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Review

α-Crystallins, versatile stress-proteins

Wilbert C. Boelens & Wilfried W. de Jong
Department of Biochemistry, University of Nijmegen, P.O. box 9101, 6500 HB Nijmegen, The Netherlands

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Introduction

α-Crystallins owe their name to the fact that they are major eye lens proteins in vertebrates. They are abundantly present in the lens and have a prominent role in maintaining the transparency and refractile properties of the lens (reviewed in [1–3]). There are two types of related subunits, αA and αB, each of about 20 kDa, of which αB is also expressed at significant levels in many different tissues outside the lens [4]. α-Crystallins exist as large homo- or heteromeric complexes, containing about 30–40 subunits. Their tertiary and quaternary structures are unknown. Initially it was observed that, on the basis of sequence homology, α-crystallins belong to the family of small heat shock proteins (hsps) [5]. This family is characterized by the presence of an approximately 100 amino acid long conserved domain, often called the α-crystallin domain. α-Crystallins and small hsps are not only evolutionarily related but they also behave very similarly in many respects. They actually can form mixed complexes in tissues were both proteins are expressed [6, 7]. α-Crystallins, like other small hsps, have chaperone-like properties in that they can prevent stress-induced aggregation of proteins [8]. Furthermore, mammalian αB-crystallin is stress-inducible, and the presence of α-crystallins in cultured cells leads to an enhanced survival of these cells after a period of stress [9]. αB-Crystallin is also implicated in the pathogenesis of various degenerative diseases.

In this mini review we will mainly discuss the structural and functional aspects of α-crystallins. For gene regulation [10], evolutionary relationships [11] and post-translational modifications [12] of α-crystallins we refer to other recent reviews.

Structure of α-crystallins

Electron microscopic pictures of normal 700–800 kDa α-crystallin complexes display heterogeneous globular particles of approximately 14–18 nm [13–15]. They have sometimes been observed to have a torus-like structure [16, 17]. α-Crystallin is predominantly a β-sheet protein with less than 10% α-helical structure [18, 19]. The subunits presumably have a two-domain structure [20–22] with an about 10 amino acids long flexible C-terminal extension [23, 24]. Various models have been proposed for the quaternary structure of the α-crystallin complex. A favored model is the three-layered spherical structure based on studies that imply three different environments for α-crystallin [25, 26] (see Fig. 1 A and B). A micellar complex has also been proposed [27, 28]. In this structure, the rather hydrophobic N-terminal domains of the subunits are oriented towards the center of the aggregate and the more hydrophilic C-terminal domains are exposed to the surface. Another model is based upon a minimal subunit of tetrameric arrangement [29] which is formed when the N-terminal domain of α-crystallin is removed [21] or in the presence of 1% deoxycholate [30] (see Fig. 1C). More recently, a GroEL-like structure has been proposed, consisting of two annular layers of approximately 20 subunits, able to bind unfolded proteins in the hole in the middle of the complex [31, 32] (see Fig. 1D). These models may help to explain the function of α-crystallin. Complete understanding of

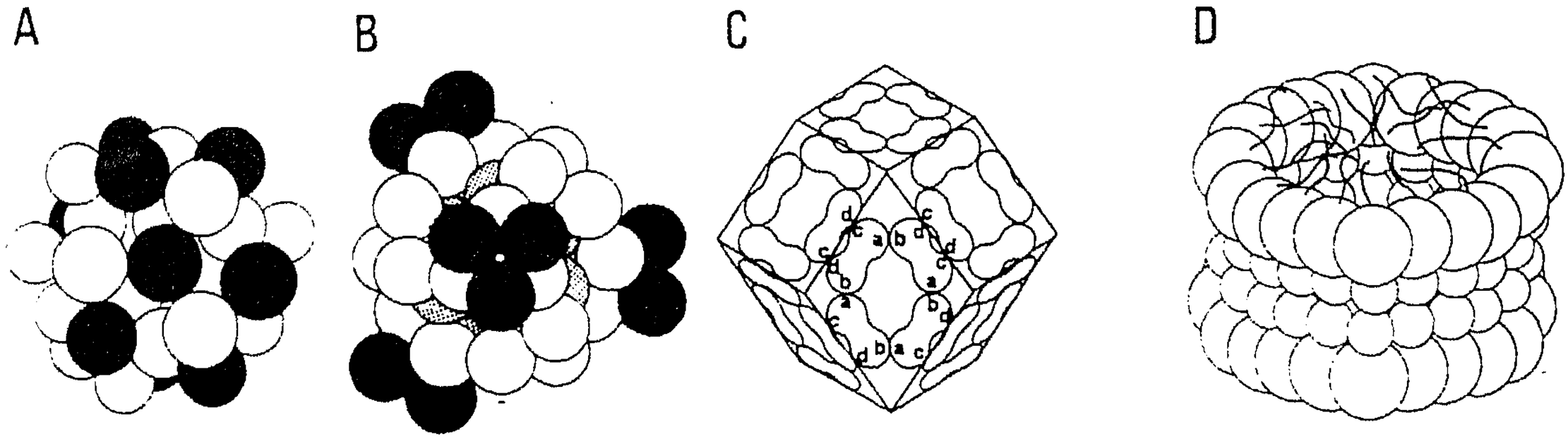

Fig. 1. Schematic representations of various models for the quaternary structure of α-crystallin. (A) Three-layer model of Bindels *et al.* [25] composed of a core of 13 subunits, a second layer of 14 subunits and an outer layer of 16 chains. The white and dark spheres indicate the αA and αB subunits, respectively. (B) Three-layer model of Tardieu *et al.* [26]. First layer is made up of 12 subunits (grey spheres) second layer of 24 subunits (white spheres) and third layer of 12 subunits (dark spheres). (C) Rhombododecahedric structure model by Wistow [29] is composed of 48 subunits and has 12 faces. Each face consists of the C-terminal domains (indicated by peanut-shapes) in a tetrameric arrangement formed through identical a-b interactions. The tetramers associate by identiacal c-d interactions. (D) GroEL–like structure of Carver *et al.* [31]. Two annuli each of 20 subunits, laid on top of each other. The smaller spheres indicate the N-terminal domain of each subunit and the larger spheres the C-terminal domains. The squiggly lines indicate the flexible C-terminal tails.

the spatial configuration, however, clearly awaits X-ray crystallographic analysis.

The chaperone-like function of α-crystallins

Lens tissue contains a very high concentration of proteins – over 50% of wet weight in some species – of which the soluble structural proteins, the various unrelated crystallins, constitute over 90% [3]. Transparency of the lens is essential for its function, and depends on a balanced interplay of attractions and repulsions of the crystallins to obtain a proper short-range order [33, 34]. Disturbance of this order by protein modifications or physical stress may induce the formation of large protein aggregates. Such aggregates would cause light-scattering, leading to opacification of the lens.

In vitro experiments have shown that α-crystallins may be essential for preventing protein aggregation in the lens [8]. The total soluble protein fraction of a lens homogenate is very heat stable. It can be heated to 60 °C without protein aggregation and scattering to occur. If, however, α-crystallin is selectively removed by ultracentrifugation, the remaining lens proteins aggregate when heated at 60 °C. α-Crystallin binds to the soluble denaturing proteins and in this way probably prevents random protein aggregation. The denatured proteins bind relatively stable to the α-crystallin complex [35]. Although α-crystallin can bind ATP [36], the denatured substrate is not released upon incubation with ATP [37]. Stoichiometric analysis of the α-crystallin complex with denatured γ-crystallin demonstrated that α-crystallin can bind the soluble denatured substrate up to a 1:1 monomer ratio [38]. Together with the finding that the proteins bound to the α-crystallin complex are not clustered [39], it is likely that every monomer in the α-crystallin aggregate can bind a denatured substrate.

α-Crystallin not only suppresses heat-induced aggregation of lens proteins, but also of non-lenticular proteins such as alcohol dehydrogenase, citrate synthase, α-glucosidase and carbonic anhydrase [8, 35, 37]. The efficiency of aggregate prevention is not the same for different proteins and may depend on how well α-crystallin can interact with the unfolded protein [38, 40]. Prevention of aggregation of an enzyme by α-crystallin seems not to preserve the functional activity, as has been shown for alcohol dehydrogenase [8, 41]. This is very likely caused by partial unfolding of the protein but may also be a result of blocking the active site of the enzyme by the interaction with α-crystallin.

Interestingly, refolding of urea- or guanidine-denatured proteins is under certain conditions facilitated by the presence of α-crystallin. Removal of the denaturant often results in a non-functional aggregation of the protein. In the presence of α-crystallin, however, such aggregation can be prevented [8], and for α-glucosidase and citrate synthase a more efficient refolding could be observed [37]. Under normal physiological conditions, several types of insults, such as UV light and protein oxidation and glycation, can damage proteins in the lens. This may eventually lead to the formation of cataract. Under these conditions α-

crystallin also may act as a chaperone. Wang and Spector have shown that γ-crystallin aggregates after oxidation, which can be partially prevented by the presence of α-crystallin [42]. Glycation-induced inactivation of glucose-6-phosphate, an enzyme which looses activity in cataractous lenses, can be prevented by α-crystallin [43]. α-Crystallin can also prevent UV-induced aggregation of γ-crystallin, but only at elevated temperatures [44]. Below 30 °C α-crystallin does not protect the UV-damaged γ-crystallin, suggesting that at lower temperatures no binding sites for non-native proteins are available.

In the lens, up to 30% of αA and αB occur in a phosphorylated form. In αA-crystallin a single serine at position 122, and in αB two or three serines at positions 19, 45 and 59 can be phosphorylated [45–47]. This phosphorylation is probably catalyzed by cAMP-dependent protein kinase [48] and is essentially irreversible in the lens-fiber cells, but may be reversible in other cell types [49]. Interestingly, α-crystallin is capable of serine specific autophosphorylation *in vitro* [50], which in the case of αA is strongly enhanced by the conversion of the high molecular weight aggregate to the tetrameric form [30]. Phosphorylation of α-crystallin does not seem to affect the ability of the subunits to associate [51], but may enhance the chaperone-like function, especially of αA, *in vitro* (M. A. M. van Boekel, unpubl.).

Other modifications may also affect the chaperone-like function. In rodents up to 15% of αA-crystallin is present in a modified form, αA^{ins}, which contains an insert of 23 amino acid residues as a result of alternative splicing. Purified αA^{ins} forms larger oligomers and displays a diminished chaperone activity compared with αA [52]. In cataractous lenses truncated forms of α-crystallin can be detected with reduced chaperone activity [53]. Removal of about 10 amino acid residues at the C-terminus of α-crystallin caused already the loss of the chaperone activity [24].

Lens α-crystallins have a very long half-life and undergo a whole series of modifications, such as deamidation, racemization, acetylation, glycation and age-dependent truncation [12]. Several of these types of post-translational modifications decrease the chaperone-like activity of α-crystallin (M. A. M. van Boekel, unpubl., and [19]).

Function of α-crystallins outside the lens

Several eye lens crystallins, especially in non-mammalian vertebrates, have been identified as housekeeping enzymes (for recent review see [3, 54]). In the course of evolution such genes have been upregulated in the lens, and now serve an additional function as structural lens proteins. According to this model, also the primordial α-crystallin gene already coded for a small hsp in non-lens tissue before having been recruited as a crystallin gene. Around that time it must have undergone a gene duplication, giving rise to the αA and αB-crystallin genes [11]. α-Crystallin is predominantly a lens protein. Outside the lens it is present in the retina [17] and in very low amounts in spleen and thymus [4, 55]. So far, no heat inducibility of αA-crystallin has been described. In addition to being a lens protein, αB-crystallin is also expressed in many different tissues. Relatively high levels are found in heart, striated muscle, kidney and brain tissue [4, 56, 57].

αB-Crystallin is stress-inducible in different cell types. In NIH 3T3 fibroblasts expressing certain oncogenes, enhanced αB-crystallin expression is induced under several stress conditions such as heat shock, cadmium or arsenite exposure [58]. Also in various glioma cell lines different types of physical and chemical stress enhance αB-crystallin expression [59, 60]. Like the small hsp genes, the αB-crystallin gene contains a heat-shock element in its 5′ flanking region (reviewed in [10]).

αB-Crystallin is often expressed and induced together with the small hsp. However, their expression is differentially regulated. In rat astrocytes, some stimuli cause an increase in both αB and hsp27 mRNA, whereas other types of stress, such as hypertonic stress or TNFα exposure, result in αB-mRNA accumulation without a change in the level of hsp27-mRNA [61].

One important function of the enhanced expression of αB-crystallin is the protection of the cell during periods of stress. Evidence for this is the strong correlation between increased expression of αB-crystallin and the enhanced resistance of the cell to stress [9, 62, 87]. Also αA-crystallin, which is not stress inducible, confers cellular thermoresistance [63]. How α-crystallin is able to increase the thermotolerance of the cell is not understood at all.

Several reports suggest that αB-crystallin interacts with, and thus may protect the cytoskeletal structures in the cell. Studies on Alexander's disease, a neurodegenerative disorder in humans, first revealed the

association of αB-crystallin with glial fibrillary acidic protein (GFAP) which is a major type III intermediate filament protein of astrocytes [64]. Other examples of redistribution of intermediate filament networks exist in human pathologies, in which αB-crystallin appears as associated inclusions of the neurofilament-containing Lewy body and the cytokeratin-containing Mallory body [65–67]. The cause of the accumulation of αB-crystallin in diseased organs is unclear, but may represent the reaction to some types of stress. In heart and slow muscle, αB-crystallin is localized in the Z bands where the desmin filaments occur [68]. Intermediate filament arrays can be dramatically rearranged by either heat shock or exposure to heavy metals or chemical poisons [69, 70]. In cell lines in which αB-crystallin is abundantly present, there is a transient relocalization of αB-crystallin from the detergent-soluble cytoplasmic fraction to the non-ionic detergent-insoluble nuclear/cytoskeletal fraction [58, 71, 72]. The disappearance from the cytoplasmic fraction is fast, within 15 min after heat shock, and remains for about 2 h [73]. Both the cytoskeletal rearrangement and the relocalization of αB-crystallin are fully reversible events, which allows the speculation that αB-crystallin plays an active role in the redistribution of intermediate filaments after stress.

The relocalisation of αB-crystallin is dependent on the type of stress. Under arsenite exposure human glioma cells αB-crystallin expression is induced, but αB remains in the soluble fraction [59]. Furthermore, treatment of human ovarian carcinoma cells with colchicin causes a collapse of the intermediate filaments which is independent of the relocalisation of αB-crystallin [71]. This may mean that the protective role of αB-crystallin is dependent upon the type of stress-condition.

α-Crystallin may not only be implicated in the remodelling of intermediate filaments under stress but also under non-stress conditions. An indication for this is that during the development of certain tissues αB-crystallin is present in the cells which undergo extensive morphological changes [74, 75]. Furthermore, reduction of the amount of αB-crystallin in glioma cells by antisense-transfection changed the morphology of the cells [62]. Especially a loss of stress fibers could be observed.

The possible protective role of αB-crystallin with regard to the cytoskeletal network in cells exposed to stress has been underlined by *in vitro* data. *In vitro* experiments have shown that αB-crystallin is able to bind to actin, desmin (a muscle-specific type III intermediate filament protein), GFAP filaments [68, 76], CP49/CP115 filaments [77] and tubulin [78].

Spontaneous aggregation of desmin filaments *in vitro* can be prevented by αB-crystallin [68]. Furthermore, αB-crystallin is able to prevent low pH (6.0) induced aggregation of actin filaments at physiological ionic strength, a process which might be induced by acidification of the cytosol during ischemic stress. There is, however, no indication that αB-crystallin can act as an inhibitor of actin filament assembly *in vitro* [78]. Such a property has been reported for the small hsp [79] and implicated in the actin filament dynamics after a stress period [80, 81].

α-Crystallin is able to inhibit the *in vitro* assembly of GFAP and vimentin. The inhibition is independent of ATP and of the phosphorylation status of the α-crystallin [76]. When added to preformed filaments, α-crystallins can increase the soluble pool of GFAP [76]. Thus α-crystallin may be implicated in the protection and remodelling of intermediate filaments which are important processes during development and cell differentiation and stress situations. There are some additional properties of α-crystallin that may turn out to be physiological relevant. α-Crystallin and also small hsps have protease-inhibitory activity *in vitro*. One mole of α-crystallin is able to bind 13–19 mole of elastase [82, 83]. Such a function could be useful to prevent degradation of transiently denatured proteins during stress. It is, however, not clear if such a function exists *in vivo*.

α-Crystallin, especially αA, is known to interact specifically with lens membranes. It appears that binding to lens membranes requires the presence of the major intrinsic protein called MIP or MP26 [84, 85]. In lens extract, α-crystallin was detected to be present in a DNA-binding protein complex able to bind specifically to the sense DNA strand of a 21-bp conserved region located in the murine γE-crystallin promoter [86]. This may point to an intriguing function of α-crystallin.

In summary, α-crystallins are chaperone-like proteins which are abundantly present in the lens but also in many other tissues. They have, most likely, an important role in preventing protein aggregation in the cell and may also be involved in maintaining the integrity of the cytoskeleton and in eliminating or sequestering non-native proteins. Establishing how these functions are performed is a major challenge for the years to come.

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