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Therapeutic Potential of α-Crystallin

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Abstract

Background—The findings that α-crystallins are multi-functional proteins with diverse biological functions have generated considerable interest in understanding their role in health and disease. Recent studies have shown that chaperone peptides of α-crystallin could be delivered into cultured cells and in experimental animals with beneficial effects against protein aggregation, oxidation, inflammation and apoptosis.

Scope of Review—In this review, we will summarize the latest developments on the therapeutic potential of α-crystallins and their functional peptides.

Major conclusions—α-Crystallins and their functional peptides have shown significant favorable effects against several diseases. Their targeted delivery to tissues would be of great therapeutic benefit. However, α-crystallins can also function as disease-causing proteins. These seemingly contradictory functions must be carefully considered prior to their therapeutic use.

General significance—αA and αB-Crystallin are members of the small heat shock protein family. These proteins exhibit molecular chaperone and anti-apoptotic activities. The core crystallin domain within these proteins is largely responsible for these prosperities. Recent studies have identified peptides within the crystallin domain of both α- and αB-crystallins with remarkable chaperone and anti-apoptotic activities. Administration of α-crystallin or their functional peptides have shown substantial inhibition of pathologies in several diseases. However, α-crystallins have been shown to promote disease-causing pathways. These two sides of the proteins are discussed in this review.

1. Introduction

α-Crystallin is a major protein in the lens, and it consists of two subunits, αA (HspB4) and αB (HspB5), which possess nearly 55% sequence homology between them [1]. It belongs to the family of small heat shock proteins (sHSPs). All sHSPs contain a core "α-crystallin domain" (ACD) that is approximately 90 amino acids and that is flanked by a variable hydrophobic N-terminal domain and a hydrophilic C-terminal extension [2]. Both αA and αB are polydisperse oligomeric proteins, and their oligomeric size depends on their

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environment. The average molecular weights for the αA and αB homooligomers are 660 kDa and 620 kDa, respectively [3, 4]. α-Crystallin constitutes approximately 40% of the protein in the human lens, with the αA and αB subunits present in approximately a 3:1 molar ratio that is proposed to be optimal for protecting the β- and γ-crystallins of the lens [5]. αA- and αB-crystallins spontaneously exchange subunits with each other [6]. In the lens, α-crystallin is both a structural and a functional protein. The αA- and αB-crystallin oligomer is polydisperse in nature, with a molecular weight ranging from 300 to 1200 kDa [7]. In addition to being a major protein in the lens, α-crystallin is present in other tissues. αA is predominantly present in the lens, although small amounts are present in the retina, thymus and spleen [8, 9]. However, αB-crystallin is present in relatively large quantities in the retina, skeletal muscles, kidneys and heart [10, 11].

α-Crystallin exhibits molecular chaperone-like activity. Numerous studies have shown that both αA- and αB-crystallins bind structurally perturbed proteins and prevent their aggregation in an ATP-independent manner. This property has been projected to help cells in coping with various stresses. In addition to the chaperone-like activity, both αA- and αB-crystallins are strongly anti-apoptotic. Under stress conditions, an up-regulation of αB-crystallin protects against cell death. In a similar manner, cells that are genetically manipulated to overexpress these proteins are more resistant to stress conditions. Given that α-crystallins protect cells against the undesirable consequences of cellular stress and protein denaturation, it seems reasonable to hypothesize that they can be used therapeutically. In this review, we will summarize the use of α-crystallin as a therapeutic agent to block protein aggregation and apoptosis.

1.1. Chaperone activity of α-crystallin

In 1992, Horwitz reported that α-crystallin inhibited the thermal aggregation of β-crystallin in the lens and proposed that α-crystallin possesses chaperone-like activity [12]. This was in line with the findings on another prominent small heat shock protein, Hsp27, which was established at that time as a molecular chaperone. Subsequent studies confirmed this initial finding and expanded the repertoire of client proteins, which included randomly selected proteins that aggregated by chemical or thermal insults in addition to physiological client proteins. The physiological client proteins originated from virtually all parts of the cell. It has been shown that α-crystallin binds to intermediate filament glial fibrillary acidic protein, desmin [13], filensin, phakinin, vimentin [14] and actin [15–17] and that it prevents their aggregation. A recent study using the HuProt microarray system showed that more than 100 proteins could bind to αA-crystallin [18].

α-Crystallin's chaperone activity increases with temperature [19] and is accompanied by an increased hydrophobicity of the protein. This behavior is especially true for αA-crystallin [20]. However, the question of whether the increased hydrophobicity is a prerequisite for the increase in the chaperone activity remains unclear, as some studies show a direct relationship between hydrophobicity and the chaperone activity, while others do not [21]. Subunit exchange occurs actively in α-crystallin between homooligomers and heterooligomers [6, 22]. The subunit exchange rate has been linked to the chaperone

activity; however, the subunit dimers and potentially the larger structures appear more important to the chaperone activity than does monomer exchange [6, 23, 24].

1.2. Influence of post-translational modifications on the chaperone activity of α-crystallin

The chaperone activity of α-crystallin is affected by posttranslational modifications, with the most widely studied posttranslational modification being phosphorylation. One proteomic analysis of human fiber cells detected 22 residues in αA and 17 residues in αB that were phosphorylated [25]. In vivo αA-crystallin is phosphorylated at serine residues at 45, 122 and 148, and αB- at serines residues 19, 45 and 59 [26–31]. The phosphorylation at these residues reduces the oligomeric size of the proteins [29] and enhances the chaperone activity [32]. However, in some studies, phosphorylation reduced the chaperone activity [29], and the reduction in oligomeric size has also been disputed [33]. Phosphorylation is required for αB-crystallin's binding to actin during cellular stress [17]. Phosphorylation of αB-crystallin may also modulate anti-apoptotic activity, as phosphorylation enhances the nuclear translocation of αB-crystallin [34] and appears to be necessary for its anti-apoptotic activity [35]. However, some have found evidence against this hypothesis as well [36, 37]. In addition to phosphorylation, α-crystallin also undergoes deamidation [38], which decreases the chaperone activity [39]. C-terminal truncation is another modification that reduces the chaperone activity [40], but this type of modification can be cleared by the ubiquitin system [41]. Diabetic lenses have exhibited increased C-terminal truncation [42], which could lead to enhanced protein aggregation, resulting in diabetic cataracts. A recent study showed that the O-GlcNAcylation of αB-crystallin regulates its nuclear translocation and cytoprotection [43]. Glycation is another major modification [44]; glycation by sugars has been shown to decrease the chaperone activity of α-crystallin [45], while glycation by methylglyoxal enhances chaperone activity [46]. The specific arginine residue modification responsible for this increase in activity has been mapped [47]. Additionally, these glycation pathways appear to be mutually exclusive because the methylglyoxal modification has been shown to prevent a glycation-mediated loss of chaperone function [48]. Acetylation of lysine residues is another modification [49, 50] that improves chaperone activity [51]. Acetylation at K92 in αB-crystallin was shown to increase both chaperone and anti-apoptotic activities [52]. Taking these findings together, these observations suggest a discordant effect of post-translational modification on the functions of α-crystallin.

1.3. Anti-apoptotic activity

In addition to the chaperone activity, α-crystallins inhibit apoptosis induced by various factors such as UV light, TNFα, high glucose, okadaic acid and staurosporine in several different cell types [53–59]. One study showed that αA-crystallin is better than αB-crystallin with regard to the anti-apoptotic function [58]. α-Crystallins inhibit apoptosis in both mitochondrial and death receptor-mediated pathways. αB-Crystallin has been shown to interact with procaspase-3 and to inhibit its maturation to caspase-3 [60, 61]. Other studies have shown that both αA and αB directly interact with caspase-3, Bcl-X(S) and Bax [62–64]. Additionally, αA-crystallin has been shown to increase PI3 kinase activity by inactivating PTEN [65]. In lens epithelial cells, α-crystallins inhibit UVA-induced apoptosis through the regulation of PKCα, RAF/MEK/ERK and AKT signaling pathways [66]. αB-Crystallin has also been shown to inhibit cytochrome c release from mitochondria and the

downregulation of Bcl-2 in H_2O_2-treated cells [67]. The anti-apoptotic activity of αB-crystallin has also been linked to its translocation to mitochondria during oxidative stress and to its binding to cytochrome c, mitochondrial voltage-dependent anion channels, caspase-3 and caspase-12 [68]. Furthermore, a recent study showed that a reduction in αB-crystallin leads to an increase in endoplasmic reticulum stress-mediated apoptosis in retinal pigment epithelial cells [69]. Together, these observations demonstrate that α-crystallin is a robust anti-apoptotic protein that can prevent cell death under various conditions of cellular stress.

1.4. Copper binding and ROS inhibition

α-Crystallin binds to transitional metal ions such as Cu^{2+} and renders them redox inactive [70]. Raju et al. identified a peptide sequence in αA-crystallin that binds to Cu^{2+} and prevents ROS formation from ascorbate oxidation [71]. Whether this property of α-crystallins endows them with the ability to reduce oxidative stress and to inhibit apoptosis *in vivo* has yet to be established.

1.5. Intracellular translocation

An interesting property of the normally cytoplasmic αB-crystallin is that it translocates to the nucleus in stressed cells [72]. αB-Crystallin does not contain a nuclear localization signal (NLS), unlike many proteins that translocate to nucleus. The mechanism of nuclear translocation in the absence of NLS is not known. It is possible that αB-crystallin is transported to the nucleus after it binds to other proteins that contain an NLS. It is believed that phosphorylation is essential for such translocation [34]. The reason that αB translocates to the nucleus is not entirely clear, but studies suggest that it binds to proteins such as intranuclear lamin A/C and the splicing factor SC-35 [72]. αB-crystallin can also translocate to the mitochondria under stress conditions. Phosphorylated αB-crystallin has been found in the mitochondria of cardiac myocytes during ischemic/reperfusion injury [73, 74]. The function of αB-crystallin in mitochondria is not clear, but the prevention of mitochondria-mediated apoptosis is likely.

1.6. Chaperone activity sequences in α-crystallin

After the initial discovery of the chaperone function, numerous studies have attempted to map the chaperoning sequences in α-crystallin. Sharma and colleagues have conducted extensive work in this area. For example, they used protein crosslinking methods to determine the interaction sites between α-crystallin and target proteins. Their methods resulted in the identification of peptides within the ACD domain of α-crystallin. These peptides corresponded to the sequence ^{70}FVIFLDVKHFSPEDLTVK^{88} in αA [75] and ^{73}DRFSVNLDVKHFSPEELKVK^{92} in αB-crystallin [76], both of which reside within the ACD of α-crystallin. For the sake of simplicity, these two peptides are henceforth referred to as “mini alpha-crystallin chaperones”, or “MACs”. These two peptides were shown to possess chaperone activity against various target proteins that was similar to the full-length parent molecules. It is important to note that the chaperoning sequences in α-crystallin need not be client protein binding sites. Using protein pin array, Clark and colleagues have also identified a number of peptides within the N-terminus, C-terminus and

the ACD region that possess substrate-binding properties [77], even though some of those segments of the protein may not function as chaperones. Several other studies have identified interaction sequences in α-crystallin [78, 79]. Several binding sites in client proteins have also been identified [80, 81]. Finally, anti-chaperone peptides that bind to α-crystallin and that decrease chaperone activity have also been identified in human lenses [82].

2. Therapeutic use of α-crystallins and MACs

2.1. For eye diseases

The ability of α-crystallin to inhibit protein aggregation and apoptosis has been exploited for its therapeutic use. For example, the intravenous injection of α-crystallin protected both retinal ganglion cells against apoptosis and ganglion cell axons after optic nerve crush in rats [83, 84]. Intravitreally injected α-crystallin also promoted axonal regeneration after optic nerve crush in rats [85]. The intravitreally injected α-crystallin also promoted axonal regeneration after optic nerve crush in rats [85]. In addition, the direct delivery of α-crystallin to retinal ganglion cells was shown to increase their survival after optic nerve axotomy [86]. In the early phase of autoimmune uveoretinitis in mice, αA-crystallin is upregulated in the retina through Toll-like receptor 4 [87], but in the absence of αA-crystallin, retinal degeneration is enhanced in this animal model. Such retinal degeneration can be inhibited by the systemic administration of αA-crystallin [88]. This effect has been ascribed to the reduction in the synthesis of pro-inflammatory cytokines and the expression of Toll-like receptors. Exogenous administration of αB-crystallin rescued optic nerve oligodendrocytes through the inhibition of microglial activation in an experimental model of anterior ischemic optic neuropathy in mice [89]. Another study showed that adenovirus-mediated delivery of αA-crystallin reduced vascular leakage and pericyte apoptosis in experimental diabetes, suggesting its usefulness in halting early lesions in diabetic retinopathy [90]. The exogenous administration of αA-crystallin reduced suture- and burn-induced corneal neovascularization in mice, which was proposed to be through the upregulation of VEGFR-1 [91]. In the absence of α-crystallins, retinal degeneration was enhanced in chemically induced hypoxia [92]. The absence of αB-crystallin enhanced retinal apoptosis during bacterial endophthalmitis [93] and following sodium iodate injection [94]. Whether administration of αB-crystallin would have protected against such apoptosis is not known. Because of the benefits of α-crystallin in cells, attempts are being made to deliver α-crystallin tagged with a cell penetration peptide [95]. This strategy to deliver α-crystallin into cells has shown improved protection against heat and oxidative stress in lens epithelial cells [96].

In addition to the whole protein, the administration of MACs has also shown promising results. A recent study showed that the intraperitoneal injection of MACs or of their acetyl derivatives inhibited selenite-induced cataracts in rats, which was accompanied by the inhibition of protein aggregation and lens epithelial cell apoptosis [97]. A MAC derived from αB-crystallin has been shown to inhibit oxidative stress-mediated apoptosis in cultured retinal pigmented epithelial cells [98]; this study also showed that MAC entry into cells was mediated by sodium-coupled oligopeptide transporters. The inhibition of amyloid

fibrillogenesis and toxicity of the αA-crystallin MAC [99] could be further exploited for therapy against Alzheimer's disease.

2.2. For other diseases

The administration of human αB-crystallin during the first week following a contusion injury to the central nervous system led to an improvement in locomotor skills and inhibited secondary tissue damage in mice [100]. In a mouse model for cerebral ischemia, the absence of αB-crystallin resulted in increased lesion size and diminished neurologic function, which was partially inhibited by the systemic administration of αB-crystallin [101]. The absence of αB-crystallin led to a worsening of experimental autoimmune encephalomyelitis (EAE) in mice, which was reversed by the exogenous administration of αB-crystallin [102]. The therapeutic benefit of αB-crystallin in animal models of multiple sclerosis and ischemia is thought to be due αB-crystallin's capacity to bind pro-inflammatory molecules [103]. A recent study from Steinman's group has also shown that a hexameric peptide of αB-crystallin (residues corresponding to 76–81 and 89–94) can inhibit neuro-inflammation in an experimental model for EAE [104]. A later study showed that the chaperone activity of αB-crystallin is necessary for this inhibitory action [105]. However, in contrast to these findings, one study did not find any beneficial effect from the overexpression of αB-crystallin in spinal motor neurons in a mouse model for paralysis [106]. The administration of αB-crystallin has also improved cardiac function after ischemia-reperfusion injury in mice, possibly by blocking the apoptosis of endothelial cells [107]. Recently, it was shown that the administration of αB-crystallin prevented ventricular arrhythmia by attenuating inflammation and oxidative stress associated with autoimmune myocarditis in mice [108].

2.3. The other side of α-crystallin

Even though α-crystallin administration proves to be beneficial in many diseases, in other diseases, inhibition of its expression could be beneficial to prevent the disease pathology. For example, in idiopathic pulmonary fibrosis, αB-crystallin is overexpressed, and pulmonary fibrosis is curtailed in its absence [109]. αB-Crystallin is highly expressed in basal-like breast tumors, and it independently predicts a shorter survival of patients [110]. Remarkably, a recent study has identified a small molecule inhibitor of αB-crystallin that inhibits tumor growth in human breast cancer xenografts in mice [111]. The binding of the inhibitor to the ACD domain of αB-crystallin has been proposed as the mechanism for this property. αB-Crystallin has also been thought to regulate breast cancer metastasis in the brain [112]. Similarly, α-crystallin is overexpressed in non-small cell lung cancer, colorectal cancer and retinoblastoma [113–115]. In addition, αB-crystallin has been shown to be a chaperone for VEGF-A during angiogenesis [116], which could have implications for angiogenesis-associated pathologies.

3. Concluding remarks

It is remarkable that α-crystallins exhibit beneficial effects through multiple mechanisms. The major attribute for such effects appears to be anti-apoptotic, at least in diseases where apoptosis is a contributory factor and in which α-crystallin supplementation has shown disease amelioration. However, its chaperone activity could also be working hand in hand

with its anti-apoptotic activity to cause such favorable effects. The binding of plasma anti-inflammatory proteins is one example in which chaperone activity seems to be essential for αB-crystallin to work against multiple sclerosis [103]. Additionally, binding and inhibiting denatured cytoskeletal proteins during cellular stress may also be important. Further evidence for such codependency of chaperone and anti-apoptotic activities has stemmed from the work of Pasupuleti et al. [65], who have shown that the chaperone activity is directly related to the anti-apoptotic activity. Other attributes such as its ability to bind to copper and quench ROS formation also could contribute to the beneficial effects.

The posttranslational modifications of α-crystallin appear to modulate the anti-apoptotic and chaperone activities, thus it remains to be determined whether the introduction of modifications that enhance these activities (such as methylglyoxal-mediated modification and acetylation) would further improve the beneficial effects of the exogenously administered proteins. Tagging the protein with cell-permeable peptides for better delivery of the protein is another exciting area needing further research. As described above, some studies have shown phosphorylation and nuclear translocation appear to be necessary for α-crystallin's anti-apoptotic functions. However, it is unclear how α-crystallin gains entry into the nucleus when it lacks an NLS peptide and why translocation is necessary for its anti-apoptotic function. If these aspects are better understood, then α-crystallin's efficacy against diseases could be further improved. Systemic administration has limitations such as, rapid clearance of the protein and off-target effects. The targeted delivery of the protein to the intended tissues and improvements in the half-life of the protein warrant further research.

The demonstrations of beneficial effects of the whole protein are in itself very promising and exciting areas for future research, but even more exciting are the discovery of MACs. These peptides show remarkably similar activities to the whole proteins. Furthermore, unlike the whole proteins, peptides are easier to produce and are more amenable to manipulations for better delivery and for improvements in activities. The acetylation of αB-crystallin-derived MAC has already shown improved activity compared to the nonacetylated peptide, and such acetylation of lysine residues could also improve the pharmacokinetics by thwarting protease digestion. Remarkably, Sharma and colleagues have recently shown that the MAC of αA-crystallin substituted with D-amino acids in the place of L-amino acids retains its chaperone activity [117]. Because this peptide is expected to be refractory to proteases as well, it might be retained longer in the system and thus might better protect cells. The discovery of oligopeptide transporters for α-crystallin [98] is another exciting area. If such transportation can be improved and engineered for selected delivery to tissues, the functionality of the MACs could not only be improved but could also be directed toward specific tissues. In conclusion, α-crystallin appears to function both as a disease-causing and disease-inhibiting protein (Fig. 1); thus, these two seemingly contradictory functions must be carefully considered prior to its therapeutic use.

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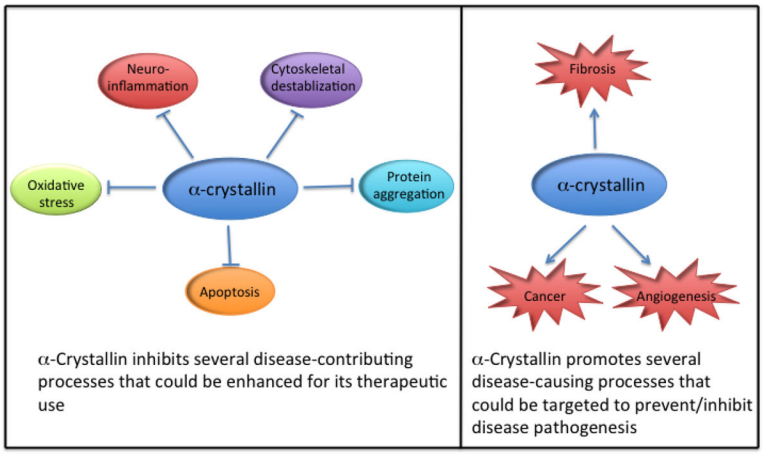

Fig. 1.