Invited Lecture

Investigating UV damage in cataract formation with serial crystallography

Jake Hill[1], Yvonne Nyathi Helen Ginn [2] , Briony Yorke[1]

[1] University of Leeds, [2] Universitat Hamburg
cmjhi@leeds.ac.uk

Cataract is the leading cause of blindness worldwide, characterised by progressive opacification of the eye lens due to aggregation of its constituent proteins [1]. The major monomeric protein in the human lens is human gamma D crystallin (HGD). Localised to the lens fibre cells which lack the machinery for protein synthesis, HGD must therefore remain correctly folded and functional for the entire human lifetime. Despite showing remarkable stability, continual exposure to UV light contributes to the eventual aggregation of HGD [2]. Exposure to UV radiation results in primary photodamage to aromatic groups as well as secondary damage via the formation of reactive oxygen species (ROS).

In order to combat this, high levels of the ROS scavenger glutathione (GSH) are present in the lens. GSH may also act to prevent intermolecular crosslinks by reversing the oxidation of surface thiols. However, ageing is associated with a reduction in GSH levels and an increased in the oxidised form (GSSG) alongside an increase in oxidised surface thiols. GSSG may be regenerated to GSH via formation of S-glutahionlyated cysteine, as is reported in γ-S and γ-C crystallins [3].

Using serial crystallography, we show that with aging crystals of HGD accumulate covalent modifications on surface cysteines. Studies of oxidised crystals, with and without UV irradiation reveal that UV irradiation disrupts the covalent modification of surface cysteines and results in a conformational shift towards a more native fold [4]. Taken together we propose a UV aided mechanisms which allows for both the dissipation of UV energy and recycling of antioxidants in the lens.

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[2] Slingsby, C., Wistow, G.J. and Clark, A.R. (2013) Evolution of crystallins for a role in the vertebrate eye lens. Protein Science 22 (4), 367–380.

[3] Zetterberg, M., Zhang, X., Taylor, A., Liu, B., Liang, J.J. and Shang, F. (2006) Glutathiolation enhances the degradation of gammaC-crystallin in lens and reticulocyte lysates, partially via the ubiquitin-proteasome pathway. Investigative Ophthalmology & Visual Science 47 (8), 3467–3473.

[4] Hill, J.A., Nyathi, Y., Horrell, S. et al. An ultraviolet-driven rescue pathway for oxidative stress to eye lens protein human gamma-D crystallin. Commun Chem 7, 81 (2024).