


# Dysregulated Polarized Secretion of Small Extracellular Vesicles in the Retinal Pigment Epithelium: Mechanisms and Pathological Roles in Age-Related Macular Degeneration

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**Abstract:** The pathogenesis of age-related macular degeneration (AMD) is intrinsically driven by retinal pigment epithelium (RPE) dysfunction. Under physiological conditions, the strictly polarized secretion of small extracellular vesicles (sEVs) by the RPE dictates outer retinal homeostasis. In response to oxidative and hypoxic stress, this secretory architecture is profoundly disrupted, transforming sEVs into mediators of drusen formation, inflammation, and neovascularization. This review systematically delineates the molecular machinery governing RPE-sEV trafficking, unveiling the distinct protein and miRNA cargo profiles segregated between the apical and basolateral domains. We highlight the unique secretory features of RPE and elucidate how AMD stressors disrupt this polarity via cytoskeletal collapse, secretory autophagy, and Rab GTPase dysregulation. Consequently, this altered sEV secretion abolishes apical neurotrophic support while deteriorating the basolateral microenvironment. Crucially, this establishes a vicious pathological loop where microenvironmental deterioration and sEV dysregulation are mutually causative. Recognizing dysregulated sEV polarity as a contributing factor to AMD, we propose that repairing RPE intracellular trafficking offers a fundamental strategy to restore secretory homeostasis and impede disease progression.

**Keywords:** small extracellular vesicles, age-related macular degeneration, retinal pigment epithelium, vesicular trafficking, polarization

## Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the aging population worldwide.<sup>1</sup> AMD is categorized into drusen-associated dry AMD and choroidal neovascularization (CNV)-driven neovascular AMD. Therapeutic options for AMD remain restricted: anti-VEGF injections for neovascular AMD only suppress downstream angiogenesis without rescuing cellular degeneration, while effective therapies for dry AMD are largely unavailable.<sup>2,3</sup> These therapeutic limitations underscore the need to target early pathogenic events.

The pathogenesis of AMD is intrinsically related to the dysfunction of the retinal pigment epithelium (RPE).<sup>4</sup> As a highly polarized epithelial monolayer, the RPE features distinct apical and basolateral membrane domains partitioned by tight junctions. At the apical domain, microvilli interdigitate with photoreceptor outer segments (POS) to drive both the visual cycle and rhythmic POS phagocytosis. At the opposite side, the basolateral surface anchors firmly to Bruch's membrane via complex plasma membrane infoldings, facilitating nutrient uptake and the clearance of intracellular metabolic end-products into the choroidal circulation.<sup>5</sup> Such exquisite structural asymmetry serves as the anatomical prerequisite for RPE functionality. It not only maintains the integrity of the outer blood-retinal barrier but also enables the establishment of distinct molecular microenvironments at opposing domains through precisely targeted secretion.<sup>4</sup>

Crucially, the breakdown of RPE polarity homeostasis acts as a shared pathological basis for both dry and neovascular AMD, driven by a complex interplay of oxidative stress, chronic inflammation, complement activation, and lipid dysregulation.<sup>2,6,7</sup>

Small extracellular vesicles (sEVs), historically referred to as “exosomes,” are 30–150 nm membranous vesicles released upon the fusion of multivesicular bodies (MVBs) with the plasma membrane.<sup>8</sup> sEVs can selectively package proteins, lipids, and nucleic acids to facilitate information transfer and material exchange between donor and recipient cells.<sup>9</sup> Rather than a stochastic diffusion process, sEV release in highly polarized epithelia such as the RPE is a strictly directional event orchestrated by the cytoskeleton and Rab GTPases.<sup>10</sup> This polarized secretion establishes distinct, region-specific signaling microenvironments at the apical neuroretinal and basolateral choroidal compartments.<sup>11</sup> Emerging evidence suggests that sEV secretion in the RPE exhibits distinctive regulatory features compared to typical epithelia, and that the dysregulation of this polarized secretion plays a pivotal role in AMD development.<sup>11–13</sup> In this context, this review aims to systematically elucidate the mechanisms underlying the dysregulated polarized secretion of RPE-sEVs and their pathological roles in AMD, thereby providing a conceptual framework to identify novel therapeutic targets aimed at restoring secretory homeostasis for impeding disease progression.

## Molecular Regulatory Mechanisms of Polarized sEV Secretion in RPE

### MVB Heterogeneity and Differential Cargo Sorting

The foundation for polarized sEV secretion is established early during MVB biogenesis. This process is driven by the coordinated interplay between the endosomal sorting complex required for transport (ESCRT)-dependent machinery and ESCRT-independent pathways, such as ceramide- and tetraspanin-enriched microdomains.<sup>14</sup> Concomitant with MVB maturation, the invagination of the limiting endosomal membrane generates intraluminal vesicles (ILVs), a process coupled to the selective package of bioactive molecules.<sup>15</sup> Crucially, the specific cargo repertoire packaged within these ILVs acts as the primary determinant of the MVB trajectory, dictating whether the late endosome is committed to lysosomal degradation or routed to the plasma membrane for exocytosis.<sup>15–17</sup>

Upstream of MVB biogenesis, the initial sorting of protein cargoes at the trans-Golgi network (TGN) predetermines their ultimate extracellular fate.<sup>18</sup> A defining feature of the RPE is the intrinsic absence of the adaptor protein (AP)-1B, a complex that classically segregates cargoes in typical epithelia by recognizing basolateral motifs.<sup>19,20</sup> This absence abrogates canonical basolateral retention, redirecting these cargoes to the apical membrane.<sup>21</sup> This enables the apical release of sEVs enriched with basolateral signature proteins, allowing them to exert specialized functions within the neuroretinal microenvironment. Furthermore, Golgi-mediated post-translational modifications function as molecular tags, partitioning specific cargoes into distinct secretory ILV subpopulations.<sup>22,23</sup>

### Cytoskeleton-Guided Directional Transport Networks

The intracellular trafficking of mature MVBs is governed by a highly orchestrated cytoskeletal network comprising microtubules and actin filaments.<sup>24</sup> RPE cells exhibit a robust cytoskeletal polarity: the microtubule-organizing center (MTOC) is anchored at the apical subcortex, establishing a longitudinal array where microtubule minus-ends face apically and plus-ends extend basolaterally.<sup>25</sup> This polarity dictates the long-range trajectory of MVBs via specific motor proteins: dyneins mediate minus-end-directed transit toward the apical pole, whereas kinesins drive plus-end-directed transport toward the basolateral membrane.<sup>25,26</sup>

Upon arriving at the subcortical region, MVBs transition from microtubule tracks to the cortical actin network.<sup>27</sup> This handover relies on unconventional myosins, which mediate the short-range vesicular displacement along actin filaments required to reach the plasma membrane.<sup>16</sup> At the apical domain, the effector protein Myrip recruits the actin motor Myosin VIIa, orchestrating the transfer of MVBs from microtubules and tethering them to parallel F-actin bundles within the microvilli.<sup>28,29</sup> Although this tethering machinery was classically characterized in the context of melanosome transport—where *MYO7A* mutations precipitate Usher syndrome type 1B<sup>30</sup>—MVBs share extensive biogenetic and transport machineries with melanosomes.<sup>31,32</sup> Consequently, the Rab27a-Myrip-Myosin VIIa axis is hypothesized to

function as the central molecular nexus governing apical MVB exocytosis. Ultimately, this bipartite system of long-range microtubule navigation coupled with short-range actin tethering forms the structural scaffold for polarized sEV release.

## Rab GTPase Conversion and SNARE-Mediated Fusion

The terminal subcortical tethering and exocytosis of MVBs are governed by Rab GTPase molecular switches and the SNARE fusion machinery. Following their maturation from Rab5-positive early endosomes, MVBs undergo a critical Rab identity switch—transitioning from a Rab7-dominant state to a Rab27a-positive state, concomitant with the recruitment of Arl8b. This conversion endows them with the secretory competence required to target specific membrane domains.<sup>33,34</sup> Within this cascade, Rab27 paralogs exhibit a functional and spatial dichotomy: perinuclear Rab27b propels MVB transport toward the microtubule-actin interface, whereas peripherally localized Rab27a coordinates precise vesicular tethering and plasma membrane fusion.<sup>35</sup> Studies in Madin-Darby Canine Kidney (MDCK) cells have revealed that polarized sEV secretion is governed by distinct Rab subsets, with Rab27a/b and Rab37 primarily directing apical release, and Rab39 regulating basolateral exocytosis.<sup>36</sup> This paradigm implies that RPE may deploy similarly compartmentalized Rab isoforms to dictate the polarized sEV routing, but this extrapolation remains hypothetical and requires further validation. Furthermore, the apical recycling endosome resident Rab11a acts as a central regulatory node in the RPE apical secretory pathway, operating in concert with the kinesin motor KIF16B to drive directed vesicular delivery and tethering at the apical plasmalemma.<sup>21</sup>

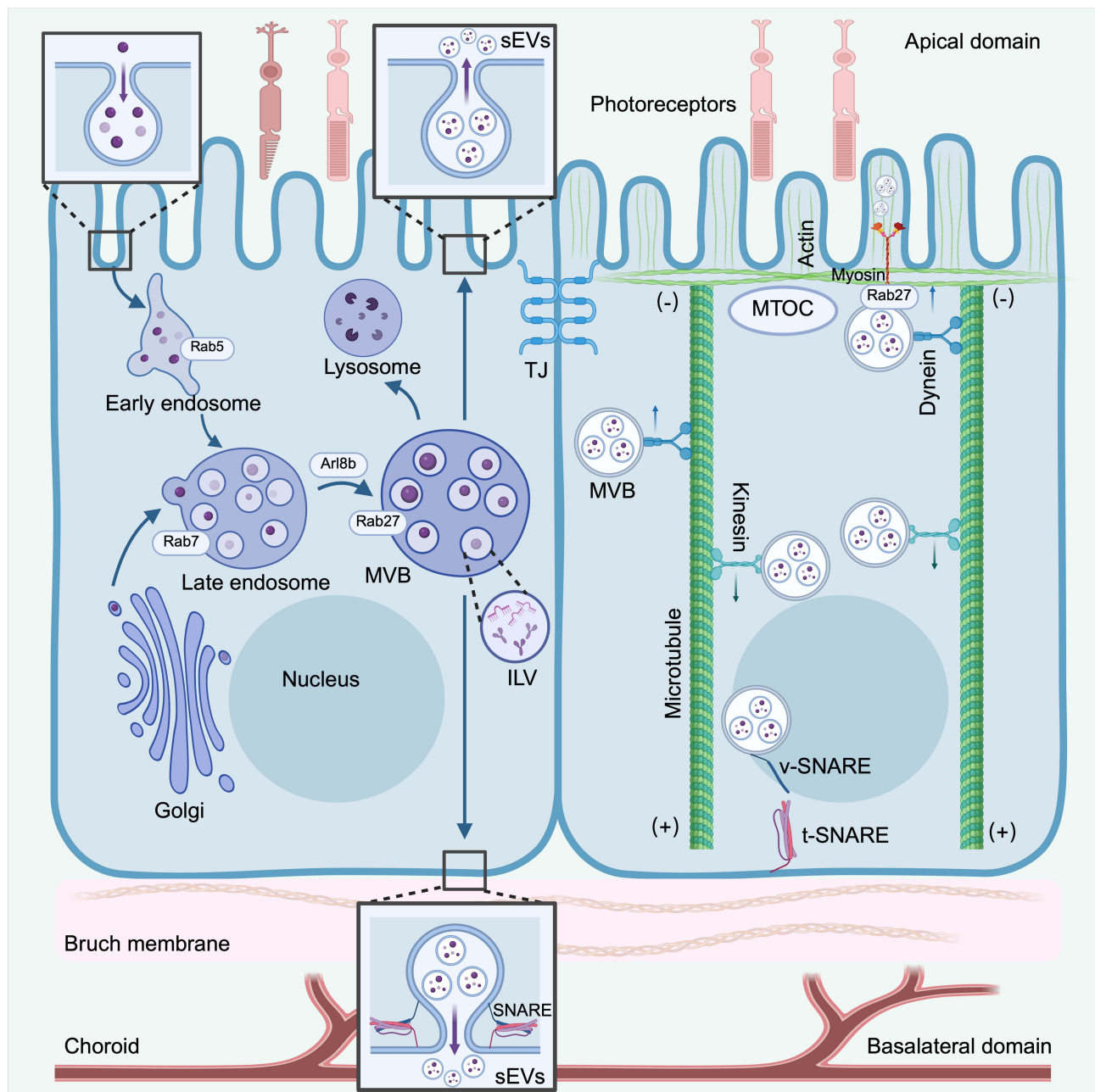
In the terminal fusion phase, the mutual recognition and zippering of vesicular v-SNAREs and target-membrane t-SNAREs into a stable four-helix bundle catalyzes the fusion of the MVB limiting membrane with the plasma membrane. This dynamic rearrangement dilates a fusion pore, extruding ILVs into the extracellular space as mature sEVs.<sup>37</sup> Notably, the RPE exhibits a highly atypical SNARE profile compared to canonical epithelia. As illuminated by Low et al,<sup>13</sup> the RPE lacks the apical t-SNARE Syntaxin 3 and instead expresses Syntaxin 1A and 1B, isoforms classically restricted to neuronal and neuroendocrine lineages. Furthermore, the polarity of Syntaxin 2 is inverted in the RPE, shifting from the apical surface to co-assemble with Syntaxin 4 at the lateral membrane domain, immediately subjacent to the tight junctions. This highly specialized SNARE topology implies that RPE cells harbor a dedicated secretory locus within this lateral sub-tight-junction region, explicitly tailored to mediate the basolateral exocytosis of sEVs.

Collectively, the polarized secretion of RPE-sEVs requires the precise integration of selective cargo sorting, cytoskeletal navigation, and Rab/SNARE-mediated fusion to sustain the physiological homeostasis of the outer retina. [Figure 1](#) depicts the molecular regulatory mechanisms of polarized sEV secretion in RPE.

## Polarized Cargo Signatures of RPE-sEVs and Their Physiological Implications

sEVs secreted from the apical and basolateral domains of RPE cells exhibit strictly compartmentalized molecular signatures. By leveraging Transwell culture systems to recapitulate the native RPE monolayer, researchers can effectively isolate these domain-specific sEV populations. Proteomic analysis by Klingeborn et al<sup>38</sup> of primary porcine RPE revealed that among 631 identified sEV proteins, over half exhibited strictly unidirectional release: 299 were exclusively partitioned to the apical domain, whereas 94 were restricted to the basolateral compartment. This stringent spatial segregation extends to the miRNA repertoire, underscoring the intrinsic capacity of the RPE for spatially resolved, bidirectional signaling. [Table 1](#) summarizes the representative protein and miRNA cargoes differentially segregated into apical and basolateral sEVs.

The apical sEV profile is exquisitely tailored to confer neurotrophic and structural support to the overlying photoreceptors. Specifically, apical sEVs are enriched in classical sEV markers (eg, CD9, CD63, and CD81), suggesting a more active sEV secretion process at the apical surface.<sup>38,39</sup> Furthermore, they selectively package the zinc transporter SLC39A12, which mediates photoreceptor adaptation to chronic hypoxia,<sup>40</sup> and  $\alpha$ B-crystallin, a heat shock protein predominantly released apically to shield photoreceptors against oxidative insult.<sup>41</sup> Additionally, human iPSC-derived RPE models exhibit preferential apical secretion of vitronectin (VTN) and apolipoprotein E (ApoE), which function to suppress subretinal complement overactivation and maintain lipid homeostasis.<sup>42–44</sup> Synergizing with this protein landscape, apical sEVs harbor a highly polarized miRNA payload, notably enriched in miR-182 and miR-183.<sup>48</sup> These



**Figure 1** Molecular mechanisms of polarized sEV secretion in RPE. The left panel illustrates the biogenesis and maturation of MVBs. Cargo from the Golgi network transitions through Rab5-positive early endosomes to Rab7-positive late endosomes, eventually forming Rab27/Arl8b-positive secretory MVBs packed with ILVs. These MVBs are either targeted for lysosomal degradation or routed to the plasma membrane. The right panel depicts the bipartite cytoskeleton-guided transport network. With the MTOC anchored apically, dynein motors drive MVB transit toward the apical domain (minus-end), whereas kinesin motors mediate basolateral transport (plus-end). Terminal short-range transport and membrane fusion rely on myosin-actin interactions and specific v-SNARE/t-SNARE complex assembly, ultimately facilitating the polarized release of sEVs into either the subretinal space (facing photoreceptors) or the basolateral microenvironment (facing Bruch's membrane and choroid). (Created with BioRender.com).

**Abbreviation:** TJ, tight junction.

miRNAs are essential for the maintenance and differentiation of POS<sup>49</sup> and putatively modulate photoreceptor glutamate transporters (eg, Slc1a1) to sustain optimal visual signal transduction.<sup>50</sup>

At the opposing pole, basolaterally secreted sEVs are dedicated to the structural and homeostatic maintenance of the underlying Bruch's membrane and the choroid. Basolateral sEVs are specifically enriched in the chloride channel Bestrophin-1 and extracellular matrix (ECM) constituents (eg, COL18A1, Fibronectin, Integrins), underscoring their active involvement in BrM remodeling and regional ionic balance.<sup>38,45,46</sup> Notably, while proteins such as clusterin

**Table 1** Representative Protein and miRNA Cargoes in Apical and Basolateral sEVs

Category	Cargo	Polarization	Primary Physiological Function	Ref.
Protein	CD9, CD63, CD81	Apical	Active apical sEV secretion	[38,39]
	SLC39A12	Apical	Photoreceptor hypoxic adaptation	[38,40]
	$\alpha$ B-crystallin	Apical	Anti-oxidative/apoptotic neuroprotection	[38,41]
	VTN, ApoE	Apical	Complement suppression and lipid homeostasis	[42–44]
	Bestrophin-1	Basolateral	Chloride channel-mediated ionic homeostasis	[38,45]
	COL18A1, Fibronectin, Integrins	Basolateral	Bruch's membrane ECM turnover	[38,46]
	CLU, APP, A $\beta$	Basolateral	Metabolic waste clearance	[42,47]
miRNA	miR-182, miR-183	Apical	POS integrity maintenance and glutamate transport regulation	[48–50]
	miR-122	Basolateral	Choriocapillaris endothelial regulation	[48,51]
	miR-142	Basolateral	Immune tolerance modulation	[48,52]

(CLU), amyloid precursor protein (APP), and amyloid-beta (A $\beta$ ) are core constituents of drusen, they exhibit a homeostatic basolateral secretion preference. This physiological extrusion acts as an essential clearance mechanism to mediate BrM turnover and prevent intracellular metabolic toxicity.<sup>42,47</sup> Paralleling this protein asymmetry, basolateral sEVs selectively package specific miRNAs, notably miR-122 and miR-142.<sup>48</sup> Given that miR-122 regulates choriocapillaris endothelial cell function<sup>51</sup> and miR-142 modulates angiogenesis and microglial activation,<sup>52</sup> their directional basolateral delivery indicates that the RPE tonically modulates choroidal vascular homeostasis and immune tolerance.

## Mechanisms of Dysregulated sEV Secretion Under AMD Stress

### Cytoskeletal Collapse

Elevated reactive oxygen species (ROS) can dismantle the microtubule network, causing its fragmentation and disorganization by impairing the nucleating capacity of the MTOC and reducing tubulin acetylation levels.<sup>53–55</sup> Specifically, 4-hydroxynonenal (4-HNE), a highly electrophilic byproduct of lipid peroxidation, targets tubulin by forming irreversible covalent adducts via Michael addition. This pathological modification triggers aberrant tubulin cross-linking, potentially paralyzing the polymerization of functional microtubules.<sup>56,57</sup>

Concurrently, oxidative stress ruptures the homeostatic rheostat of the Rho GTPase family. The activities of Cdc42 and Rac1—key orchestrators of epithelial polarity and cortical actin assembly—are suppressed, whereas the RhoA/ROCK pathway, which drives cellular contractility, is aberrantly hyperactivated. This signaling inversion precipitates the breakdown of the characteristic circumferential actin belt in RPE cells, driving the reorganization of the F-actin network into thick, transcellular stress fibers.<sup>58–60</sup> Ultimately, the collapse of these microtubule and microfilament architectures deprives sEVs of the structural tracks required for polarized trafficking, resulting in either their intracellular retention or non-directional, stochastic release.

### Secretory Autophagy

Lysosomal overload is a hallmark of RPE senescence and AMD pathogenesis.<sup>61</sup> The relentless accumulation of lipofuscin, stemming from incomplete POS digestion, impairs lysosomal proton pump function, elevates luminal pH, and curtails hydrolase activity.<sup>62</sup> This degradation deficit not only stalls normal autophagic flux but also induces RPE cells to initiate a compensatory secretory autophagy pathway.<sup>63</sup> This process redirects the vesicular trajectory, forcing the extracellular release of metabolic waste via sEVs—thereby acting as an inciting factor for drusen biogenesis and the inflammatory priming of the retinal microenvironment.<sup>64,65</sup>

Mechanistically, Ghosh et al<sup>66</sup> demonstrated that the dysregulation of the AKT2/SIRT5/TFEB signaling axis serves as the upstream driver that simultaneously impedes lysosomal biogenesis and activates secretory autophagy. This rerouting dictates a precise molecular reprogramming: the cargo receptor TRIM16 selectively sorts pathological cargo into secretory autophagosomes, while the autophagosomal membrane recruits the secretory SNARE SEC22B instead of the

lysosome-fusion protein syntaxin 17 (STX17), thereby sealing a secretory fate.<sup>64</sup> Furthermore, autophagosomes can fuse with MVBs to form amphisomes. This event marks a pathogenic convergence of the autophagic and sEV biogenesis pathways. Ultimately, orchestrated by key molecules including Rab8a, Rab27a, and GRASP55, these amphisomes bypass the Golgi apparatus to fuse directly with the RPE plasma membrane, co-releasing cytosolic pathological aggregates alongside sEVs.<sup>64,65</sup>

Although this cargo extrusion mechanism temporarily alleviates intracellular stress within the RPE under conditions of lysosomal suppression,<sup>67</sup> the basolateral discharge of sEVs enriched with A $\beta$ , lipofuscin, and damaged mitochondrial components—accompanied by the aberrant modification of complement C3<sup>65</sup>—contributes directly to drusen formation. In addition, this pathway mediates the unconventional secretion of leaderless inflammatory cytokines and angiogenesis-related factors,<sup>64</sup> thereby establishing the pathological foundation for chronic outer retinal inflammation and choroidal CNV.

## Rab GTPase Aberration

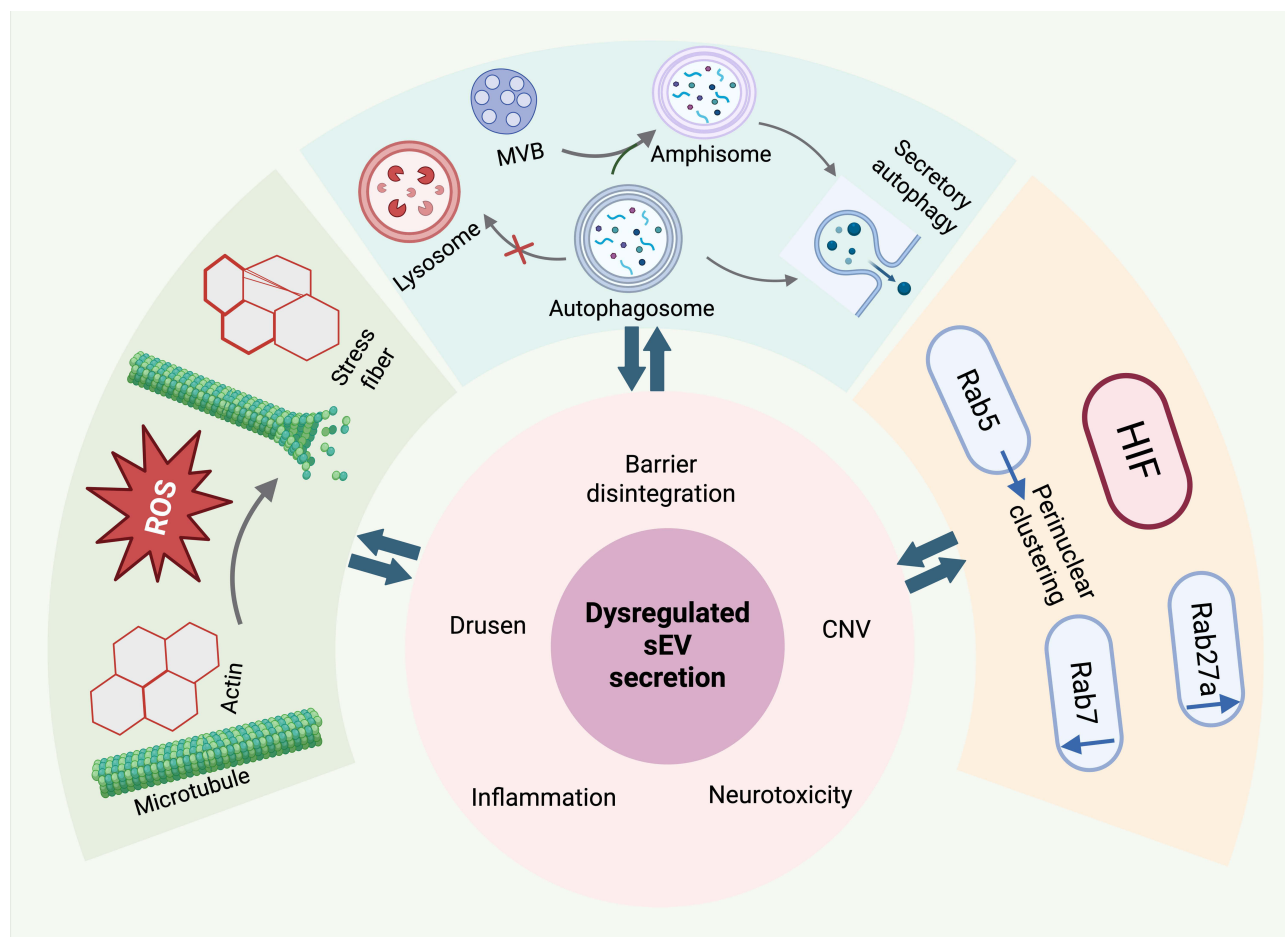
Oxidative stress and hypoxic microenvironments can directly derail the core molecular switches governing vesicular routing. Rab GTPases are acutely susceptible to oxidative perturbation. Hoppe et al<sup>68</sup> demonstrated that oxidized lipoproteins impair normal phagosome maturation, postulating that this defect arises from the disrupted membrane recruitment and activation of Rab5. This dysfunction is particularly pronounced during POS phagocytosis. Keeling et al<sup>69</sup> observed that oxidative stress triggers the premature derailment of POS-containing phagosomes from the classical Rab5/Rab7 degradation pathway, inducing pathological vesicular swelling. This oxidative derailment dismantles the homeostatic control of Rab GTPases, rendering the highly metabolic RPE exquisitely vulnerable to vesicular trafficking failure.

The modulatory impact of hypoxia on Rab GTPases, which have been extensively delineated in tumor biology, provides a compelling mechanistic framework for AMD pathogenesis. In the tumor microenvironment, hypoxia-inducible factors fundamentally reprogram the expression and spatial distribution of Rab proteins.<sup>70</sup> Analogous to the coordinated upregulation of Rab27a and downregulation of Rab7 in ovarian cancer cells,<sup>71</sup> alongside the perinuclear clustering of Rab5-positive vesicles in prostate cancer cells,<sup>72</sup> the RPE likely activates a similar molecular program under hypoxic stress to hyperactivate sEV secretion. Nevertheless, translating these mechanisms from tumor microenvironments to retinal physiology is inherently speculative and necessitates targeted confirmation. While this vesicular extrusion initially serves as an adaptive cellular triage to purge metabolic waste during oxygen deprivation, it becomes maladaptive within the specialized retinal niche. The hypoxia-driven deluge of RPE-sEVs carrying pro-angiogenic payloads, notably VEGF, acts as a molecular catalyst for CNV initiation.

Taken together, AMD-related stress dismantles the RPE intracellular trafficking machinery via cytoskeletal collapse, Rab GTPase derailment, and secretory autophagy. This collective breakdown abolishes apical-basolateral polarity, exacerbating cellular stress and driving a vicious cycle. [Figure 2](#) illustrates the mechanisms of dysregulated sEV secretion under AMD-associated stress.

## Dysregulated sEV Secretion Induces Outer Retinal Pathology Drusen Formation

The pathological deposition of drusen along Bruch's membrane represents the clinical hallmark of dry AMD. Existing evidence indicates that drusen are not merely passive extracellular precipitates, but rather actively extruded metabolic byproducts, a process triggered by the disruption of intracellular proteostasis within the RPE.<sup>64</sup> Wang et al<sup>73</sup> revealed that in the eyes of aged mice and human AMD donors, drusen is not only enriched with the sEV markers CD63 and CD81, but also exhibits colocalization with autophagic markers, complement components, and A $\beta$ . This discovery validates that sEVs extruded via secretory autophagy directly constitute drusen. Paralleling these *in vivo* findings, utilizing a polarized iPSC-RPE cell model, Flores-Bellver et al<sup>42</sup> demonstrated that exposure to cigarette smoke extract (CSE) significantly augmented the basolateral secretion of RPE-sEVs. These sEVs are highly enriched with CLU, A $\beta$ , vinculin (VIN), VTN, and ApoE—all of which are hallmark protein constituents of drusen.



**Figure 2** Mechanisms of dysregulated sEV secretion under AMD-associated stress. The outer panels depict the tripartite collapse of the RPE intracellular trafficking machinery in response to cellular stressors. (Left) ROS destabilizes microtubule networks and remodels actin cytoskeletons into stress fibers. (Top) Impaired lysosomal degradation drives secretory autophagy, leading to the exocytosis of either autophagosomes or amphisomes formed via MVB fusion. (Right) HIF induces abnormal Rab GTPase signaling, characterized by the perinuclear clustering of Rab5, alongside the concurrent downregulation of Rab7 and upregulation of Rab27a. As shown in the central core, this collective breakdown leads to dysregulated sEV secretion, directly contributing to hallmark AMD pathologies including barrier disintegration, CNV, neurotoxicity, inflammation, and drusen formation. The bidirectional arrows highlight a vicious feedback loop where these microenvironmental deteriorations further amplify the initial RPE cellular stress. (Created with BioRender.com).

## Neurotoxicity and Inflammatory Propagation

Under AMD-associated stress conditions, RPE-sEVs act as pathogenic messengers that drive neuroretinal degeneration and the pro-inflammatory remodeling of the outer retinal microenvironment. Zhang Z. et al<sup>74</sup> revealed that under oxidative stress, RPE-sEVs exhibit a profound depletion of neuroprotective miRNAs (eg, miR-125b-5p, miR-128-3p) alongside an aberrant upregulation of pro-apoptotic miRNAs such as miR-7-5p. These differentially expressed miRNAs predominantly target cell survival pathways, including MAPK and PI3K-Akt. Subretinal injection of these stress-derived sEVs *in vivo* directly provokes outer nuclear layer apoptosis, exacerbates ROS production, and triggers a cascading release of pro-inflammatory cytokines, including IL-1 $\beta$  and IL-6. Corroborating the role of sEVs in inflammatory propagation, Zhang W. et al<sup>75</sup> demonstrated that photo-oxidative stress activates the NLRP3 inflammasome, prompting the sEV-mediated secretion of active caspase-1, IL-1 $\beta$ , and IL-18, thereby sustaining the chronic inflammatory milieu of the outer retina.

## Barrier Disintegration and CNV Initiation

The hallmark of neovascular AMD is the formation of CNV. During this pathogenesis, RPE-sEVs mediate the disintegration of the RPE barrier and trigger the proliferation and migration of choroidal endothelial cells. Atienzar-Aroca et al<sup>76</sup> and Maisto et al<sup>77</sup> demonstrated that oxidative stress induces RPE cells to secrete sEVs enriched in angiogenic

**Table 2** Stress-Induced Cargo Alterations in RPE-sEVs and Their Pathogenic Roles in AMD

Category	Cargo	Alteration	Primary Pathogenic Effect	Ref.
Protein	CLU, A $\beta$ , ApoE, VTN, Vinculin	Increased	Drusen core formation	[42,73]
	Caspase-1	Increased	Inflammatory factor diffusion	[75]
	IL-1 $\beta$ , IL-18	Increased	Chronic inflammatory microenvironment	[75]
	Desmosomes, Hemidesmosomes	Increased	RPE barrier disintegration	[79]
	VEGFA, VEGFR	Increased	CNV initiation	[76,77]
miRNA	miR-125b-5p, miR-125a-5p, miR-128-3p, let-7a-5p	Decreased	Loss of neurotrophic support	[74]
	miR-7-5p	Increased	Neuroretinal degeneration	[74]

factors, including VEGFA and VEGFR, establishing the molecular foundation for CNV initiation. Furthermore, these sEVs orchestrate a pathological bidirectional crosstalk between the RPE and macrophages. Otsuki et al<sup>78</sup> revealed that stress-derived RPE-sEVs exhibit a pro-inflammatory molecular signature, instructing macrophages to upregulate tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). This upregulation, in turn, reciprocally stimulates the RPE to release monocyte chemoattractant protein-1 (MCP-1). The subsequently recruited and activated macrophages release matrix metalloproteinases (MMPs) to proteolytically degrade Bruch's membrane, thereby eliminating structural constraints to facilitate neovascular invasion. Klingeborn et al<sup>79</sup> proposed that oxidative stress prompts the RPE to basolaterally shed desmosomes and hemidesmosomes via sEVs. This extracellular expulsion of junctional proteins directly compromises RPE barrier integrity and serves as a prelude to epithelial-mesenchymal transition (EMT), rendering the subretinal space permissive to CNV ingrowth.

Table 2 shows the key cargo alterations of RPE-sEVs under AMD-associated stress and their primary pathogenic roles in AMD.

## Conclusion and Perspectives

In conclusion, the dysregulated polarized secretion of RPE-sEVs is a critical contributing factor to both dry and neovascular AMD, rather than a mere bystander phenomenon. As synthesized above, the stress-induced collapse of intracellular trafficking machineries abolishes secretory polarity, perpetuating a vicious feedback loop of microenvironmental deterioration.

To advance the understanding of the mechanisms of RPE-sEV secretory dysfunction, future research must pivot away from paradigms extrapolated from canonical epithelia and tumor models to construct an RPE-specific polarized regulatory atlas. Currently, the isoform-specific functional partitioning among Rab GTPases dictating apical versus basolateral sEV routing remains elusive. For instance, whether the RPE-specific melanosome transport apparatus (Rab27a-Myrip-Myosin VIIa axis) genuinely orchestrates apical sEV tethering requires rigorous validation. Furthermore, the RPE exhibits a unique distribution of SNARE proteins, such as the polarized inversion of Syntaxin 2. This distinct molecular architecture likely underpins the specific sEV secretory profile that distinguishes the RPE from other epithelial tissues. Systematically deconstructing the RPE-specific molecular circuitries governing sEV polarity will establish the theoretical cornerstone required to precisely intercept AMD progression.

Methodologically, future investigations should transition from phenomenological descriptions of sEV cargo alterations to high-resolution mechanistic decoding. A critical imperative is to elucidate exactly how pathological stressors remodel the endolysosomal sorting machinery to force the aberrant rerouting of sEVs. This necessitates transcending the inherent limitations of bulk vesicle population analyses. By leveraging emerging single-vesicle analysis technologies,<sup>80</sup> researchers can untangle the heterogeneous vesicular subpopulations within the RPE. Identifying endogenous sorting motifs and their cognate chaperone networks that dictate cargo entry into distinct secretory pathways will clarify the fundamental differences between physiological and stress-induced secretion, ultimately unraveling the intricate interplay between physiological maintenance and pathological aggravation.

From a translational perspective, current therapeutic strategies predominantly focus on the regenerative potential and delivery vehicle utility of exogenous sEVs. For instance, using engineered or stem cell-derived sEVs to deliver therapeutic agents has demonstrated robust efficacy in preclinical models.<sup>81,82</sup> In contrast, the mechanisms elucidated here propose a shift toward endogenous functional rescue. In this regard, subthreshold retinal laser has been clinically established as a physical modality to normalize general RPE function by utilizing sublethal thermal stress to trigger adaptive hormesis.<sup>83,84</sup> Investigating how such established physical treatments modulate RPE microvesicle physiology may represent an essential research frontier. Ultimately, the strategy of rectifying apical-basal secretory flux at its intracellular origin offers a theoretical framework to halt microenvironmental deterioration, potentially advancing AMD therapy from symptomatic management to structural and functional restoration.

## Data Sharing Statement

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

## Author Contributions

Haixin Guo: Conceptualization, Investigation, Formal analysis, Writing – original draft. Ruiyi Yan: Data curation, Investigation, Writing – review & editing. Xiaoxu Han: Investigation, Writing – review & editing. Weihong Yu: Conceptualization, Supervision, Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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