Denaturation of alpha-Crystallin by replacement of amino-acid residue

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We have investigated on the mechanism of the abnormal aggregation of protein with the eye lens protein, α-Crystallin. Alpha-Crystallin with its molecular weight of ca 800 kDa is a major protein in eye lens. Native α-Crystallin is a hetero-aggregate with 20-30 subunits. There are two kinds of subunits, αA-Crystallin and αB-Crystallin. On the molecular level study, Fujii found that there exist racemized aspartyl residues (D-Asp) in the abnormal aggregates of α-Crystallin of Cataractous and elder eye lens. Therefore, we have supposed the racemization of aspartyl residue should be a trigger of abnormal aggregation. In addition, we have also proposed a pathway to Cataract as follows: Under external stresses such as UV irradiation, X-ray irradiation, low temperature and so on, aspartyl residues are racemized. The D-Asp on the polypeptide chain induces the strain in the regular folding of the polypeptides and the strain makes the structural deformation of the subunits, αA-Crystallin and/or αB-Crystallin. The aggregates with these deformed subunits gather and make the abnormal aggregates.

As the first step to prove above the hypothesis, we prepared for two mutant samples of which an aspartyl residue was replaced with an asparagine residue.
Mutant αA-crystallin (Asp $\rightarrow$ Asn@151)
Mutant αB-crystallin (Asp $\rightarrow$ Asn@36)
In addition, as a reference, we also prepared for normal αA-crystallin and αB-crystallin. It is espected that asparagine acid can make racemization more easily than aspartyl acid.

With these samples, SANS experiments were perfomed with SANS-U spectrometer. Figure 1 shows the SANS profiles of nromal and mutant αA-crystallins and those of nromal and mutant αB-crystallins. The structual change of mutant αB-crystallin is larger than that of mutant αA-crystallin. It means that an aspartyl residue in αB-crystallin plays more important role than that in αA-crystallin.

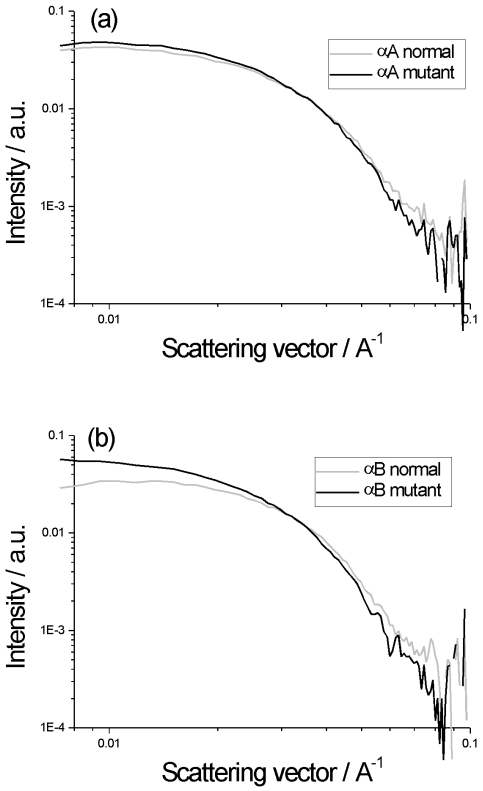

Fig. 1. SANS profiles of nromal and mutant αA-crystallins (a) and those of nromal and mutant αB-crystallins (b).