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

Douglas Brash[1]

1 Yale University

Potential competing interests: No potential competing interests to declare.

Summary:

The authors review the requirements for a clear crystallin lens; the failure of these requirements; the resulting phase separation of crystallins during the path to cataract; and the role of melatonin and ATP in opposing these failures.

Evaluation:

This is a very interesting application of several physical biochemistry topics that are not widely known amongst biologists (which is why I looked forward to reading it). The review has the potential to explain both the application to cataract and the underlying topics, which might apply to other aspects of biology as well. These include crystallization, domain swapping, phase separation, and non-standard roles of melatonin, ATP, and water.

Suggestions:

However, these topics don't get explained; instead, they are just mentioned, as if talking to a grad student in the field who might have missed some of the facts. Few readers are going to look up more than a couple of the 368 references to find out what the underlying ideas and evidence are. Perhaps the review could use a section on physical biochemistry for the biologist.

Among the concepts that don't get an explanation are:

Why a high concentration of crystallins provides transparency.

In what way crystallins have chaperonin-like activity, and why they would have such activity.

What dehydration entropy, phase separation (and, for that matter, the phases that are getting separated and the causes of phase formation), and why the former drives the latter.

The relation between an amorphous condensate and a phase.

The chemical basis of why melatonin and ATP would have any effect on phases or solubilizing aggregates. Hydrogen bonding is mentioned, but what is bonding to what is not explained, nor how this has an effect.

Domain swapping is not defined until several pages after first mention, and still does not get an explanation of how the cell

performs it.

What molecule is absorbing the UV and then leads to the effect on aggregation?

The electric double layer and how it generates •OH.

Definitions of kosmotrope and hydrotrope would be helpful to most readers, as would be a statement of the surfactant that is being helped by the hydrotrope. (ATP's two ends are acting like a phospholipid or detergent?)

All these would be helped by a diagram for the novice showing the anatomy of the lens, fiber cells, and condensates or phases (e.g., the "protein-rich rim at the condensate interface"), as well as the chemical structure of the crystallins.

In addition, there are some grammatical problems that obscure what is being said. One example is in the Abstract, "... scavenging ... preventing removal ... water ... shells that can ...". Does "that can" refer to the scavenging, preventing, removal, water, or shells? This problem comes from having sentences that are too long.

Another example on p. 2 is "resist phase separation from domain swapping that can ...". Does "that can" refer to resist, separation, or domain swapping?

A third is the 100-word sentence on page 10, where it is impossible to tell which part of the preceding sentence "implying" refers to.

These long sentences also seem to lose the authors, generating grammatically incomplete sentences such as "The fact that the condensate interface EDL can generate redox reactions that produce •OH that may cause dehydration via its binding with water molecules, the formation of pathogenic amyloid aggregates as a result of phase separation appears almost inevitable."

Improving these issues could provide an insightful review.