

Review of: "[Review Article] Melatonin, ATP, and Cataracts: The Two Faces of Crystallin Phase Separation"

Walter Manucha¹

¹ Universidad Nacional de Cuyo

Potential competing interests: No potential competing interests to declare.

Manuscript report titled: "Melatonin, ATP, and Cataracts: The Two Faces of Crystallin Phase Separation"

General features:

1. If possible, replace long, complex sentences with shorter ones for clarity and impact.
2. For example, this single sentence can be replaced by shorter ones: "Therefore, regardless of initiating temperature and/or mechanism, whether the phase-separated aggregates retain non-toxic, highly-disordered, partially-unfolded, amorphous, intermediate structures .
3. Held together by their exposed hydrophobic patches, or continue to mature over time into toxic, highly-ordered, misfolded, amyloidogenic aggregates, ultimately determines the fate of the lens.
4. A brief discussion on how the information presented in this paper can be applied in a clinical setting may be helpful for readers.

Specific review/recommendation:

5. If melatonin is found in archaea per reference #125, then the timeline for melatonin on Earth should be pushed back by ~500 million years to 4 billion years ago, instead of 3.5 billion years.
6. The authors mentioned early living organisms using melatonin to regulate phase separation. Melatonin is known as a free radical scavenger of products derived from oxygen. It may be necessary to address the potential conflict where oxygen radicals are responsible for promoting aberrant phase separation in present-day organisms, whereas the atmosphere between 4-2.5 billion years ago was largely devoid of oxygen.
7. Reference #217 is now published in Nature Chemistry. Please update accordingly.
8. Lines 980-982 - it is unclear why the use of arginine residues in crystallins of cold-dwelling Antarctic fish is relevant in phase separation. The authors can consider adding more details and including a reference.
9. Antarctic fish is relevant in phase separation. The authors can consider adding more details and including a reference.

Finally, this report provides interesting new information that many ophthalmologists may not be familiar with. It is important



they are exposed to these advances in the field. I rate this report high.