αB-crystallin as a promising target in pathological conditions – A review

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Abstract

Introduction and objective. αB-crystallin belongs to the ubiquitous family of small heat-shock proteins. It was discovered as a physiological protein of the eye lens, maintaining its liquid-like property. Furthermore, αB-crystallin was proved to play a bipolar role in both physiological and pathophysiological conditions. This review discusses current knowledge about the biology and genetics of αB-crystallin, and summarizes recent advances in understanding its role in ophthalmic and neurological disorders, as well as breast cancer, renal cancer and other malignancies.

State of knowledge. A-crystallins are established as important elements of the protein quality control network, and consequently their defects are related to multiple human diseases. New studies highlight αB-crystallin's involvement in proliferative diabetic retinopathy angiogenesis and point out its therapeutic potential in age-related macular degeneration. αB-crystallin is thought to be associated with the disease-causing protein aggregates, leading to its connection with such neurological disturbances as anaplastic astrocytoma, Parkinson disease, aging deficits in the peripheral nervous system and multiple sclerosis. In breast cancer, it was proven to be a marker of aggressive behaviour and cerebral metastases. Strong expression of αB-crystallin promoted growth and migration of clear cell renal cell carcinoma cells and was correlated with lower overall survival rate. Considering other malignancies, its various roles were established in colorectal and gastric cancers, head and neck squamous cell carcinomas and osteosarcomas.

Conclusions. Further studies concerning αB-crystallin seem to be enormously promising, as they might improve our understanding of common human pathologies as well as contemporary diagnostics and treatment.

Key words

αB-crystallin, small heat-shock proteins, breast cancer, renal cell carcinoma

INTRODUCTION AND OBJECTIVE

αB-crystallin, called also HspB5, belongs to the ubiquitous family of small heat-shock proteins (sHsps) [1]. sHsps is a class of ATP-independent chaperones, whose characteristic feature is the presence of a conserved α-crystallin domain consisting of two β-sheets flanked by a non-conserved long N-terminal extension and a short C-terminal segment [2]. αB-crystallin is a part of the Class I of sHsps family of small heat-shock proteins (sHsps) [1]. sHsps is a regulator of angiogenesis, enhancer of cell migration and cancer behavior and resistance to neoadjuvant chemotherapy, regulator of angiogenesis, enhancer of cell migration and inducer of rapamycin-resistance in clear cell renal cell carcinoma (ccRCC) [9–11].

Due to the wide range of the role of αB-crystallin in the organism, further investigation is necessary. Nowadays, medicine faces new difficulties associated with the treatment of various diseases (including neural diseases) and cancers; thus, scientists need to search for new markers, and enhance knowledge about those which have been newly discovered. This review discusses the well-established knowledge about the biology and genetics of αB-crystallin, and summarized recent advances in understanding its role in ophthalmic and neurological disorders, as well as breast cancer, renal cancer and other malignancies. To-date, according to the best knowledge of the authors, similar reviews encompassing the described area have not been published.
**STATE OF KNOWLEDGE**

**Biology.** αB-crystallin belongs to the family of sHsps, based on the presence of a conserved 90-residue-long α-crystallin domain [12]. α-crystallins form large oligomers with more than 20 subunits, tending to be extremely labile and rapidly exchange association and dissociation. Jehle et al. (2011) suggested the following organization of three-domain αB-crystallin:
1) an N-terminal domain of approximately 60 residues;
2) a central α-crystallin domain of about 90 residues involved in dimerization;
3) a C-terminal domain of 25 residues with hydrophobic motif I-X-I.

Interaction between two α-crystallin domains forms a dimer. Three dimers connected by their C-terminal region define a hexameric unit, and higher-order multimers are formed by variable interactions involving the N-terminal region [13, 14]. HspB5 uses its structural plasticity to expose different binding interfaces [15].

Stress, disease or mutation may lead to protein aggregation representing a major threat to the whole organism. αB-crystallin as a part of sHsps poses an ATP-independent chaperone function and can bind partially unfolded proteins in order to prevent their accumulation. Thus, α-crystallins have proved to be important elements of the protein quality control network, and consequently, their defects cause multiple human diseases [5]. αB-crystallin is placed as the first responder to cell stress due to being capable of immediately binding unfolding proteins. Discussed substrate binding is facilitated by a huge increase in the available hydrophobic surface on the α-crystallins [16]. The potency of sHsps to suppress aggregation is correlated with their ability to form stable substrate complexes – HspB5 binds tightly to variety of proteins. In the study by Mymrikov et al. (2017), HspB5 bounded one of the highest numbers of different substrates (a total of 88) [2]. Research by Peschek et al. (2013) proved that the chaperone activity of αB-crystallin protected more than 300 proteins from aggregation, as shown using HeLa cells exposed to heat stress [17]. HspB5 preferentially binds relatively large (50–100kDa) and slightly acidic (pH 5.4–6.8) proteins. Noticeably, α-crystallins are suspected to be the most active and promiscuous sHsps in temperature-induced aggregation assays due to forming large oligomers, although, the ability to form large oligomer does not seem to influence reduction-induced aggregation [2, 18].

αB-crystallin has proved to play a crucial role in the biogenesis of multipass transmembrane proteins (TMPs) by assisting their folding from the cytosolic face of the endoplasmic reticulum (ER) [19]. Furthermore, Ciano et al. (2016) established that phosphorylation of serine, resident at position 59, finely regulates the chaperone activity of HspB5 with studied TMPs [20]. Recent studies demonstrated the competence of HspB5 to interact with membrane channels. Analysis by Huang et al. (2016) validated the interaction between Na,5 (the pore-forming subunit of the cardiac voltage-gated Na+ channel complex) and αB-crystallin. The crystallogram increases I,Na densities and, what is more, knock-out of its expression significantly decreases cell surface of Na,5 [21]. In some studies, αB-crystallin showed affinity to Bax and Bcl-X, – proapoptotic agents. HspB5 suppresses the mitochondrial translocation of these agents and, as a result, prevents apoptosis. Regarding cancers cells, overexpression of HspB5 and its antiapoptotic function may be connected with faster progression and worse prognosis [22].

**Genetics.** Various mutations of CRYAB gene have been described and associated with human pathologies (Tab. 1). Ngo et al. (1989) localized the αB-crystallin gene at chromosome 11 locus q22.3–23.1 [23]. CRYAB gene is 3–4 kb long with three exons and an open reading frame of 175 codons [24]. Diverse expression of αB-crystallin between different tissues, both physiologically and under the influence of stress factors, requires sophisticated regulatory mechanisms at the transcriptional level. Dubin et al. (1991) studied the murine CRYAB gene and described a promoter expanding from position -661 to +44, as well as an upstream enhancer (at positions −426/−257) especially active in murine myoblasts and myotubes [25]. CRYAB contains a canonical heat shock promoter, which shows significant conservation of nucleotide sequence when compared between humans and rats [26]. Due to presence of the heat shock element (HSE), it is a target of heat shock transcription factors HSF1 and HSF4; nevertheless, the outcome of such interaction varies between different cell-types [27]. Moreover, Sadamitsu et al. (2001) linked HSF2 with increased expression of the CRYAB gene in human glioma U-251MG cells in response to high extracellular concentrations of potassium [28]. In addition to those highly universal HSE sequences, Jing et al. (2014) identified a 10-bp gene-specific promoter sequence (GPS), deletion of which resulted in the absence of αB-crystallin expression in transgenic mice [29]. Gopal-Srivastava et al. (1994) showed that proximal sequence (-164/ +44) of the CRYAB gene is not sufficient for the expression of αB-crystallin in the skeletal muscle and cardiomyocytes, while allowing the expression of αB-crystallin in the lens of transgenic mice. This sequence is referred to as lens-specific regulatory region (LSR), and is activated synergically by paired box protein PAX6 and its second form PAX6(5a), which play a crucial role in eye development [30–32]. LSR is also targeted by retinoic acid receptor RAR and retinoid X receptor RXR [33]. In later studies, LSR was found to be also sufficient for CRYAB expression in corneal epithelial cells [34].

Enhancer of CRYAB gene is crucial for αB-crystallin expression in structures other than the lens and cornea. There is ongoing search for signaling pathways leading to the regulation of CRYAB enhancer activity, thus influencing αB-crystallin expression in various tissues. Several control elements have been described among enhancer sequences: αBE-1, αBE-2 and αBE-3, showing activity both in lens and muscle cell lines; MRF containing E-box, specific for the skeletal muscle and αB-4 required for the expression of αB-crystallin in cardiomyocytes [35–37]. MRF control element, crucial for CRYAB transcription in skeletal muscles, is known to bind via E-box to the MyoD, myogenin or a different member of this protein family [35]. Increased CRYAB expression was shown in cardiomyocytes in response to biochemical stress stimuli [38]. In their study on mice with hypertrophic hearts, Manukyan et al. (2010) proposed a signaling pathway activating αBE-4 control element of CRYAB enhancer. They observed that transcription factors NFAT, Nished and STAT3 form a dynamic ternary complex in the presence of hypertrophic stimuli, and interact with the αBE4 promoter element, indicating the important role
of calcineurin/NFAT and Jak/STAT signaling pathways in the transcription of CRYAB gene in cardiomyocytes [39].

**Ophthalmic disorders.** Despite being widely expressed in many tissues, αB-crystallin is the ubiquitous structural protein of lens and retina. It is considered to be soluble and obtain high concentration, enabling creation of the phenotype of transparency during development of the ocular lens [60, 61]. The non-crystallin/catalytic functions of this protein remain unknown; thus, on the basis of finding αB-crystallin and VEGF with angiogenic activity [65].

αB-crystallin is being taken into consideration in the cataractogenesis. In 2016, Yang et al., proved in a study from 2016 in which Dong et al. stated that phosphorylation of αB-crystallin may play a role as a molecular chaperon for VEGF in the pathogenesis of epiretinal membranes in PDR [7].

**Table 1. Mutations of CRYAB gene in combination with corresponding changes in the protein product and related diseases.**

| Report                  | Mutation | Probable impact on the resulting protein                                                                 | AD/AR | Associated disease               |
|-------------------------|----------|-----------------------------------------------------------------------------------------------------------|-------|----------------------------------|
| Chen et al., 2009 [40]  | R11H     | alteration of pi and electrostatic potential, changed tertiary structure                                    | AD    | congenital nuclear cataract      |
| Jiao et al., 2015 [41]  | R11C, R12C | disturbance of the electrostatic potential                                                                | AR    | cataract                         |
| Xia et al., 2014 [42]   | P20R     | alteration of the stability and solubility                                                               | AD    | PPC                             |
| Li et al., 2008 [43]    | P20S     | decreased subunit-exchange rate and chaperone activity, increased ability to trigger apoptosis            | AD    | PPC                             |
| Del Bigio et al., 2011 [44] | S21AsX24 | highly truncated non-functional product                                                                    | AR    | infantile muscular dystrophy    |
| Safae et al., 2009 [45], Khan et al., 2010 [46] | R56W | disturbance in interaction with αB-crystallin                                                          | AR    | juvenile cataract, predisposition for retinal degeneration |
| Sun et al., 2011 [47]   | R69C     | damaging effect on highly conserved residues                                                            | AD    | cataract                         |
| Sacconi et al., 2012 [48] | D109H | affects an aspartate residue causing change in surface charge                                             | AD    | cardiomyopathy, MM, PPC          |
| Fichna et al., 2017 [49] | D109A | aggregates formation                                                                                   | AD    | MM                              |
| Brodel et al., 2017 [50] | D109G | aggregates formation                                                                                   | AR    | restrictive cardiomyopathy      |
| Forrest et al., 2011 [51] | S115PfsX14 | aberrant protein consisting of 127 residues                                                              | AR    | infantile onset myofibrillar myopathy |
| Vicart et al., 1998 [52] | R120G | aggregates formation                                                                                   | AD    | desmin-related myopathy         |
| Liu et al., 2006 [8]    | D140N    | alterations in tertiary and/or quaternary structure; aggregates formation                               | AD    | congenital lamellar cataract     |
| Berry et al., 2001 [53] | K150fs   | aberrant protein consisting of 184 residues                                                               | AD    | PPC                             |
| Selcen et al., 2003 [54] | Q151X, P155RfsX9 | impairment of solubilization and chaperone activity                                                  | AD    | MM                              |
| Pilotto et al., 2006 [55], Reilich et al., 2010 [56] | G154S | damaging effect on highly conserved residues                                                             | AD    | DC, late-onset distal vacuolar myopathy |
| Inagaki et al., 2006 [57] | R157H | decreased binding to titin/connectin heart-specific N2B domain                                             | AD    | DC                              |
| Devi et al., 2008 [58]  | A171T    | disturbance in the chaperone function                                                                   | AD    | lamellar cataract                |
| Van der Smagt et al., 2014 [59] | X17W6F6X19 | elongation of the normal protein with 19 amino acid residues                                           | AD    | PPC, adult onset DC            |

AD - autosomal dominant; AR - autosomal recessive, DC - dilating cardiomyopathy, MM - myofibrillar myopathy; pI – isoelectric point; PPC - posterior polar cataract.
αB-crystallin is constitutively expressed by the peripheral nervous system (PNS) axons and Schwann cells. It was proved to be important for recovery after PNS nerve injury [77]. In 2017, Lim et al. observed a reduction in αB-crystallin expression one day after injury; they therefore assumed that it is a negative regulator of early events, such as axon degradation, Schwann cell differentiation and proliferation. On the other hand, it was established as a positive modulator of late events – regeneration and remyelination, due the fact that its level increased 28 days after crush. What is more, the contribution of αB-crystallin to remyelination of peripheral axons was confirmed by its absence in attenuated myelin formation [78]. Furthermore, Lim et al. (2017) examined the correlation between expression of HspB5 and aging deficits in mice PNS. First of all, they observed thinner myelin sheaths at 28 days after injury in mice without expression of αB-crystallin, compared to mice with expression, which proved αB-crystallin to be involved in remyelination. In both young and older animals, HspB5 may be important in ensuring optimal myelin thickness. What is more, a significant decrease was found in HspB5 after one month of mice age and therefore assumed that the crystallin was inversely correlated with the increased deficits typical of the aging PNS [74].

αB-crystallin and a few other small heat shock proteins have been shown in demyelinating plaques of multiple sclerosis (MS) brains [75]. The crystallin was established as one of the triggers responsible for microglia and macrophages activation, playing a crucial role in demyelination during MS. Bisbì et al. (2014) suggest that INF-γ can act like a cofactor, reprogramming local microglia and macrophages, causing αB-crystallin-triggered release of TNF-α, IL-6, IL-12 and drive of demyelination and oxidative damage [79]. In 2015, van Noort et al. described therapeutic intervention in MS with αB-crystallin. HspB5 was applied in relapsing-remitting MS using doses sufficient to support its protective effects, but low enough to avoid triggering T-cell response. This proved the favourable safety profile of HspB5, and the MRI data demonstrated progressively suppressive effects on lesions development in patients, which was not observed in the placebo group [80].

Breast cancer. In the human mammary epithelial cells, overexpression of αB-crystallin leads to neoplastic-like changes by disrupting mammary acinar morphology. Moyano et al. (2006) observed that cells with overexpression of αB-crystallin had higher levels of total and phosphorylated ERK1/2, Akt, and p38. Additionally, overexpression conferred EGF- and anchorage-independent growth and enhanced MEK-dependently migration and invasiveness [81]. Afterwards, αB-crystallin proved to be a sensitive and specific marker for aggressive breast cancer behaviour [9]. In a study by Tsang et al. (2012) of 395 cases of breast carcinoma, αB-crystallin demonstrated high sensitivity and specificity as a triple negative breast cancer (TNBC) and basal-like breast cancer (BLBC) marker, and in 2011, Chan et al. highlighted it as an adjunct marker of mammary metaplastic carcinoma [82, 83]. In 2015, Kim et al. studied 82 breast tissue samples obtained from patients with stage IA – IIIC infiltrating ductal carcinoma. Their study showed both in the univariate and multivariate analysis of αB-crystallin expression a shorter overall survival rate (OS), suggesting that αB-crystallin is an independent prognostic factor of infiltrating ductal carcinoma [84]. Also, Kabbage et al. (2012) confirmed the upregulation of αB-crystallin in infiltrating ductal breast carcinoma [85].

Due to the fact that αB-crystallin is highly expressed in TNBC and BLBC, recent studies focused on the discovery of its molecular inhibitor. In 2014, Chen et al. investigated a small potent molecular inhibitor – NCI-41356, which disrupted the interaction between αB-crystallin and VEGF165. In vitro it triggered anti-tumour cell proliferation and invasive effects. Moreover, in vivo breast cancer xenograft models it inhibited the tumour growth and vascularization [86].

For a long time, αB-crystallin has been known as a marker of lymph nodal involvement and metastases [87]. Only recently it proved to be a promising predictor of breast cancer
metastases to the brain. This connection was discovered in two independent studies. In 2014, Malin et al. verified an association between αB-crystallin expression and TNBC, and studied its high expression in breast cancer brain metastases. In vitro they proved that overexpression of αB-crystallin in TNBC enhanced adhesion to human brain microvascular endothelial cells, transendothelial migration and blood-brain barrier [88]. In 2015, Voduc et al. determined αB-crystallin expression as the strongest predictor of brain metastasis and the only independent predictor of brain metastasis as the first site of distant relapse. They suggested that αB-crystallin may become a marker for identifying patients with breast cancer who are at high risk connected with brain metastasis [89].

Renal cell carcinoma (RCC). αB-crystallin was found to be abundantly expressed in the epithelial tissues of healthy kidneys. Its amount increased from the renal cortex to the inner medulla, where it constitutes approximately 2% of the protein mass. αB-crystallin expression is not homogeneous, concentrated in thin limbs of Henle, proximal convoluted tubules and collecting ducts, while being absent in glomerular components [90, 91].

Michl et al. (2006) investigated the influence of environmental factors on αB-crystallin expression in rat kidneys and canine kidney cell culture. They found a strong positive correlation between the level of αB-crystallin expression and increasing osmolarity of the environment [90]. Thus, its role in the renal physiology is currently considered to be a cell-protective agent in the hyperosmotic environment of renal medulla, given the chaperone and anti-apoptotic activity of αB-crystallin [90, 92]. A different study showed that the level of αB-crystallin, among many other proteins, increased in the kidneys of mice foetuses exposed in utero to cigarette smoke [93]. Lou et al. (2016) conducted a study on mice and cultured renal proximal tubular cells with or without knockdown of heat shock factor 1 (HSF1) treated with nephrotoxic cisplatin. Exposure to cisplatin induced the expression of αB-crystallin in an Hsf1+ specimen, showing cytoprotective activity. HSF1 knockdown led to decreased αB-crystallin expression and susceptibility to the nephrotoxic activity of cisplatin [94]. These results suggest that αB-crystallin protects tubular cells against apoptosis while exposed to toxic agents, and that this activity is mediated by HSF1 [93, 94].

The presence of αB-crystallin in renal tissues provoked an investigation into its role in neoplastic processes occurring in the kidneys. αB-crystallin expression in RCC varies among different subtypes based on their place of origin [91]. The most common of them, clear-cell and papillary types, which originate from proximal convoluted tubules, were observed to show a strong expression of αB-crystallin [11, 91]. Chromophobe subtype of RCC develops from cortical collecting ducts and are reported to show no expression of αB-crystallin similarly to uroepithelial carcinomas. Thus, immunohistochemical staining for αB-crystallin may prove as a useful tool in differentiating between subtypes of RCC and uroepithelial carcinoma, especially in poorly differentiated cases [91]. Antioxidant activity of αB-crystallin, crucial for proper functioning of cells, in a challenging environment of renal medulla, becomes a double-edged sword when neoplastic processes occur. Strong expression of αB-crystallin promoted growth and migration of ccRCC cells and was correlated with lower OS in patients with clear-cell RCC [11]. On the contrary, Shi et al. (2004) associated a higher expression level of αB-crystallin with lower grade RCC tumors; nevertheless, the material included only 11 RCC samples [95]. αB-crystallin is suggested to be involved in the development of rapamycin resistance in patients diagnosed with RCC, and treated with mTOR targeted therapies [11]. However, different study have not confirmed a significant correlation with OS; therefore, further investigation is necessary [91].

Thedieck et al. (2008) proposed another role of αB-crystallin in renal tissue, observing its co-localization with kidney-specific cadherin (Ksp-cad) at the basal side of collecting duct cells [96]. Ksp-cad belongs to a small family of 7D-cadherins that do not interact with cytoplasmatic catenins. It plays an important role in maintaining proper architecture of tissues by regulating cell adhesion. αB-crystallin was suggested to be a partner of Ksp-cad involved in its signaling pathways. In renal-cell carcinomas, reduced Ksp-cadherin expression, possibly due to dysregulation of its interaction with αB-crystallin, causes disturbed cell adhesion leading to distant metastases [97].

Other malignancies. The role of αB-crystallin in tumourigenesis in currently being studied in various types of malignancies, producing evidence of its crucial effect on the aggressiveness of the disease and its prognosis (Tab. 2). Shi et al. (2014) studied 118 samples obtained from patients with colorectal cancer and showed an increased level of αB-crystallin protein and mRNA, compared with healthy tissue. Moreover, the expression of HspB5 protein was significantly correlated with distant metastases and poor OS [98]. Another study by Shi et al. (2017), conducted on colorectal cancer cell line SW480 transfected with lentiviral vector inhibiting CRYAB expression, showed decreased expression of markers of epithelial-mesenchymal transition (EMT), such as E-cadherin, fibronectin and vimentin. Suppression of CRYAB gene not only inhibited EMT, but also increased apoptosis and G1 arrest, as well as reduced migration capability of the colorectal cancer cells [99]. Similar results were obtained by Li et al. (2017) in a study conducted on 70 samples of colorectal cancer; they found up-regulation of αB-crystallin and its positive association with tumour stage and level of matrix metalloproteinase-7 (MMP-7). They also provided evidence that EMT induced by αB-crystallin may be regulated by ERK, PI3K and p38 signaling pathways [100].

Wu et al. (2018) studied CRYAB C-802G (rs14133) polymorphism in association with colorectal cancer risk and survival. CG/GG genotype carriers were associated with increased risk of CRC in comparison of CC genotype carriers [101].

ERK signaling pathway involvement in increased aggressiveness and MPP-9 expression was described in osteosarcoma cell lines and samples obtained from biopsies. Similar to colorectal cancer, a high expression of CRYAB was correlated with shorter OS and earlier relapse in patients surgically-treated with osteosarcoma [102]. In a study by Wang et al. (2017), the up-regulation of αB-crystallin in patients with osteosarcoma was associated with a decreased level of serum miR-491, which is correlated with increased metastases, worse response to chemotherapy, and lower survival rate [103]. αB-crystallin’s expression was also studied by Chen et al. (2018) in gastric cancer. Their results were similar to
previously mentioned studies, showing up-regulation of CRYAB in close correlation with distant metastases and poorer OS. Moreover, high expression of CRYAB promoted epithelial-mesenchymal transition of cancer cells via the NF-κB signaling pathway, thus increasing cells migration and invasion abilities [104].

αB-crystallin has also been suggested as a negative prognostic marker in head and neck squamous cell carcinomas (HNSCC). In a study by Annertz et al. (2014) conducted on samples obtained from 55 patients with oropharyngeal and oral SCC, disease specific survival of patients with oral SCC was correlated with the presence of αB-crystallin expression (27.3 months for CRYAB-negative tumours, but only 7.5 months for CRYAB-positive tumours) [105]. Up-regulation of αB-crystallin was also described by Yilmaz et al. (2014) in laryngeal SCC, although without any correlation with the presence of distant metastases or tumour TNM stage [106]. A different study conducted on HNSCC showed correlation between the expression of αB-crystallin and markers of hypoxia associated with therapeutic resistance of HNSCC and presence of distant metastases [107].

CONCLUSIONS

As the very first responder to cell stress and an extremely important element of protein quality control network, αB-crystallin plays a bipolar role both in physiological and pathophysiological conditions. Recent studies have proved its involvement in the development of many disorders, including cancers. Unfortunately, the connection between its biology, genetics and pathological condition remains unclear. Nevertheless, αB-crystallin seems to be an enormously promising protein, which may improve contemporary diagnostics and treatment. It has already been suggested as a potential therapeutic target in AMD and trialed in relapsing-remitting MS with positive reports.

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