expression and is implicated in various diseases. *created with*BioRender.com

injuries increase susceptibility to RNA dysregulation, which can contribute to dry AMD by impairing cellular stress responses, immune regulation, cytokine expression, lipid metabolism, and complement system activation [70–73]. Numerous physical, chemical, and biological factors can induce oxidative stress, resulting in the generation of reactive oxygen species (ROS). Under normal conditions, ROS can act as effectors and signaling molecules; however, chronically, when produced in excess or mislocalized, they can impact the epitranscriptome [16]. In this way, oxidative stress particularly affects noncoding RNAs, causing abnormalities in their expression, which may contribute to the pathophysiology of many diseases, including cancer and neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and AMD [16, 74–80].

Other environmental factors, such as nutrition, exercise, pollution, and smoking, also trigger the activation of specific cellular programs that respond quickly through changes in gene expression [47, 73, 81].

RNA dysfunction in the developing and aging retina

Aging is the primary risk factor for major human pathologies. As a result, extensive research has focused on understanding the molecular basis of biological aging [82, 83]. Indeed, aging and many age-related diseases share similar hallmarks of RNA dysfunction, as AS alterations can occur in both healthy aging and several diseases [36, 84]. RNA processing and splicing are among the major categories of age-related differentially spliced transcripts shared across human tissues [84, 85].

During their lifetime, aging cells accumulate DNA mutations and unrepaired damage. Nonetheless, aging is not caused by a single type of damage. Despite differences between tissues, aging is associated with several hallmark modifications at the cellular and molecular levels, as shown in Fig. 4 [36, 83, 86–89]. These include some alterations as follows:

- epigenetic and epitranscriptome modifications
- changes in chromatin structure
- genomic instability
- telomere attrition
- metabolic changes

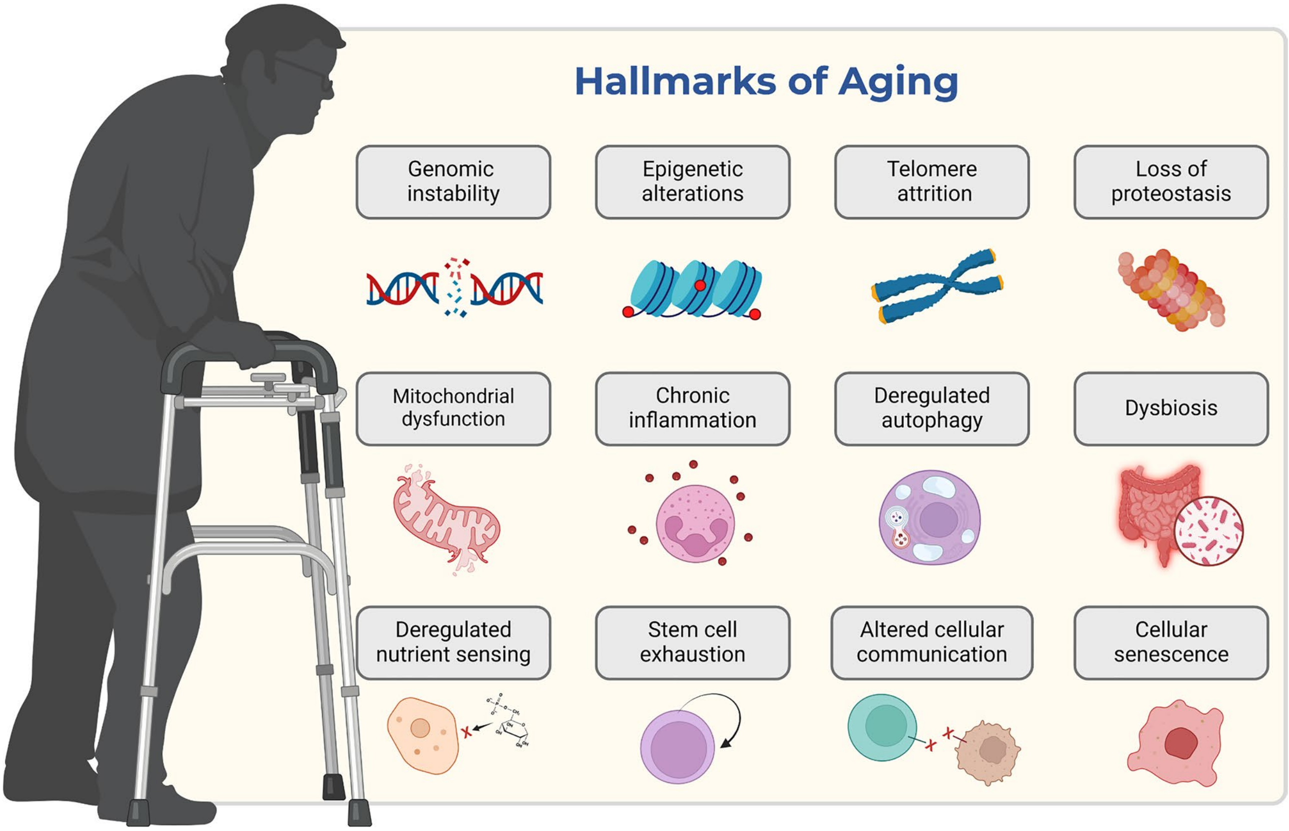

Fig. 4 The key biological mechanisms of aging are related to the interconnected processes and molecular basis of biological aging that contribute to tissue decline and aging-related health deterioration. *created with*BioRender.com

- lipid peroxidation
- misfolded proteins
- decline in proteasomal function
- impaired autophagy and phagocytosis
- accumulation of senescent cells
- chronic inflammation
- impaired cellular communication
- loss of stem cell renewal capabilities

These factors contribute to physiological decline, chronic diseases, and increased mortality. The brain and retina are highly susceptible to these injuries, but several repair mechanisms work to correct these events before they lead to mutations. However, the efficiency of these repair pathways decreases with age [82, 90–93].

There is a clear relationship between aging and altered U1 snRNP homeostasis [24]. With age, reduced U1 snRNP levels impair cotranscriptional processing, leading to premature transcriptional termination of long genes. This, in turn, results in the accumulation of nonfunctional RNAs, truncated proteins, and altered gene isoforms that compromise cellular function [36, 54, 59, 94], all of which share common hallmarks with neurodegenerative and age-related diseases [84].

The differential regulation of short and long genes with age appears to be a relevant factor in the aging process, affecting tissue health and potentially influencing the onset of age-related diseases [95]. During aging, the transcriptional machinery becomes less efficient and more prone to errors [36, 96, 97]. This inefficiency disproportionately affects long genes because their transcription requires more time and energy, increasing their vulnerability to interruptions. Short genes, otherwise, tend to be transcribed more quickly and may be less affected by these age-related inefficiencies, allowing them to maintain higher expression levels in aging cells than long genes [96]. Thus, shorter genes tend to either maintain or even increase their expression with age, whereas longer genes often show decreased expression [98]. Another mechanism contributing to the age-related decline in long-gene expression is chromatin remodeling that accompanies aging, which alters histone methylation patterns and reduces histone abundance, thereby changing chromatin compaction and accessibility [99–102]. Because long genes require coordinated regulation and a stable chromatin landscape to sustain transcriptional elongation, these changes promote polymerase pausing and premature termination, ultimately lowering their expression [95, 103].

Understanding these mechanisms is essential for developing strategies to mitigate age-related decline. One potential approach could involve discovering ways to support the transcription of critical long genes in aging cells, which may help preserve cellular function and delay the onset of age-related diseases, especially in tissues that depend on these genes for specialized functions, such as the brain and retina [95, 98, 104].

Potential mechanism of AMD pathogenesis related to U1 snRNP dysfunction

The retina is a highly metabolically active tissue that is acutely susceptible to oxidative stress because of its continuous exposure to high levels of light and oxygen. Over time, aging and environmental agents exert a chronic, cumulative burden on RPE cells. These postmitotic cells are particularly vulnerable to damage, as they cannot dilute toxic byproducts through cell division. Age-related changes in the RPE include alterations in pigmentation, increases in lipofuscin granules, decreases in mitochondrial function, accumulation of proinflammatory substances, and decreases in RPE cell density due to apoptosis [105–109]. Oxidative stress in the RPE is also attributed to lipofuscin, which is a pigment granule composed of lipid-containing residues from lysosomal digestion that generate ROS upon blue light excitation [110]. ROS levels are controlled and maintained by the antioxidant system. However, when ROS levels surpass the antioxidant capacity of the cell, oxidative stress ensues [108, 111]. As a result of ROS overproduction and subsequent mitochondrial DNA damage, several mitochondrial proteins involved in the apoptosis cascade, such as cytochrome c and apoptosis-inducing factor, are released [112].

Oxidative stress and mitochondrial injury activate the intrinsic apoptotic pathway, culminating in cytochrome c release, apoptosome assembly, and the activation of caspase 9 and caspase 3. The extrinsic apoptotic pathway, triggered by inflammatory cytokines such as TNF-α, also converges on caspase 3 activation [108].

Activated caspase 3 cleaves essential nuclear proteins, including the U1–70k and Sm proteins, which are required for the proper assembly and function of the U1 snRNP complex [113]. These modified U1 snRNP components relocate to apoptotic bodies near the cell surface [114, 115]. These alterations may contribute to the breakdown of the mRNA splicing machinery during apoptosis and potentially trigger autoimmune responses in susceptible individuals [114]. Disruption of this complex impairs RNA splicing, leading to the accumulation of misprocessed transcripts, protein aggregation, and cellular stress. In the cytoplasm, caspase-3 also cleaves key regulators of autophagy and phagocytosis, including Beclin-1 and ATG5, which are essential for autophagosome formation, and MerTK, a tyrosine kinase crucial for the daily phagocytosis of PR outer segments by the RPE [116, 117]. Efficient autophagy is essential for maintaining homeostasis in RPE cells, as it allows for the clearance of damaged proteins and organelles [77, 78, 80, 118–121].

The cleavage of these proteins contributes to autophagy failure, phagocytic impairment, and the accumulation of cellular debris, further exacerbating inflammation and cell dysfunction [77, 80, 119–123]. Moreover, aging (the time of continuous chronic injury) and genetic variants in the complement system can exacerbate the progression of AMD, leading to earlier onset or increased severity (Fig. 5) [56, 108, 124, 125].

These interrelated processes establish a vicious cycle and support a model in which U1 snRNP dysfunction, triggered by oxidative stress and apoptotic cleavage, acts as a central driver of splicing failure, autophagy impairment, and neurodegeneration in dry AMD, highlighting these pathways as promising therapeutic targets.

RNA spliceosome dysfunction in inherited retinal diseases

Inherited retinal diseases (IRDs) have placed the retina at the forefront of gene and RNA therapeutics owing to its surgical accessibility, relative immune privilege, and the ability to noninvasively track disease progression and

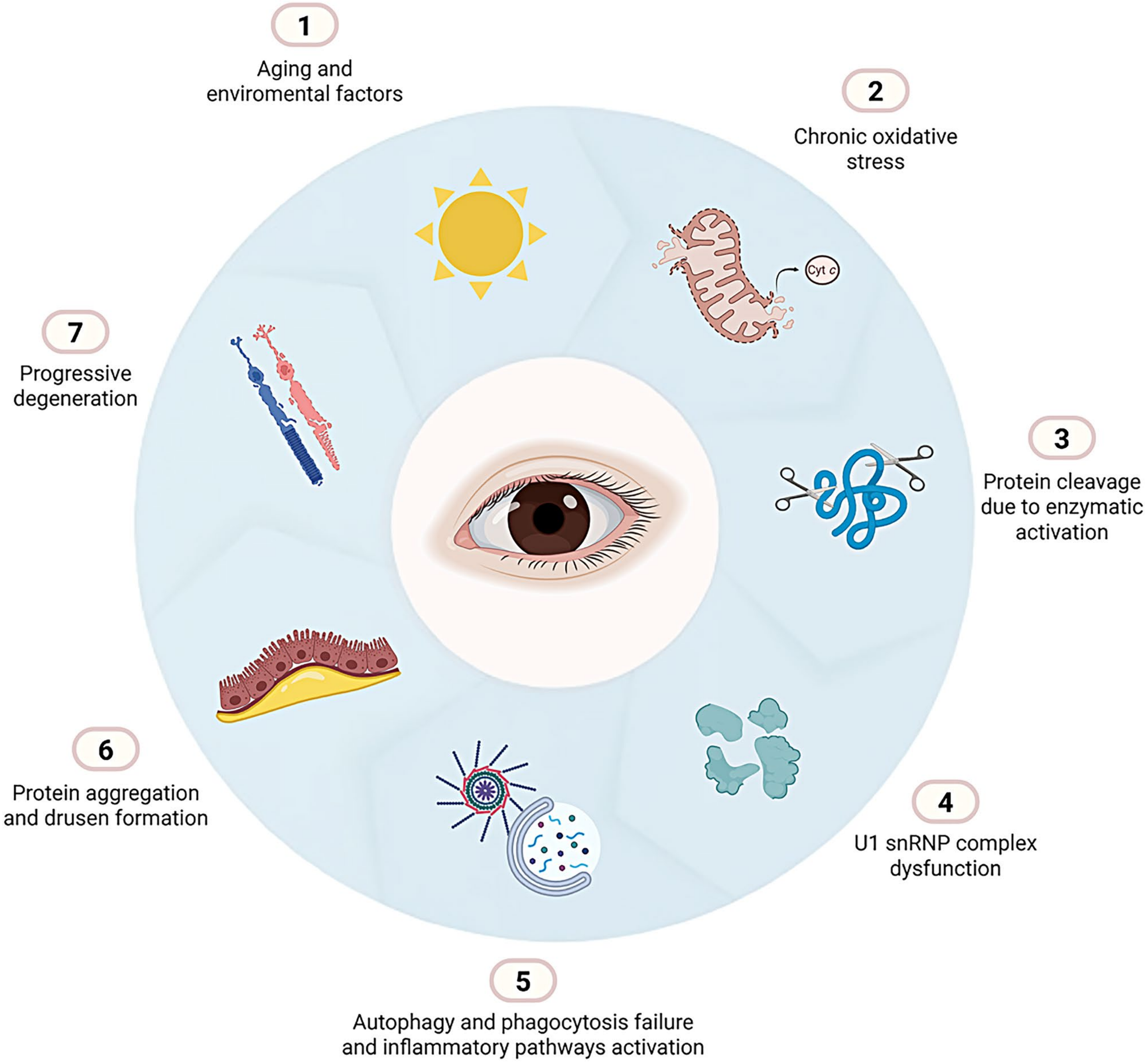

Fig. 5 Pathogenic cascade in dry AMD associated with U1 snRNP dysfunction. (1) aging and environmental stressors chronically damage RPE cells. (2) persistent oxidative stress and mitochondrial injury induce cytochrome c release, apoptosome formation, and activation of caspases-3/9. (3) caspase-3 cleavage disrupts U1-70K and Sm proteins essential for U1 snRNP assembly, and targets beclin-1, ATG5, and MerTK, compromising autophagy and phagocytosis. (4) U1 snRNP dysfunction leads to defective splicing and transcript misprocessing. (5) impaired clearance mechanisms exacerbate debris accumulation and chronic inflammation. (6) misprocessed transcripts and protein aggregation promote drusen formation. (7) these processes reinforce a self-perpetuating cycle of cellular dysfunction that drives progressive retinal degeneration. *created with*BioRender.com

treatment response [126]. While most IRDs are caused by single-gene mutations that primarily affect PRs and, less often, the RPE, an important subset arises from errors in pre-mRNA processing. Variants in spliceosome proteins—or in factors that regulate them—disrupt normal isoform production and impair retinal cell function. Because vision relies on the accurate splicing of long, highly expressed retinal transcripts, even small splicing defects tend to accumulate over time, driving progressive dysfunction and degeneration. These mechanistic insights have motivated RNA-directed interventions—allele-specific silencing with small-interfering RNA (siRNA), short hairpin RNA (shRNA), antisense oligonucleotides (ASO) to correct or modulate splicing, and engineered RNA-guided strategies (ERGS)—that can address variants previously considered untreatable [127].

Neural tissues are known to exhibit the greatest number of AS events [56], as variations in transcript isoforms, AS, and ncRNAs increase gene and phenotypic diversity and complexity, allowing cells to function distinctly from one another [47, 51]. The importance of AS in the retina has been demonstrated by numerous examples. In PR, AS is important for generating the protein diversity necessary for light detection, signal transduction, and cellular maintenance. Many PR-specific genes, including those encoding opsins (light-sensitive proteins) and components of the phototransduction pathway, undergo AS. Proper splicing is required for the precise function and structure of these proteins, which are critical for normal vision [124, 128].

Some SFs are specifically important for processing retinal transcripts since their mutations cause retinal dystrophy. Notably, most of these factors, including PRPF3, PRPF4, PRPF6, PRPF8, and PRPF31, are necessary for mediating interactions between U4/U6 and U5 snRNPs, which are fundamental components of the spliceosome machinery [56].

In addition to the previously mentioned genes, mutations in genes encoding SFs include SNRNP200, DHX38, PAP1, RPGR, BBS8, DYNC2H1, CEP290, CWC27, and others [129, 130]. All these genes are associated with a variety of IRD [131, 132], such as cone−rod dystrophy, recessive Usher syndrome type 2, X-linked and dominant retinitis pigmentosa (RP), recessive Bardet–Biedl syndrome, recessive Senior–Loken syndrome, recessive Joubert syndrome, recessive Leber congenital amaurosis, recessive Meckel syndrome, syndromic retinal degeneration, and Stargardt disease [56].

Mutations in SFs can result in a phenotype restricted to the retina and other neural cells while being tolerated by other tissues. This phenomenon may be explained by the fact that the retina presents relatively high levels of certain specific and unique SFs that regulate PR-specific genes involved in phototransduction and the visual cycle [21, 56, 133, 134].

U1 snRNP dysfunction in neurodegenerative and other diseases

Splicing defects in long genes have been implicated in several neurodegenerative disorders, including AD, PD, Huntington's disease, amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy (SMA). Disruption of U1 snRNP biogenesis and function has been observed in conditions such as AD, FUS-linked ALS, SMA, and pontocerebellar hypoplasia [42, 96, 135–137]. In addition to neurodegeneration, U1 snRNP dysfunction is also implicated in other human pathologies such as autoimmune diseases, as systemic lupus erythematosus and mixed connective tissue disease, where autoantibodies target U1 snRNP components, contributing to disease pathogenesis [138, 139]. Additionally, alterations in U1 snRNP expression or function have been observed in various cancers, influencing oncogenic splicing programs and genome stability (Fig. 6) [140–143].

Given that U1 snRNP is universally expressed across all cell types, the higher vulnerability of neurons to its dysregulation raises the question of why other cell types remain relatively unaffected. Neuronal susceptibility may arise from their dependence on the accurate expression of long genes essential for synaptic function and integrity [24, 59, 95, 104, 144–146].

In AD and other neurodegenerative disorders, changes in the levels of U1 snRNPs, particularly U1-70K (one of the components of the U1 complex), are associated with the dysregulation of genes essential for neuronal maintenance and synaptic function [147]. Many of these critical genes, such as those that encode the amyloid-beta (Aβ) peptide and TAU protein, are classified as long genes and contain numerous introns, making them especially reliant on precise splicing [54, 59, 148]. This is the case of the amyloid precursor protein (APP), which encodes the Aβ peptide. Under physiological conditions, APP plays important roles in neurons, including neurogenesis, synaptic plasticity, neurite outgrowth, and neuroprotection [149]. However, the abnormal processing of APP generates Aβ peptide isoforms that are prone to misfolding and aggregation. These peptides have been identified in drusen deposits in the brain and retina associated with both AD and AMD, supporting a shared pathogenic mechanism involving long misfolded proteins and chronic inflammation [150–153].

The microtubule-associated protein TAU (MAPT) gene encodes the TAU protein, which is essential for microtubule stability and function. This long gene undergoes extensive AS, which increases its functional complexity and results in the generation of multiple transcript isoforms. Disruptions in MAPT are associated with

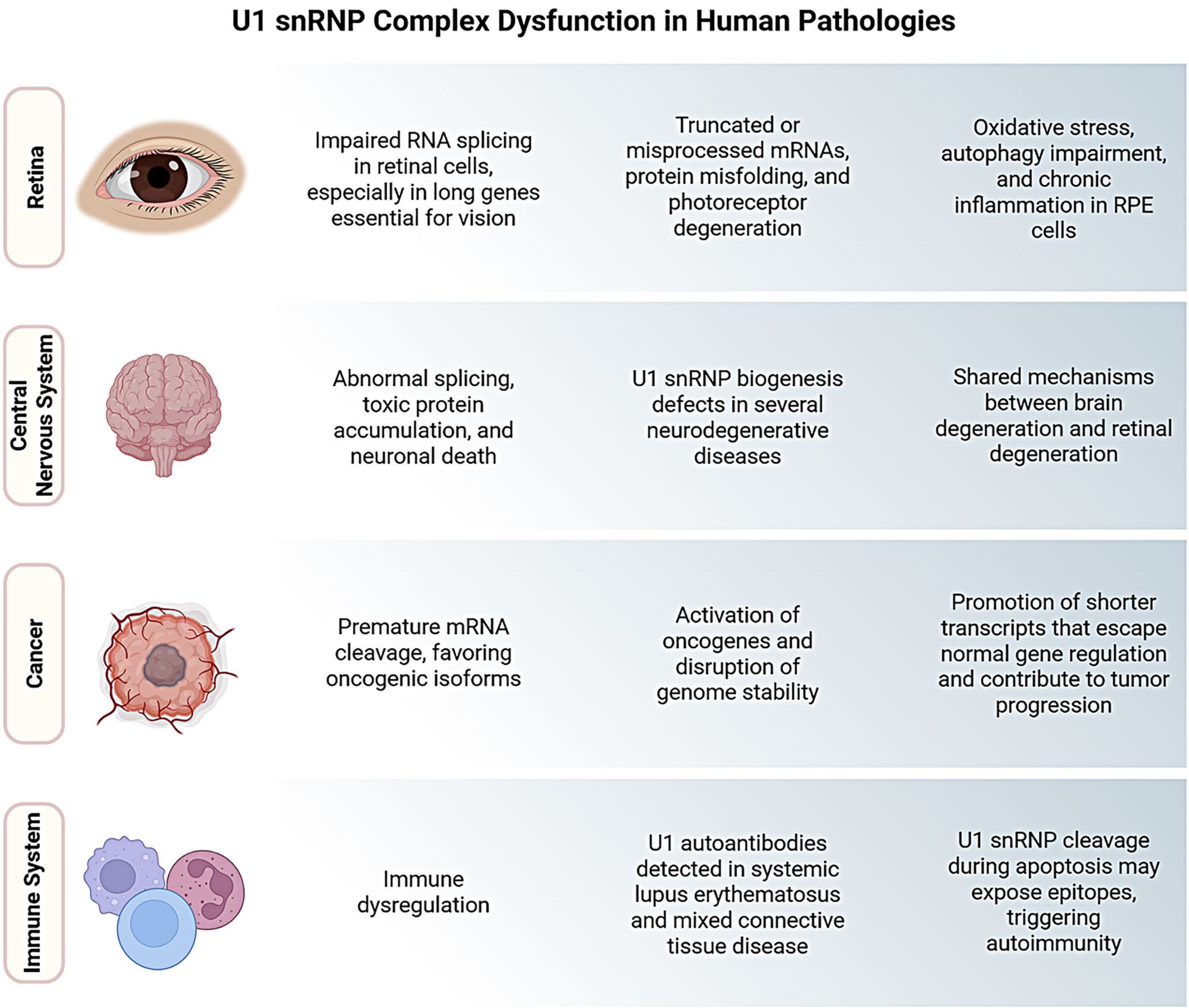

Fig. 6 U1 snRNP complex dysfunction impairs RNA splicing, triggering widespread effects that contribute to eye diseases, CNS disorders, cancer, and autoimmune disorders, revealing its central role in cellular integrity. *created with*BioRender.com

tauopathies, including AD and frontotemporal dementia. Abnormal TAU phosphorylation (p-TAU) results in the formation of neurofibrillary tangles, a hallmark pathological feature of these neurodegenerative diseases [154, 155]. Additionally, p-TAU is related to the disruption of cytoskeletal integrity in both brain tauopathies and retinal ganglion cells (RGCs), the primary cells affected by aging glaucomatous optic neuropathy (GON) [155–159]. Given their long axons, RGCs are highly dependent on TAU to maintain microtubule stability and efficient axonal transport, making them particularly vulnerable to TAU-related dysfunction [159, 160]. Owing to the importance of TAU in these processes, RGCs are disproportionately affected by p-TAU pathology compared with other retinal cells [161, 162].

Disruption of U1 snRNP biogenesis, a mechanism implicated in AD, may also contribute to retinal neurodegenerative disorders such as AMD and GON. This shared disruption, associated with pathological hallmarks as extracellular Aβ plaque accumulation and intracellular neurofibrillary tangles [148, 158, 159, 163–165] raises the hypothesis that AD, AMD, and GON may represent distinct phenotypic outcomes of a common underlying mechanism centered on U1 snRNP dysfunction, modulated by cell-type specificity. Targeting U1 snRNP regulation could thus represent a unifying therapeutic strategy for age-related neurodegenerative diseases affecting both the brain and retina.

Implications for novel RNA therapeutic strategies for AMD

The retina has historically been central to RNA therapy development. The first ASO, fomivirsen, was approved in 1998 for intravitreal treatment of CMV retinitis [166].

Later, the field advanced with voretigene neparvovec (Luxturna, Spark Therapeutics), the first FDA-approved gene therapy for inherited retinal dystrophy, in 2017 [167]. Pegaptanib—the first anti-VEGF agent approved for neovascular AMD—validated the aptamer class [168]; the C5 inhibitor avacincaptad pegol has shown efficacy in slowing geographic-atrophy (GA) lesion growth [9, 169]; and the C3 inhibitor pegcetacoplan likewise reduces GA progression, but the magnitude of benefit remains modest and functional gains are limited, underscoring the need for upstream RNA-targeted advances [5].

Yet these approaches generally act downstream on single pathways. By contrast, U1 snRNP–targeted strategies address an upstream defect in RNA homeostasis. U1 snRNP safeguards full-length transcription and isoform fidelity—processes vulnerable in aging tissues such as the retina [31, 59].

Several U1-centric modalities (Table 2) remain at the pre-clinical stage but have corrected pathogenic splicing in IRD models: mutation-adapted/engineered U1 and exon-specific U1 (ExSpeU1) rescued defects in RHO (autosomal-dominant RP) and RPGR (X-linked RP) in patient cells and reporter systems; combining engineered U1 with ASO improved correction of a BBS1 splice-site mutation causing Bardet–Biedl–related rod–cone dystrophy; and adeno-associated virus (AAV)-delivered engineered U1 restored Opa1 expression with short-term ocular safety in an Opa1-mutant mouse model of autosomal-dominant optic atrophy [186, 187, 187–190, 194, 195]. By stabilizing transcriptomes rather than neutralizing single effectors, U1-directed therapies could surpass current options in scope and durability.

APT20TTMG has a strategic sequence, structure, and chemical modifications to bind to U1 snRNP and pre-mRNAs' conserved regions, ensuring the correct assembly during the splicing initiation process of all transcripts, without silencing or inhibiting genes.

Cross-disease evidence reinforces this rationale. Leal et al. (2024) [147] demonstrated that therapeutic correction of U1 snRNP function with a novel platform (APT20TTMG) in Alzheimer's disease models not only normalized global splicing patterns but also downregulated aberrant expression of long genes vulnerable to premature transcriptional termination. APT20TTMG binds conserved U1 snRNP and pre-mRNA binding sites to stabilize spliceosome assembly at initiation across transcripts, without directly silencing genes. This treatment reduced pathological TAU accumulation in neurons, decreased Aβ burden, and lowered insoluble p-TAU across multiple brain regions. These findings suggest that restoring U1 snRNP integrity can re-establish transcriptomic homeostasis and attenuate hallmark neurodegenerative processes [147].

Given the molecular parallels between AD and AMD—including TAU phosphorylation, Aβ deposition, and long-gene vulnerability—these findings provide preclinical support for U1-targeted therapies as a unifying strategy across neurodegenerative disorders such as AD—where U1 dysfunction is well established—to age-related retinal disease, including AMD.

Translation to AMD will require optimized macular delivery (e.g., AAV vectors or chemically stabilized oligonucleotides), rigorous off-target and splice-isoform profiling, and validated biomarkers to monitor therapeutic impact. Nevertheless, by acting at an upstream regulatory node, U1-based therapeutics represent a promising next generation of RNA medicines for dry AMD [31, 59, 140, 147].

Conclusions

Studying DNA alone is insufficient to uncover the complete genetic basis of complex diseases, such as AMD. The RNA transcriptome represents a vast layer beyond the DNA sequence that is now widely acknowledged and can drive research linking genetic variation to cellular pathology [47]. Future research is essential to unravel this complex relationship between neuronal function and dysregulation of RNA metabolism.

This review highlights the emerging role of the age-sensitive dysfunction of the U1 snRNP complex in the pathophysiology of AMD, proposing a model in which aging and environmental stressors can disrupt cotranscriptional and splicing processes.

Perturbation at this node unifies premature termination of long genes, isoform imbalance, chronic inflammation, as well as impaired autophagy and proteostasis, offering a mechanistic bridge to broader neurodegenerative conditions. By framing RNA metabolism dysregulation as a central driver of the pathology, this perspective introduces a novel therapeutic approach that may extend beyond AMD. It also provides insights into a potentially shared pathogenic mechanism and could contribute to addressing significant unmet medical needs across multiple neurodegenerative conditions.

Table 2 U1-based and engineered U1 snRNA therapeutics: preclinical evidence

Therapeutic Area	RNA therapeutic	Strategy	Disease	Gene	Reference	Year
Dermatology	ExSpeU1	Restores LEKTI (SPINK5) splicing	Netherton syndrome	SPINK5	[170]	2015
Hematology	ExSpeU1	ExSpeU1 splice correction	Hemophilia B	F9	[171]	2016
	mutation-adapted U1	Suppressor U1 enhances correct splicing at mutant donor	Fanconi anemia	FANCC	[172]	2010
	engineered U1 snRNA	Rescues exon-8 definition disrupted by atypical mutations	Fanconi anemia	FANCA	[173]	2014
Hepatology	adapted U1/ExSpeU1	Efficient in-vitro rescue of splice-site mutations	PFIC1/BRIC1 spectrum	ATP8B1	[174]	2015
	engineered U1 snRNA	Somatic c.1061C > A counteracts c.1062 + 5 G > A enabling U1 rescue	Tyrosinemia type I	FAH	[175]	2018
	engineered U1 snRNA	Compensatory U1 5′ss	Tyrosinemia type I	FAH	[176]	2020
Metabolic	mutation-adapted U1	Compensatory U1 5′ss	Propionic Acidemia	PCCA	[177]	2011
	engineered U1 snRNA	Modified U1 binds downstream enhancer to restore exon inclusion	Phenylketonuria	PAH	[178]	2018
Neurology	engineered U1 snRNA	Corrects DDC (AADC) splicing	AADC deficiency	DDC	[179]	2016
	ExSpeU1 (AAV9)	ExSpeU1 splice correction	Familial Dysautonomia	ELP1 (IKBKAP)	[180]	2018
	ExSpeU1	CDKL5 splicing rescue	CDKL5 Deficiency Disorder	CDKL5	[181]	2019
	ExSpeU1 (AAV9)	ELP1 exon-20 splicing correction	Familial Dysautonomia	ELP1 (IKBKAP)	[182]	2022
	U1-based (APT20TTMG)	Binds U1 snRNP	Alzheimer's disease (preclinical)	U1 snRNP target (global)	[147]	2024
Oncology	U1 adaptor oligonucleotides	U1i gene silencing targeting BCL2 and GRM1	Melanoma	BCL2; GRM1	[183]	2013
	U1 adaptor oligonucleotides	U1i gene silencing targeting KRAS and MYC	Pancreatic cancer	KRAS; MYC	[184]	2017
	engineered U1	Low U1 dependence at NF1 exon-29 donor	Neurofibromatosis type 1	NF1	[185]	2009
Ophthalmology	engineered U1 snRNA	Compensatory U1 5′ss	Autosomal dominant Retinitis Pigmentosa	RHO	[186]	2009
	engineered U1 snRNA	Compensatory U1 5′ss	X-linked Retinitis Pigmentosa	RPGR	[187]	2011
	Engineered U1 + ASO	U1+ASO combined	Bardet–Biedl syndrome	BBS1	[188]	2019
	U1_asRNA (chimeric antisense U1)	U1_asRNA exon skipping	Retinitis pigmentosa (RPGR E9a)	RPGR	[189]	2022
	engineered U1 snRNA	AAV-delivered engineered U1 corrects Opa1 splice defect in vivo	Autosomal Dominant Optic Atrophy	OPA1	[190]	2023
	ExSpeU1 (AAV2 intravitreal)	ExSpeU1 splice correction	Familial Dysautonomia –optic neuropathy (TgFD9)	ELP1 (IKBKAP)	[191]	2025
Pulmonology	ExSpeU1	ExSpeU1 splice correction	Cystic Fibrosis	CFTR	[192]	2012
	ExSpeU1	Rescue of common exon-skipping CFTR mutations	Cystic Fibrosis	CFTR	[193]	2020

Table 2 summarizes studies that engage the U1 snRNP either through engineered U1 snRNA (compensatory U1 and ExSpeU1) or U1-targeting approaches (U1_asRNA, U1 adaptors/U1i, U1-binding modulators). Inclusion was limited to modalities that directly leverage U1 snRNP for splice correction, exon skipping, poly(A) interference, or related U1-mediated mechanisms. CRISPR editing, standard ASOs without U1 engagement, and general RNAi agents were excluded. This concise table complements the main text's focus on U1 snRNP dysfunction. When multiple reports exist for a given program, the earliest peer-reviewed study that provides the clearest description of the modality is listed. Chekuri et al., 2025 [191] is a preprint flagged in the Reference field and should be interpreted with caution until peer review. Data cutoff: August 2025. Abbreviations: ExSpeU1, exon-specific U1; U1i, U1 interference; AAV, adeno-associated virus, U1_asRNA, U1 antisense RNA

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-beta
ALS	Amyotrophic lateral sclerosis
AMD	Age-related macular degeneration
APP	Amyloid precursor protein
AS	Alternative splicing
ASO	Antisense oligonucleotide
AAV	Adeno-associated virus
ceRNA	Competing endogenous RNA
circRNA	Circular RNA
DNA	Deoxyribonucleic acid
ERGS	Engineered RNA-guided strategy
ExSpeU1	Exon-specific U1

GA	Geographic atrophy
GON	Glaucomatous optic neuropathy
IRD	Inherited retinal dystrophies
lincRNA	Long intergenic noncoding RNA
m6A	N6-methyladenosine
MAPT	Microtubule-associated protein TAU
miRNA	MicroRNA
mRNA	Messenger RNA
NATs/OS	Natural antisense transcripts/Opposite strand RNA
ncRNA	Noncoding RNA
p-TAU	TAU phosphorylation
PA	Polyadenylation
PD	Parkinson's disease
piRNA	PIWI-interacting RNA
PolyA	Polyadenosine
PR	Photoreceptor
pre-mRNA	precursor messenger RNA
RGC	Retinal ganglion cell
RNA	RNA polymerase II
RNA Pol II	PIWI-interacting RNA
RNP	Ribonucleoprotein
ROS	Reactive oxygen species
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelial
rRNA	Ribosomal RNA
SF	Splicing factors
siRNA	Small interfering RNA
shRNA	Short hairpin RNA
piRNA	PIWI-interacting RNA
SMA	Spinal muscular atrophy
snoRNA	Small nucleolar RNA
snRNA	PIWI-interacting RNA
piRNA	Small nuclear RNA
snRNP	PIWI-interacting RNA
piRNA	Small nuclear ribonucleoprotein
tRNA	Transfer RNA
UTR	Untranslated region
U1i	U1 interference
U1_asRNA	U1 antisense RNA
VEGF	Vascular endothelial growth factors

Acknowledgements

The authors gratefully acknowledge Rafael Bottos, CEO of Aptah Bio, for his outstanding scientific and strategic leadership and critical insights, whose vision and dedication greatly contributed to the direction and development of this review.

Author contributions

JMB and CBQSL were involved in conceptualization. JMB prepared the original manuscript draft. JMB and ESS prepared the table and all the figures, whereas all the authors contributed significantly to the revision and finalization. All the authors have approved the final manuscript. This manuscript was developed as part of JMB's postdoctoral research (Department of Ophthalmology, Federal University of São Paulo) and reflects the culmination of an in-depth investigation into the molecular mechanisms underlying retinal degeneration. She conducts her postdoctoral research under the supervision of JMFS and CBQSL.

Funding

This manuscript was supported as part of regular employment duties at Aptah Bio Inc. No additional funding was provided.

Data availability

Not applicable.

Declarations

Ethics and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

JMB is a postdoctoral researcher and a member of the scientific advisory board of Aptah Bio, Inc. She conducts her postdoctoral research under the supervision of JMFS and CBQSL. CBQSL is a cofounder of Aptah Bio, Inc., and has filed a patent related to this work (US11946050B2). ESS, CGMZ and VVCS are PhD professionals at Aptah Bio, Inc.

Received: 22 July 2025 / Accepted: 20 September 2025

References

1. Chakravarthy U, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC ophthalmol. 2010;10.
2. Wong WL, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2.
3. Hollyfield JG. Age-related macular degeneration: the molecular link between oxidative damage, tissue- specific inflammation and outer retinal disease: the Proctor lecture. Invest Ophthalmol & Visual Sci. 2010;51 Preprint at https://doi.org/10.1167/iovs.09-4478.
4. Ammar MJ, Hsu J, Chiang A, Ho AC, Regillo CD. Age-related macular degeneration therapy: a review. Curr Opin In ophthalmol. 2020;31 Preprint at https://doi.org/10.1097/ICU.0000000000000657.
5. Heier JS, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022;399.
6. Wei CX, et al. Challenges in the development of therapy for dry age-related macular degeneration. Adv Exp Med And Biol. 2016;854.
7. Pfau M, et al. Association of complement C3 inhibitor pegcetacoplan with reduced photoreceptor degeneration beyond areas of geographic atrophy. Sci Rep. 2022;12.
8. Liao DS, Metapally R, Joshi P. Pegcetacoplan treatment for geographic atrophy due to age-related macular degeneration: a plain language summary of the FILLY study. Immunotherapy. 2022;14 Preprint at https://doi.org/10.2217/imt-2022-0078.
9. Jaffe GJ, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. Ophthalmology. 2021;128.
10. Sarkar A, Jayesh Sodha S, Junnuthula V, Kolimi P, Dyawanapelly S. Novel and investigational therapies for wet and dry age-related macular degeneration. Drug Discov Today Today. 2022;27 Preprint at https://doi.org/10.1016/j.drudis.2022.04.013.
11. Zelinger L, Swaroop A. RNA biology in retinal development and disease. Trends Genet. 2018;34 Preprint at https://doi.org/10.1016/j.tig.2018.01.002.
12. Brenner S, Jacob F, Meselson M. An unstable intermediate carrying information from genes to ribosomes for protein synthesis. Nature. 1961;190.
13. Chen F, Evans A, Gaskell E, Pham J, Tsai MC. Regulatory RNA: the new age. Mol Cell. 2011;43 Preprint at https://doi.org/10.1016/j.molcel.2011.09.001.
14. Yoon-Been P, Jun-Mo K. Identification of long non-coding RNA-mRNA interactions and genome-wide lncRNA annotation in animal transcriptome profiling. J Anim Sci Technol. 2023;65 Preprint at https://doi.org/10.5187/jast.2023.e17.
15. Wilkes MC, Repellin CE, Sakamoto KM. Beyond mRNA: the role of non-coding RNAs in normal and aberrant hematopoiesis. Mol Genet Metab. 2017;122 Preprint at https://doi.org/10.1016/j.ymgme.2017.07.008.
16. Hyttinen JMT, Blasiak J, Kaarniranta K. Non-coding RNAs regulating mitochondrial functions and the oxidative stress response as putative targets against age-related macular degeneration (AMD). Int J Mol Sci. 2023;24 Preprint at https://doi.org/10.3390/ijms24032636.
17. Sharp PA. Split genes and RNA splicing. Cell. 1994;77.
18. Shampo MA, Kyle RARJ. Roberts-nobel laureate for discovery of split genes. Mayo Clinic Proc. 2003;78.
19. Chow LT, Gelinas RE, Broker TR, Roberts RJ. An amazing sequence arrangement at the 5′ ends of adenovirus 2 messenger RNA. Cell. 1977;12.
20. Sharp PA. Split genes and RNA splicing (nobel lecture). Angew Chem Int Ed In Engl. 1994;33 Preprint at https://doi.org/10.1002/anie.199412291.

21. Nik S, Bowman TV. Splicing and neurodegeneration: insights and mechanisms. Wiley Interdiscip Rev RNA. 2019;10 Preprint at https://doi.org/10.1002/wrna.1532.
22. Will CL, Lührmann R. Spliceosome structure and function. Cold Spring Harb Perspect Biol. 2011;3.
23. Wahl MC, Will CL, Lührmann R. The spliceosome: design principles of a dynamic RNP machine. Cell. 2009;136 Preprint at https://doi.org/10.1016/j.cell.2009.02.009.
24. Campagne S. U1 snRNP biogenesis defects in neurodegenerative diseases. Chembiochem. 2024;25.
25. Wilkinson ME, Charenton C, Nagai K. RNA splicing by the spliceosome. Annu. Rev. biochem. 2020;89 Preprint at https://doi.org/10.1146/annurev-biochem-091719-064225.
26. Licatalosi DD, Darnell RB. Splicing regulation in neurologic disease. Neuron. 2006;52 Preprint at https://doi.org/10.1016/j.neuron.2006.09.017.
27. Ran Y, Deng Y, Yao C. U1 snRNP telescripting: molecular mechanisms and beyond. RNA Biol. 2021;18 Preprint at https://doi.org/10.1080/15476286.2021.1872963.
28. Pomeranz Krummel DA, Oubridge C, Leung AKW, Li J, Nagai K. Crystal structure of human spliceosomal U1 snRNP at 5.5 resolution. Nature. 2009;458.
29. Chiu AC, et al. Transcriptional pause sites delineate stable nucleosome-associated premature polyadenylation suppressed by U1 snRNP. Mol Cell. 2018;69.
30. Buratti E, Baralle D. Novel roles of U1 snRNP in alternative splicing regulation. RNA Biol. 2010;7 Preprint at https://doi.org/10.4161/rna.7.4.12153.
31. Kaida D, et al. U1 snRNP protects pre-mRNAs from premature cleavage and polyadenylation. Nature. 2010;468.
32. Spraggon L, Cartegni L. U1 snrnp-dependent suppression of polyadenylation: physiological role and therapeutic opportunities in cancer. Int J Cell Biol Prepr At. 2013. https://doi.org/10.1155/2013/846510.
33. Zhang S, et al. Structure of a transcribing RNA polymerase II-U1 snRNP complex. Sci (1979). 2021;371.
34. Wang Y, et al. Mechanism of alternative splicing and its regulation. Biomed Rep. 2015;3.
35. Irimia M, Blencowe BJ. Alternative splicing: decoding an expansive regulatory layer. Curr Opin In Cell Biol. 2012;24 Preprint at https://doi.org/10.1016/j.ceb.2012.03.005.
36. Tyshkovskiy A, Zhang S, Gladyshev VN. Accelerated transcriptional elongation during aging impairs longevity. Cell Res. 2023;33 Preprint at https://doi.org/10.1038/s41422-023-00829-9.
37. Elkon R, Ugalde AP, Agami R. Alternative cleavage and polyadenylation: extent, regulation and function. Nat Rev Genet. 2013;14 Preprint at https://doi.org/10.1038/nrg3482.
38. Tian B, Manley JL. Alternative polyadenylation of mRNA precursors. Nat Rev Mol Cell Biol. 2016;18 Preprint at https://doi.org/10.1038/nrm.2016.116.
39. Goldtzvik Y, Sen N, Lam SD, Orengo C. Protein diversification through post-translational modifications, alternative splicing, and gene duplication. Curr Opin In Struct Biol. 2023;81 Preprint at https://doi.org/10.1016/j.sbi.2023.102640.
40. Boucard AA, Chubykin AA, Comoletti D, Taylor P, Südhof TC. A splice code for trans-synaptic cell adhesion mediated by binding of neuroligin 1 to α- and β-neurexins. Neuron. 2005;48.
41. Ule J, Darnell RB. RNA binding proteins and the regulation of neuronal synaptic plasticity. Curr Opin neurobiol. 2006;16 Preprint at https://doi.org/10.1016/j.conb.2006.01.003.
42. Li D, McIntosh CS, Mastaglia FL, Wilton SD, Aung-Htut MT. Neurodegenerative diseases: a hotbed for splicing defects and the potential therapies. Transl NeurodeGener. 2021;10 Preprint at https://doi.org/10.1186/s40035-021-00240-7.
43. Novoyatleva T, Tang Y, Rafalska I, Stamm S. Pre-mRNA missplicing as a cause of human disease. Prog Mol Subcell Biol. 2006;44 Preprint at https://doi.org/10.1007/978-3-540-34449-0_2.
44. Ward AJ, Cooper TA. The pathobiology of splicing. J Pathol. 2010;220 Preprint at https://doi.org/10.1002/path.2649.
45. Wan J, et al. Dynamic usage of alternative splicing exons during mouse retina development. Nucleic Acids Res. 2011;39.
46. Pinelli M, et al. An atlas of gene expression and gene co-regulation in the human retina. Nucleic Acids Res. 2016;44.
47. Li M, et al. RNA expression in human retina. Hum Mol Genet. 2017;26 Preprint at https://doi.org/10.1093/hmg/ddx219.
48. Kim JW, et al. NRL-Regulated transcriptome dynamics of developing rod photoreceptors. Cell Rep. 2016;17.
49. Hoshino A, et al. Molecular anatomy of the developing human retina. Dev Cell. 2017;43.
50. Farkas MH, et al. Transcriptome analyses of the human retina identify unprecedented transcript diversity and 3.5 mb of novel transcribed sequence via significant alternative splicing and novel genes. BMC Genomics. 2013;14.
51. Li M, et al. Comprehensive analysis of gene expression in human retina and supporting tissues. Hum Mol Genet. 2014;23.
52. Curinha A, Braz SO, Pereira-Castro I, Cruz A, Moreira A. Implications of polyadenylation in health and disease. Nucleus. 2014;5.
53. Di C, et al. U1 snRNP telescripting roles in transcription and its mechanism. Cold Spring Harb Symp Quant Biol. 2019;84.
54. Oh JM, et al. U1 snRNP telescripting regulates a size-function-stratified human genome. Nat Struct Mol Biol. 2017;24.
55. Nilsen TW, Graveley BR. Expansion of the eukaryotic proteome by alternative splicing. Nature. 2010;463 Preprint at https://doi.org/10.1038/nature08909.
56. Aísa-Marín I, García-Arroyo R, Mirra S, Marfany G. The alter retina: alternative splicing of retinal genes in health and disease. Int J Mol Sci. 2021;22 Preprint at https://doi.org/10.3390/ijms22041855.
57. Grishkevich V, Yanai I. Gene length and expression level shape genomic novelties. Genome Res. 2014;24.
58. McCoy MJ, Fire AZ. Intron and gene size expansion during nervous system evolution. BMC Genomics. 2020;21.
59. Berg MG, et al. U1 snRNP determines mRNA length and regulates isoform expression. Cell. 2012;150.
60. Ji Z, Lee JY, Pan Z, Jiang B, Tian B. Progressive lengthening of 3' untranslated regions of mRNAs by alternative polyadenylation during mouse embryonic development. Proc Natl Acad Sci U S A. 2009;106.
61. Sandberg R, Neilson JR, Sarma A, Sharp PA, Burge CB. Proliferating cells express mRNAs with shortened 3' untranslated regions and fewer microRNA target sites. Sci (1979). 2008;320.
62. Shepard PJ, et al. Complex and dynamic landscape of RNA polyadenylation revealed by PAS-Seq. RNA. 2011;17.
63. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. Nature. 2019;571 Preprint at https://doi.org/10.1038/s41586-019-1411-0.
64. Salvetti AE. Medecine/Sciences. 2024;40 Preprint at https://doi.org/10.1051/medsci/2024023.
65. Shen L, Ma J, Li P, Wu Y, Yu H. Recent advances in the plant epitranscriptome. Genome Biol. 2023;24 Preprint at https://doi.org/10.1186/s13059-023-02872-6.
66. Hsu PJ, Shi H, He C. Epitranscriptomic influences on development and disease. Genome Biol. 2017;18 Preprint at https://doi.org/10.1186/s13059-017-1336-6.
67. Roundtree IA, Evans ME, Pan T, He C. Dynamic RNA modifications in gene expression regulation. Cell. 2017;169 Preprint at https://doi.org/10.1016/j.cell.2017.05.045.
68. Helm M, Motorin Y. Detecting RNA modifications in the epitranscriptome: predict and validate. Nat Rev Genet. 2017;18 Preprint at https://doi.org/10.1038/nrg.2016.169.
69. Li X, et al. Potential impact of N6-Methyladenosine RNA methylation on vision function and the pathological processes of ocular diseases: new discoveries and future perspectives. Front Biosci - landmark. 2022;27 Preprint at https://doi.org/10.31083/j.fbl2707207.
70. Datta S, Cano M, Ebrahimi K, Wang L, Handa JT. The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD. Prog Retin Eye Res. 2017;60 Preprint at https://doi.org/10.1016/j.preteyeres.2017.03.002.
71. Pujol-Lereis LM, Schäfer N, Kuhn LB, Rohrer B, Pauly D. Interrelation between oxidative stress and complement activation in models of age-related macular degeneration. Adv Exp Med And Biol. 2016;854.
72. Ozawa Y. Oxidative stress in the light-exposed retina and its implication in age-related macular degeneration. Redox Biol. 2020;37 Preprint at https://doi.org/10.1016/j.redox.2020.101779.
73. Jun S, et al. The impact of lipids, lipid oxidation, and inflammation on AMD, and the potential role of miRNAs on lipid metabolism in the RPE. Exp Eye Res. 2019;181 Preprint at https://doi.org/10.1016/j.exer.2018.09.023.
74. Donato L, et al. Epitranscriptome analysis of oxidative stressed retinal epithelial cells depicted a possible RNA editing landscape of retinal degeneration. Antioxidants. 2022;11.
75. Cenini G, Lloret A, Cascella R. Oxidative stress in neurodegenerative diseases: from a mitochondrial point of view. Oxidative Med Cell Longev vol. 2019 Preprint at 2019. https://doi.org/10.1155/2019/2105607.

76. Kaarniranta K, et al. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. Prog Retin Eye Res. 2020;79.
77. Blasiak J, Hyttinen JMT, Szczepanska J, Pawlowska E, Kaarniranta K. Potential of long non-coding rnas in age-related macular degeneration. Int J Mol Sci. 2021;22 Preprint at https://doi.org/10.3390/ijms22179178.
78. Hyttinen JMT, Blasiak J, Felszeghy S, Kaarniranta K. MicroRNAs in the regulation of autophagy and their possible use in age-related macular degeneration therapy. Ageing Res Rev. 2021;67 Preprint at https://doi.org/10.1016/j.arr.2021.101260.
79. Konovalova J, Gerasymchuk D, Parkkinen I, Chmielarz P, Domanskyi A. Interplay between MicroRNAs and oxidative stress in neurodegenerative diseases. Int J Mol Sci. 2019;20 Preprint at https://doi.org/10.3390/ijms20236055.
80. Hyttinen JMT, et al. DNA damage response and autophagy in the degeneration of retinal pigment epithelial cells-implications for age-related macular degeneration (AMD). Ageing Res Rev. 2017;36 Preprint at https://doi.org/10.1016/j.arr.2017.03.006.
81. Sobrin L, Seddon JM. Nature and nurture- genes and environment- predict onset and progression of macular degeneration. Prog Retin Eye Res. 2014;40 Preprint at https://doi.org/10.1016/j.preteyeres.2013.12.004.
82. Kennedy SR, Loeb LA, Herr AJ. Somatic mutations in aging, cancer and neurodegeneration. Mech Ageing Dev. 2012;133.
83. Kirkwood TBL. Understanding the odd science of aging. Cell. 2005;120 Preprint at https://doi.org/10.1016/j.cell.2005.01.027.
84. Angarola BL, Anczuków O. Splicing alterations in healthy aging and disease. Wiley Interdiscip Rev RNA. 2021;12 Preprint at https://doi.org/10.1002/wrna.1643.
85. Wang S, et al. Autophagy dysfunction, cellular senescence, and abnormal immune-inflammatory responses in AMD: From mechanisms to therapeutic potential. Oxidative Med Cell Longev vol. 2019 Preprint at 2019. https://doi.org/10.1155/2019/3632169.
86. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186 Preprint at https://doi.org/10.1016/j.cell.2022.11.001.
87. Campisi J, Vijg J. Does damage to DNA and other macromolecules play a role in aging? If so, how? J Gerontol - Ser A Biol Sci And Med Sci. 2009;64.
88. Klettner A, et al. Cellular and molecular mechanisms of age-related macular degeneration: from impaired autophagy to neovascularization. Int J Biochem Cell Biol. 2013;45 Preprint at https://doi.org/10.1016/j.biocel.2013.04.013.
89. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet. 2012;13 Preprint at https://doi.org/10.1038/nrg3173.
90. Atamna H, Cheung I, Ames BN. A method for detecting abasic sites in living cells: age-dependent changes in base excision repair. Proc Natl Acad Sci U S A. 2000;97.
91. Imam SZ, Karahalil B, Hogue BA, Souza-Pinto NC, Bohr VA. Mitochondrial and nuclear DNA-repair capacity of various brain regions in mouse is altered in an age-dependent manner. Neurobiol Aging. 2006;27.
92. Intano GW, Cho EJ, McMahan CA, Walter CA. Age-related base excision repair activity in mouse brain and liver nuclear extracts. J Gerontol - Ser A Biol Sci And Med Sci. 2003;58.
93. Krishna TH, et al. Reduced DNA gap repair in aging rat neuronal extracts and its restoration by DNA polymerase β and DNA-ligase. J NeuroChem. 2005;92.
94. Deschênes M, Chabot B. The emerging role of alternative splicing in senescence and aging. Aging Cell. 2017;16 Preprint at https://doi.org/10.1111/acel.12646.
95. Soheili-Nezhad S, Ibáñez-Solé O, Izeta A, Hoeijmakers JHJ, Stoeger T. Time is ticking faster for long genes in aging. Trends Genet. 2024;40 Preprint at https://doi.org/10.1016/j.tig.2024.01.009.
96. Vermulst M, et al. Transcription errors induce proteotoxic stress and shorten cellular lifespan. Nat Commun. 2015;6.
97. Seroude L. Differential gene expression and aging. TheScientificworldjournal. 2002;2 Preprint at https://doi.org/10.1100/tsw.2002.135.
98. Ibañez-Solé O, Barrio I, Izeta A. Age or lifestyle-induced accumulation of genotoxicity is associated with a length-dependent decrease in gene expression. iScience. 2023;26.
99. Yu R, McCauley B, Dang W. Loss of chromatin structural integrity is a source of stress during aging. Hum Genet. 2020;139 Preprint at https://doi.org/10.1007/s00439-019-02100-x.
100. Feser J, Tyler J. Chromatin structure as a mediator of aging. FEBS Lett. 2011;585 Preprint at https://doi.org/10.1016/j.febslet.2010.11.016.
101. Song S, Johnson FB. Epigenetic mechanisms impacting aging: A focus on histone levels and telomeres. Genes. 2018;9 Preprint at https://doi.org/10.3390/genes9040201.
102. McCauley BS, Dang W. Histone methylation and aging: lessons learned from model systems. Biochim Et Biophys Acta - Gene Regul Mechanisms. 2014;1839 Preprint at https://doi.org/10.1016/j.bbagrm.2014.05.008.
103. Booth LN, Brunet A. The aging epigenome. Mol Cell. 2016;62 Preprint at https://doi.org/10.1016/j.molcel.2016.05.013.
104. Gyenis A, et al. Genome-wide RNA polymerase stalling shapes the transcriptome during aging. Nat Genet. 2023;55.
105. Delori FC, Goger DG, Hammond BR, Snodderly DM, Burns SA. Macular pigment density measured by autofluorescence spectrometry: comparison with reflectometry and heterochromatic flicker photometry. J Opt Soc Am A. 2001;18.
106. Hageman GS, et al. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res. 2001;20 Preprint at https://doi.org/10.1016/S1350-9462(01)00010-6.
107. Mullins RF, Russell SR, Anderson DH, Hageman GS. Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. Faseb J. 2000;14.
108. Somasundaran S, Constable IJ, Mellough CB, Carvalho LS. Retinal pigment epithelium and age-related macular degeneration: a review of major disease mechanisms. Clin Exp ophthalmol. 2020;48 Preprint at https://doi.org/10.1111/ceo.13834.
109. Karunadharma PP, Nordgaard CL, Olsen TW, Ferrington DA. Mitochondrial DNA damage as a potential mechanism for age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010;51.
110. Strauss O. The retinal pigment epithelium in visual function. Physiol Rev. 2005;85 Preprint at https://doi.org/10.1152/physrev.00021.2004.
111. Starkov AA. The role of mitochondria in reactive oxygen species metabolism and signaling. Ann Of The New Y Acad Sci. 2008;1147.
112. Wang C, Youle RJ. The role of mitochondria in apoptosis. Annu Rev Genet. 2009;43 Preprint at https://doi.org/10.1146/annurev-genet-102108-134850.
113. Utz PJ, Anderson P. Life and death decisions: regulation of apoptosis by proteolysis of signaling molecules. Cell Death Differ. 2000;7 Preprint at https://doi.org/10.1038/sj.cdd.4400696.
114. Malmegrim KCR, Pruijn GJM, Van Venrooij WJ. The fate of the U1 snRNP autoantigen during apoptosis: implications for systemic autoimmunity. Isr Med Assoc J. 4 Preprint at (2002).
115. Dieker J, et al. Apoptosis-linked changes in the phosphorylation status and subcellular localization of the spliceosomal autoantigen U1-70K. Cell Death Differ. 2008;15.
116. Nandrot EF, Dufour EM. Mertk in daily retinal phagocytosis: a history in the making. Adv Exp Med And Biol. 2010;664.
117. Kim JY, et al. Noncanonical autophagy promotes the visual cycle. Cell. 2013;154.
118. Blasiak J, Sobczuk P, Pawlowska E, Kaarniranta K. Interplay between aging and other factors of the pathogenesis of age-related macular degeneration. Ageing Res Rev. 2022;81 Preprint at https://doi.org/10.1016/j.arr.2022.101735.
119. Golestaneh N, Chu Y, Xiao YY, Stoleru GL, Theos AC. Dysfunctional autophagy in RPE, a contributing factor in age-related macular degeneration. Cell Death Dis. 2017;8.
120. Kaarniranta K, Tokarz P, Koskela A, Paterno J, Blasiak J. Autophagy regulates death of retinal pigment epithelium cells in age-related macular degeneration. Cell Biol And toxicol. 2017;33 Preprint at https://doi.org/10.1007/s10565-016-9371-8.
121. Mitter SK, et al. Autophagy in the retina: a potential role in age-related macular degeneration. Adv Exp Med And Biol. 2012;723.
122. Kaarniranta K, et al. Autophagy and heterophagy dysregulation leads to retinal pigment epithelium dysfunction and development of age-related macular degeneration. Autophagy. 2013;9 Preprint at https://doi.org/10.4161/auto.24546.
123. Mitter SK, et al. Dysregulated autophagy in the RPE is associated with increased susceptibility to oxidative stress and AMD. Autophagy. 2014;10.
124. Stegeman R, Hall H, Escobedo SE, Chang HC, Weake VM. Proper splicing contributes to visual function in the aging drosophila eye. Aging Cell. 2018;17.
125. Wu HP, et al. Genome-wide analysis of light-regulated alternative splicing mediated by photoreceptors in physcomitrella patens. Genome Biol. 2013;15.
126. Martinez Velazquez LA, Ballios BG. The next generation of molecular and cellular therapeutics for inherited retinal disease. Int J Mol Sci. 2021;22.

127. Gemayel MC, Bhatwadekar AD, Ciulla T. RNA therapeutics for retinal diseases. Expert Opin Biol Ther. 2021;21 Preprint at https://doi.org/10.1080/14712598.2021.1856365.
128. Murphy D, Cieply B, Carstens R, Ramamurthy V, Stoilov P. The musashi 1 controls the splicing of photoreceptor-specific exons in the vertebrate retina. PLoS Genet. 2016;12.
129. Růžičková Š, Staněk D. Mutations in spliceosomal proteins and retina degeneration. RNA Biol. 2017;14.
130. Xu M, et al. Mutations in the spliceosome component CWC27 cause retinal degeneration with or without additional developmental anomalies. Am J Hum Genet. 2017;100.
131. Liu MM, Zack DJ. Alternative splicing and retinal degeneration. Clin Genet. 2013;84 Preprint at https://doi.org/10.1111/cge.12181.
132. Wheway G, Lord J, Baralle D. Splicing in the pathogenesis, diagnosis and treatment of ciliopathies. Biochim Et Biophys Acta - Gene Regul Mechanisms. 2019;1862 Preprint at https://doi.org/10.1016/j.bbagrm.2019.194433.
133. Mustafi D, et al. Evolutionarily conserved long intergenic non-coding RNAs in the eye. Hum Mol Genet. 2013;22.
134. Ørom UA, et al. Long noncoding RNAs with enhancer-like function in human cells. Cell. 2010;143.
135. Quan Z, Zheng D, Qing H. Regulatory roles of long non-coding rnas in the central nervous system and associated neurodegenerative diseases. Front Cell neurosci. 2017;11 Preprint at https://doi.org/10.3389/fncel.2017.00175.
136. Zylka MJ, Simon JM, Philpot BD. Gene length matters in neurons. Neuron. 2015;86 Preprint at https://doi.org/10.1016/j.neuron.2015.03.059.
137. Gandhi J, et al. Protein misfolding and aggregation in neurodegenerative diseases: A review of pathogeneses, novel detection strategies, and potential therapeutics. Rev Neuro Sci. 2019;30.
138. Kattah NH, Kattah MG, Utz PJ. The U1-snRNP complex: Structural properties relating to autoimmune pathogenesis in rheumatic diseases. Immunological Rev. 2010;233 Preprint at https://doi.org/10.1111/j.0105-2896.2009.00863.x.
139. Somarelli JA, et al. Epitope mapping of the U1 small nuclear ribonucleoprotein particle in patients with systemic lupus erythematosus and mixed connective tissue disease. Lupus. 2011;20.
140. Soares ES, Leal CBQS, Sinatti VVC, Bottós RM, Zimmer CGM. Role of the <scp & amp;#x003E;U1 snRnp</scp>complex in human health and disease. WIREs RNA. 2025;16.
141. Dvinge H, Kim E, Abdel-Wahab O, Bradley RK. RNA splicing factors as oncoproteins and tumour suppressors. Nat Rev Cancer. 2016;16 Preprint at https://doi.org/10.1038/nrc.2016.51.
142. Niño CA, Di Perrotolo RS, Polo S. Recurrent spliceosome mutations in cancer: Mechanisms and consequences of aberrant splice site selection. Cancers. 2022;14 Preprint at https://doi.org/10.3390/cancers14020281.
143. Oh JM, et al. U1 snRNP regulates cancer cell migration and invasion in vitro. Nat Commun. 2020;11.
144. Mimoso CA, Adelman K. U1 snRNP increases RNA pol II elongation rate to enable synthesis of long genes. Mol Cell. 2023;83.
145. Latorre E, Harries LW. Splicing regulatory factors, ageing and age-related disease. Ageing Res Rev. 2017;36 Preprint at https://doi.org/10.1016/j.arr.2017.04.004.
146. Debès C, et al. Ageing-associated changes in transcriptional elongation influence longevity. Nature. 2023;616.
147. Leal CBQS, et al. Effects of the therapeutic correction of U1 snRNP complex on Alzheimer's disease. Sci Rep. 2024;14:30085.
148. Chen PC, et al. Alzheimer's disease-associated U1 snRNP splicing dysfunction causes neuronal hyperexcitability and cognitive impairment. Nat Aging. 2022;2.
149. Luu L, Ciccotosto GD, Cappai R. The Alzheimer's disease amyloid precursor protein and its neuritogenic actions. Curr Alzheimer Res. 2021;18.
150. O'Brien RJ, Wong PC. Amyloid precursor protein processing and alzheimer's disease. Annu Rev neurosci. 2011;34.
151. Zhao Y, et al. Beta-amyloid precursor protein (βAPP) processing in Alzheimer's disease (AD) and age-related macular degeneration (AMD). Mol neurobiol. 2015;52 Preprint at https://doi.org/10.1007/s12035-014-8886-3.
152. Westmark CJ, Malter JS. The regulation of AβPP expression by RNA-binding proteins. Ageing Res Rev. 2012;11 Preprint at https://doi.org/10.1016/j.arr.2012.03.005.
153. Sato K, Takayama KI, Hashimoto M, Inoue S. Transcriptional and post-transcriptional regulations of amyloid-β precursor protein (APP) mRNA. Front Aging. 2021;2 Preprint at https://doi.org/10.3389/fragi.2021.721579.
154. Ruiz-Gabarre D, Carnero-Espejo A, Ávila J, García-Escudero V. What's in a gene? The outstanding diversity of MAPT. Cells. 2022;11 Preprint at https://doi.org/10.3390/cells11050840.
155. Corsi A, Bombieri C, Valenti MT, Romanelli MG. Tau isoforms: gaining insight into MAPT alternative splicing. Int J Mol Sci. 2022;23 Preprint at https://doi.org/10.3390/ijms232315383.
156. Niblock M, Gallo JM. Tau alternative splicing in familial and sporadic tauopathies. Biochem Soc Trans. 2012;40.
157. Wang JZ, Liu F. Microtubule-associated protein tau in development, degeneration and protection of neurons. Prog In neurobiol. 2008;85 Preprint at https://doi.org/10.1016/j.pneurobio.2008.03.002.
158. Wang ET, et al. Alternative isoform regulation in human tissue transcriptomes. Nature. 2008;456.
159. Ashok A, et al. Retinal degeneration and alzheimer's disease: an evolving link. Int J Mol Sci. 2020;21 Preprint at https://doi.org/10.3390/ijms21197290.
160. Salvadores N, Gerónimo-Olvera C, Court FA. Axonal degeneration in AD: the contribution of Aβ and tau. Front Aging Neurosci. 2020;12 Preprint at https://doi.org/10.3389/fnagi.2020.581767.
161. Chiasseu M, et al. Tau accumulation in the retina promotes early neuronal dysfunction and precedes brain pathology in a mouse model of Alzheimer's disease. Mol NeurodeGener. 2017;12 Preprint at https://doi.org/10.1186/s13024-017-0199-3.
162. Parihar MS, Brewer GJ. Amyloid-β as a modulator of synaptic plasticity. J Alzheimer's Disease. 2010;22 Preprint at https://doi.org/10.3233/JAD-2010-101020.
163. Biscetti L, et al. Associations of Alzheimer's disease with macular degeneration. Front Biosci - Elite. 2017;9 Preprint at https://doi.org/10.2741/e794.
164. Bai B, et al. U1 small nuclear ribonucleoprotein complex and RNA splicing alterations in Alzheimer's disease. Proc Natl Acad Sci U S A. 2013;110.
165. Hales CM, et al. Aggregates of Small nuclear ribonucleic acids (snRNAs) in Alzheimer's disease. Brain Pathol. 2014;24.
166. Jabs DA, Griffiths PD. Fomivirsen for the treatment of cytomegalovirus retinitis. Am J ophthalmol. 2002;133 Preprint at https://doi.org/10.1016/S0002-9394(02)01325-9.
167. Maguire AM, et al. Efficacy, safety, and durability of voretigene neparvovec-rzyl in RPE65 mutation-associated inherited retinal dystrophy: results of phase 1 and 3 trials. Ophthalmology. 2019;126.
168. Singerman LJ, et al. Pegaptanib sodium for neovascular age-related macular degeneration: third-year safety results of the VEGF inhibition study in ocular neovascularisation (VISION) trial. Br J ophthalmol. 2008;92.
169. Khanani AM, et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. Lancet. 2023;402.
170. Dal Mas A, Rogalska ME, Bussani E, Pagani F. Improvement of SMN2 pre-mRNA processing mediated by exon-specific U1 small nuclear RNA. Am J Hum Genet. 2015;96.
171. Balestra D, et al. An exon-specific U1snRNA induces a robust factor IX activity in mice expressing multiple human FIX splicing mutants. Mol Ther Nucleic Acids. 2016;5.
172. Hartmann L, et al. Correct mRNA processing at a mutant TT splice donor in FANCC ameliorates the clinical phenotype in patients and is enhanced by delivery of suppressor U1 snRnas. Am J Hum Genet. 2010;87.
173. Mattioli C, et al. Unusual splice site mutations disrupt FANCA exon 8 definition. Biochim Biophys Acta Mol Basis Dis. 2014;1842.
174. van der Woerd WL, et al. Analysis of aberrant pre-messenger RNA splicing resulting from mutations in ATP8B1 and efficient in vitro rescue by adapted U1 small nuclear RNA. Hepatology. 2015;61.
175. Scalet D, et al. The somatic FAH C.1061C>A change counteracts the frequent FAH c.1062+5G>A mutation and permits U1snRNA-based splicing correction. J Hum Genet. 2018;63.
176. Balestra D, et al. A compensatory U1snRNA partially rescues FAH splicing and protein expression in a splicing-defective mouse model of tyrosinemia type I. Int J Mol Sci. 2020;21.
177. Sánchez-Alcudia R, Pérez B, Pérez-Cerdá C, Ugarte M, Desviat LR. Overexpression of adapted U1snRNA in patients' cells to correct a 5′ splice site mutation in propionic acidemia. Mol Genet Metab. 2011;102.
178. Martínez-Pizarro A, Dembic M, Pérez B, Andresen BS, Desviat LR. Intronic PAH gene mutations cause a splicing defect by a novel mechanism involving U1snRNP binding downstream of the 5′ splice site. PLoS Genet. 2018;14.
179. Lee NC, Lee YM, Chen PW, Byrne BJ, Hwu WL. Mutation-adapted U1 snRNA corrects a splicing error of the dopa decarboxylase gene. Hum Mol Genet. 2016;25.

180. Donadon I, et al. Exon-specific U1 snRNAs improve ELP1 exon 20 definition and rescue ELP1 protein expression in a familial dysautonomia mouse model. Hum Mol Genet. 2018;27.
181. Balestra D, et al. Splicing mutations impairing CDKL5 expression and activity can be efficiently rescued by U1snRNA-based therapy. Int J Mol Sci. 2019;20.
182. Romano G, et al. Rescue of a familial dysautonomia mouse model by AAV9-exon-specific U1 snRNA. Am J Hum Genet. 2022;109.
183. Goraczniak R, et al. U1 adaptor oligonucleotides targeting BCL2 and GRM1 suppress growth of human melanoma xenografts in vivo. Mol Ther Nucleic Acids. 2013;2.
184. Tsang AT, et al. U1 adaptors suppress the KRAS-MYC oncogenic axis in human pancreatic cancer xenografts. Mol Cancer Ther. 2017;16.
185. Raponi M, Buratti E, Dassie E, Upadhyaya M, Baralle D. Low U1 snRNP dependence at the NF1 exon 29 donor splice site. The FEBS J. 2009;276.
186. Tanner G, et al. Therapeutic strategy to rescue mutation-induced exon skipping in rhodopsin by adaptation of U1 snRNA. Hum. MutAt. 2009;30.
187. Glaus E, Schmid F, Da Costa R, Berger W, Neidhardt J. Gene therapeutic approach using mutation-adapted U1 snRNA to correct a RPGR splice defect in patient-derived cells. Mol Ther. 2011;19.
188. Breuel S, Vorm M, Bräuer AU, Owczarek-Lipska M, Neidhardt J. Combining engineered U1 snRNA and Antisense oligonucleotides to improve the treatment of a BBS1 splice site mutation. Mol Ther Nucleic Acids. 2019;18.
189. Covello G, Ibrahim GH, Bacchi N, Casarosa S, Denti MA. Exon skipping through chimeric antisense >U1 snRNAs to correct retinitis pigmentosa GTPase-regulator (RPGR) splice defect. Nucleic Acid Ther. 2022;32.
190. Swirski S, et al. In vivo efficacy and safety evaluations of therapeutic splicing correction using U1 snRNA in the mouse retina. Cells. 2023;12.
191. Chekuri A, et al. AAV2-mediated intravitreal delivery of exon-specific U1 snRNA rescues optic neuropathy in a mouse model of familial dysautonomia. bioRxiv Preprint at 2025. https://doi.org/10.1101/2025.08.21.671454.
192. Alanis EF, et al. An exon-specific U1 small nuclear RNA (snRNA) strategy to correct splicing defects. Hum Mol Genet. 2012;21.
193. Donegà S, et al. Rescue of common exon-skipping mutations in cystic fibrosis with modified U1 snRNAs. Hum. MutAt. 2020;41.
194. Schmid F, et al. U1 snRNA-mediated gene therapeutic correction of splice defects caused by an exceptionally mild BBS mutation. Hum. MutAt. 2011;32.
195. Gonçalves M, Santos JI, Coutinho MF, Matos L, Alves S. Development of engineered-U1 snRNA therapies: current status. Int J Mol Sci. 2023;24 Preprint at https://doi.org/10.3390/ijms241914617.

Publisher's Note