nature portfolio

Peer Review File

Lipid Homeostasis plays a critical role in Inherited and Acquired Retinal Diseases

Corresponding Author: Dr Vineet Choudhary

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The manuscript “The Relevance of Lipid Homeostasis in Inherited and Acquired Retinal Degeneration” by Anwesha Bhattacharyya and Vineet Choudhary reviews the literature on lipid homeostasis in retinal diseases. The review covers a very broad scope with quite shallow depth, missing important aspects in most of the covered topics. The visual cycle is covered in more detail than other aspects and perhaps the review should focus on the visual cycle and role of lipid droplets in visual cycle process. The rest of the retinal normal lipid utilization and pathologies are not covered at enough depth and often misleading. For instance, the role of inner and outer blood retinal barrier in lipid transport is not covered at all and the assumption from the review is that inner BRB does not participate in lipid transport. The role of lipid transport vs. retinal internal lipid production, especially for cholesterol, is not addressed. There is a focus on MFSD2A as transported for DHA, although recent studies questioned this specificity and identified MFSD2A as less specific lysolipids transporter.
For Stargardt disease there clear omission of Elovl4 mutation Stargardt type 3 disease. Diabetic retinopathy and AMD are missing a number of important pathways that are well know in pathology of these diseases, including LXR, RXR, PPAR, sphingolipids pathways.
In conclusion, in the present state the review is too broad and because of that it is missing several key points and is at time misleading. Refocusing on visual cycle only is recommended.

Reviewer #2

(Remarks to the Author)
The authors present a review aiming to summarize the importance of lipid homeostasis in normal retinal function and to discuss how dysregulation of lipid metabolism, whether driven by genetic or acquired factors, contributes to a range of retinal pathologies. The manuscript also intends to highlight potential therapeutic strategies for mitigating lipid-related retinal dysfunction. This is a timely and relevant topic, as lipid biology is increasingly recognized as a critical yet underappreciated driver of retinal health and disease. The review has the potential to provide a valuable synthesis for the field; however, several issues related to scope, coherence, and completeness need to be addressed before the manuscript can reach its full impact.
The overall scope of the review feels unfocused, and several sections deviate from the stated emphasis on lipid homeostasis and dyslipidemia in retinal disease. Much of the manuscript provides a solid overview of lipid biology in the retina, but other sections- particularly those covering RP and LCA- are not well integrated into the central narrative. These portions read as standalone summaries rather than components of a cohesive argument. Aside from the brief discussion of MTTP mutations, the authors do not clearly articulate how RP or LCA pathophysiology or these electrophysiological findings relate to lipid regulation, membrane homeostasis, or lipid-driven mechanisms of degeneration.
A similar issue arises in the gene therapy section, which focuses almost exclusively on RPE65 gene augmentation. While this is an important clinical milestone, its relevance to lipid biology is not explained, and the discussion remains disconnected from the review’s central theme. If the authors wish to include gene therapy as part of the translational landscape, it would be more appropriate to highlight gene-based interventions that directly involve lipid metabolism. Otherwise, the section should be streamlined to avoid diluting the focus.
Overall, the authors should either (1) explicitly clarify how these disease models and therapeutic approaches mechanistically intersect with lipid homeostasis, or (2) streamline or remove content that does not directly support the central thesis. Strengthening this conceptual alignment would greatly enhance the clarity, coherence, and impact of the review.

Additionally, several parts of the manuscript are missing references, which is concerning for a review paper. Some examples:
Line 82: Lacking reference
Lines 242-247: Lacking references
Lines 250-253: Lacking references
Lines 323-330: Lacking references
Lines 335-337: “Elevated levels…” lacking reference
Lines 348-351: Lacking references, also “affecting both men and women equally”- is this true?
Lines 446-454: Lacking references, also include results from statin use in AMD
Finally, several parts of the review are underdeveloped, and the newest works are not cited. For example:
- ADIPOR1 role in PUFA homeostasis
- MFRP1 lipid binding and its role as a molecular hub on the membrane
- Role of ceramides and VLC-PUFA in the diabetic retinopathy
- Role of PUFAs in retina aging and age-related vision loss
- The Stargardt disease section also overlooks a major lipid-linked component of the disease: mutations in ELOVL4, a key enzyme in very-long-chain polyunsaturated fatty acid synthesis. Given that ELOVL4 dysfunction directly disrupts retinal lipid composition and membrane integrity, omitting this connection misses a critical opportunity to reinforce the review’s lipid-focused framework.
- Role of ELOVL4 in health of the retina (elovanoids etc).
- No discussion about the role of cholesterol in the retina
These are the top omissions.

Other comments:
Line 379: “Currently no drugs have been approved for dry-AMD”- this is not true, see complement C3 and C5 inhibitors for late stage dry-AMD (geographic atrophy). It would be more accurate to say “early to intermediate stages of dry AMD”
Please check Author Contributions Statement. There are no methods or experiments involved in this paper.
Grammar and comma usage could be improved for clarity.

Reviewer #3

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Biology initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
The manuscript has been improved a lot. There are just few specific corrections to be made:

Line 251: a condition rescued by inhibiting ceramide synthase
Inhibiting ceramide “production” would be more accurate, was multiple drugs inhibiting different ceramide enzymes

Line 254: Reduced ELOVL2 has been associated with increased risk of dry-AMD and other retinal degenerative diseases.
It is incorrect. Variants in the ELOVL2 gene have been associated with increased progression to intermediate stage AMD.

Line 354: impaired synthesis of extremely very long-chain C28-C36 fatty acids (VLC-PUFA)
Just “very long-chain” will suffice

Reviewer #3

(Remarks to the Author)
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Point-by-point response to Reviewers concerns

Manuscript No: COMMSBIO-25-10921

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

The manuscript “The Relevance of Lipid Homeostasis in Inherited and Acquired Retinal Degeneration” by Anwesha Bhattacharyya and Vineet Choudhary reviews the literature on lipid homeostasis in retinal diseases. The review covers a very broad scope with quite shallow depth, missing important aspects in most of the covered topics. The visual cycle is covered in more detail than other aspects and perhaps the review should focus on the visual cycle and role of lipid droplets in visual cycle process.

Author: Thank you for your suggestion. We have elaborated on the visual cycle and extended the discussion on the points mentioned below.

The rest of the retinal normal lipid utilization and pathologies are not covered at enough depth and often misleading. For instance, the role of inner and outer blood retinal barrier in lipid transport is not covered at all and the assumption from the review is that inner BRB does not participate in lipid transport.

Author: We thank the Reviewer for pointing this out. We apologise for the misunderstanding. We re-wrote it to better describe the nature of blood-retina-barrier (BRB), including outer BRB and inner BRB (line 63-85).

The role of lipid transport vs. retinal internal lipid production, especially for cholesterol, is not addressed.

Author: Point well taken. We have added a section on “Cholesterol homeostasis in retina” (line 276-321).

There is a focus on MFSD2A as transported for DHA, although recent studies questioned this specificity and identified MFSD2A as less specific lysolipids transporter.

Author: Thanks for pointing this out, it has been corrected (line 207-213).

For Stargardt disease there clear omission of Elovl4 mutation Stargardt type 3 disease.

Author: We agree with the Reviewer’s suggestion. We now describe the role of ELOVL4 and VLC-PUFA in Stargardt disease (line 346-363).

Diabetic retinopathy and AMD are missing a number of important pathways that are well know in pathology of these diseases, including LXR, RXR, PPAR, sphingolipids pathways.

Author: Point well taken. We have included discussion on LXR, RXR, PPAR, and Sphingolipid pathways as suggested (line 480-534, 565-569, 589-594).

In conclusion, in the present state the review is too broad and because of that it is missing several key points and is at time misleading. Refocusing on visual cycle only is recommended.

Author: Thank you for your suggestion. We have better explained the visual cycle for reader's clarity. We have tried to streamline the central theme by removing content that did not align with the lipid homeostasis such as LCA, Electrophysiological findings in Retinitis Pigmentosa, and Gene therapy section. A new section on "Cholesterol homoestasis in retina" has been added and blood retina barrier (BRB) has been explained in simple language for reader's clarity. Apart from that we have addressed the other points related to Retinal diseases as suggested by Reviewer #1 and Reviewer #2.

Reviewer #2 (Remarks to the Author):

The authors present a review aiming to summarize the importance of lipid homeostasis in normal retinal function and to discuss how dysregulation of lipid metabolism, whether driven by genetic or acquired factors, contributes to a range of retinal pathologies. The manuscript also intends to highlight potential therapeutic strategies for mitigating lipid-related retinal dysfunction. This is a timely and relevant topic, as lipid biology is increasingly recognized as a critical yet underappreciated driver of retinal health and disease. The review has the potential to provide a valuable synthesis for the field; however, several issues related to scope, coherence, and completeness need to be addressed before the manuscript can reach its full impact.

The overall scope of the review feels unfocused, and several sections deviate from the stated emphasis on lipid homeostasis and dyslipidemia in retinal disease.

Author: We acknowledge that certain sections were not aligned with the theme of lipid homeostasis in retina. Accordingly, we have removed sections such as LCA, Electrophysiological findings in Retinitis Pigmentosa, and Gene therapy completely to better connect with the central theme of dysregulated lipid homeostasis that manifests in retinal pathologies. We have addressed all the points mentioned below and tried to fit in the scope of lipid homeostasis.

Much of the manuscript provides a solid overview of lipid biology in the retina, but other sections- particularly those covering RP and LCA- are not well integrated into the central

narrative. These portions read as standalone summaries rather than components of a cohesive argument.

Author: Thank you for your suggestion. As suggested we have removed LCA section and edited RP section to better connect with the central theme of dysregulated lipid homeostasis that manifests in retinal pathologies (line 431-458).

Aside from the brief discussion of MTTP mutations, the authors do not clearly articulate how RP or LCA pathophysiology or these electrophysiological findings relate to lipid regulation, membrane homeostasis, or lipid-driven mechanisms of degeneration.

Author: Point well taken. LCA section has been removed. Electrophysiological findings section has also been removed so as not to deviate from the central theme of dysregulated lipid homeostasis in retinal diseases.

We now better explain the lipid connection in the manifestation of RP pathophysiology. We elaborate on the role of MTTP, lack of which causes abetalipoproteinemia, a rare autosomal recessive disorder that results in malabsorption of fat soluble vitamins thereby causing a form of RP due to prolonged deficiency in photoreceptor cells. We discuss how decrease in levels of DHA and other short-chain/long chain fatty acids correlates with photoreceptor degeneration in RP (line 431-458).

A similar issue arises in the gene therapy section, which focuses almost exclusively on RPE65 gene augmentation. While this is an important clinical milestone, its relevance to lipid biology is not explained, and the discussion remains disconnected from the review's central theme.

If the authors wish to include gene therapy as part of the translational landscape, it would be more appropriate to highlight gene-based interventions that directly involve lipid metabolism. Otherwise, the section should be streamlined to avoid diluting the focus.

Author: In agreement with Reviewer's suggestion, we have removed the Gene therapy section so as to fit better within the central narrative of lipid homeostasis in retinal pathologies.

Overall, the authors should either (1) explicitly clarify how these disease models and therapeutic approaches mechanistically intersect with lipid homeostasis, or (2) streamline or remove content that does not directly support the central thesis. Strengthening this conceptual alignment would greatly enhance the clarity, coherence, and impact of the review.

Author: Thank you for your valuable suggestion. We have removed LCA section completely and description of electrophysiological findings in RP pathology. Moreover,

we have tried to streamline all the sections to better align with the theme of lipid homeostasis in retinal dieases.

Additionally, several parts of the manuscript are missing references, which is concerning for a review paper. Some examples:
Line 82: Lacking reference

Author: Thank you for pointing this out. It has been corrected.

Lines 242-247: Lacking references

Author: Thank you for pointing this out. It has been corrected.

Lines 250-253: Lacking references

Author: Thank you for pointing this out. It has been corrected.

Lines 323-330: Lacking references

Author: Thank you for pointing this out. It has been corrected.

Lines 335-337: “Elevated levels…” lacking reference

Author: Thank you for pointing this out. It has been corrected.

Lines 348-351: Lacking references, also “affecting both men and women equally”- is this true?

Author: Thank you for pointing this out. It has been corrected. We have removed the line affecting both men and women equally” and a Reference has been inserted.

Lines 446-454: Lacking references, also include results from statin use in AMD

Author: Point well taken. It has been corrected. New References have been added (No 190-195).

Finally, several parts of the review are underdeveloped, and the newest works are not cited. For example:

- ADIPOR1 role in PUFA homeostasis

Author: We appreciate your suggestion. Accordingly we have elboarted on the discussion on ADIPOR1 (line 238-252)

- MFRP1 lipid binding and its role as a molecular hub on the membrane

Author: We have extended the discussion on MFRP in the revised manuscript (line 260-274)

- Role of ceramides and VLC-PUFA in the diabetic retinopathy

Author: As suggested we have elaborated discussion on the role of ceramides and VLC-PUFA in DR (line 518-534)

- Role of PUFAs in retina aging and age-related vision loss

Author: Point well taken. We include the role of PUFA in retinal pathologies (line 238-259), (line 518-534, 589-591).

- The Stargardt disease section also overlooks a major lipid-linked component of the disease: mutations in ELOVL4, a key enzyme in very-long-chain polyunsaturated fatty acid synthesis. Given that ELOVL4 dysfunction directly disrupts retinal lipid composition and membrane integrity, omitting this connection misses a critical opportunity to reinforce the review's lipid-focused framework.

Author: We agree with the Reviewer's suggestion. In the revised section on Stargardt disease we discuss about the role of ELOVL4 in VLC-PUFA synthesis (line 346-362).

- Role of ELOVL4 in health of the retina (elovanoids etc).

Author: We briefly mention the role of elovanoids in the retina.

- No discussion about the role of cholesterol in the retina

Author: Thank you for your suggestion. A new section on Cholesterol homeostasis in the retina has been added (line 276-321).

These are the top omissions.

Other comments:
Line 379: "Currently no drugs have been approved for dry-AMD"- this is not true, see complement C3 and C5 inhibitors for late stage dry-AMD (geographic atrophy). It would be more accurate to say "early to intermediate stages of dry AMD"

Author: The Reviewer raises an important point. We apologise for the misunderstanding. We have corrected this in the revised version (line 583-594)

Please check Author Contributions Statement. There are no methods or experiments involved in this paper.

Author: Corrected. Thanks.

Grammar and comma usage could be improved for clarity.

Author: Noted and corrected to the best of our knowledge.

Reviewer #3 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Biology initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Author: Many thanks for your thoughtful suggestions.

Point-by-point response to Reviewers concerns

Manuscript No: COMMSBIO-25-10921A

REVIEWERS' COMMENTS:

Reviewer #2 (Remarks to the Author):

The manuscript has been improved a lot. There are just few specific corrections to be made:

Author: We thank the Reviewer for thoughtful and constructive feedback.

Line 251: a condition rescued by inhibiting ceramide synthase
Inhibiting ceramide “production” would be more accurate, was multiple drugs inhibiting different ceramide enzymes

Author: Point well taken. We have corrected it.

Line 254: Reduced ELOVL2 has been associated with increased risk of dry-AMD and other retinal degenerative diseases.
It is incorrect. Variants in the ELOVL2 gene have been associated with increased progression to intermediate stage AMD.

Author: Thank you for pointing this out. We changed it accordingly as suggested.

Line 354: impaired synthesis of extremely very long-chain C28-C36 fatty acids (VLC-PUFA)
Just “very long-chain” will suffice

Author: We agree with your suggestion. Have removed the word “extremely”

Reviewer #3 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Biology initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Author: We thank the Reviewer for constructive feedback.