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Crystallins as Important Pathogenic Targets for Accumulation of Structural Damages Resulting in Protein Aggregation and Cataract Development: Introduction to This Special Issue of *Biochemistry (Moscow)*

Reza Yousefi[1,2]

[1]*Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran*
[2]*Protein Chemistry Laboratory, College of Sciences, Shiraz University, Shiraz, Iran*
e-mail: yousefi.reza@ut.ac.ir, ryousefi@shirazu.ac.ir

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Abstract—This issue of *Biochemistry (Moscow)* is dedicated to the role of protein misfolding and aggregation in cataract development. In fact, many genetic mutations or chemical and physical deleterious factors can initiate alterations in the macrostructural order and proper folding of eye lens proteins, which in some cases result in the formation of large light-scattering aggregates, affecting the quality of vision and making lens more prone to cataract development. Diabetes mellitus, which is associated with oxidative stress and mass production of highly reactive compounds, can accelerate unfolding and aggregation of eye lens proteins. This journal issue contains reviews and research articles that describe the destructive effects of mutations and highly reactive metabolites on the structure and function of lens crystallin proteins, as well important molecules in the lens's natural defense system involved in protection against deleterious effects of the physical and chemical factors.

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INTRODUCTION

This issue, which is dedicated to protein misfolding and aggregation in cataract disorders, was prepared at the suggestion and with participation of Boris Ivanovich Kurganov, Chief Researcher of the Bach Institute of Biochemistry and Honored Scientist of the Russian Federation, who passed away on October 1, 2021. His unremitting research efforts in the field of enzymology, mechanisms of protein aggregation, and role of molecular and chemical chaperones in prevention of protein aggregation, which spanned more than six decades, have left an important and valuable scientific heritage. Boris Kurganov had also played a prominent role in studying the mechanism of aggregation of eye lens crystallins, proteins that have an essential role in the transparency and refractive index of the lenticular tissues [1].

* To whom correspondence should be addressed.

CRYSTALLIN PROTEINS AS IMPORTANT PATHOGENIC TARGETS FOR ACCUMULATION OF VARIOUS STRUCTURAL DAMAGES

These water-soluble structural proteins found in the vertebrate eye lenses are classified into three main types – α-, β-, and γ-crystallins – that elute from a gel filtration column in the same order due to the differences in their size and degree of oligomerization [2]. α-crystallins (αA and αB) and β-crystallins (βA1, βA2, βA3, βA4, βB1, βB2, βB3; A, acidic; B, basic) form larger and smaller oligomers, respectively, while γ-crystallins (γA, γB, γC, γD, γE, γF, γN, and γS) are essentially monomers [3]. These highly stable β-rich proteins form very regular and interactive macrostructures through subtle interactions with each other which are important for lens transparency [1, 4]. In addition to disrupting such important fine protein–protein interactions, genetic mutations and accumulation of physical and chemical damages over the lifespan result in structural changes and

exposure of protein hydrophobic regions. Eventually, these adverse molecular events lead to the unfolding and aggregation of lens crystallins, inducing cataract development. Cataract is the most common cause of blindness worldwide, affecting tens of millions of people [5-9]. Beside lenticular tissues, crystallin proteins (e.g., αB-crystallin) are found in other tissues, such as retina, heart, skeletal muscle, skin, brain, etc. [10, 11]. Therefore, structural and functional damages to these proteins are also associated with other disorders, including myopathy, neurological problems, cardiac diseases, muscular disorders, and invasive breast cancer tumors [12-15]. Along with the structural role, crystallins have several metabolic and regulatory functions, both inside and outside of lenticular tissues [16]. Although enzymatic activity has been reported for some type of crystallins [17], their most important biological function can be attributed to the chaperone activity of α-crystallin, which plays a vital role in preventing and delaying cataract diseases and increases cell resistance to various types of chemical and physical stress [18, 19]. This chaperone, which belongs to the heat shock protein (hsp) family, also plays a prominent role in the inhibition of apoptosis and cytoskeletal remodeling [20, 21]. Crystallins are highly clear and refractive proteins with abnormal hydration properties. They resist unfolding and aggregation for decades during human life [22]. However, mutations and accumulation of physical and chemical damages eventually cause unfolding and aggregation of these proteins [23]. Also, some diseases (e.g., diabetes) characterized by the elevated levels of oxidative compounds and reactive metabolites (sugars and sugar derivatives) in eye lenses, increase the extent of crystallin structural damage and thus accelerate the process of cataract formation [24, 25]. Mutations in the genes of two α-crystallin subunits are also associated with the dominant and recessive forms of cataract, as well as with a wide range of neurological, cardiovascular, and muscular disorders [26-28]. Mutations that cause severe damage to these proteins usually result in congenital cataracts, while milder mutation increase lens susceptibility to the environmental damage and are associated with the age-related cataract development [29]. Also, with age, gradual accumulation of covalent damages due to various factors, such as ultraviolet radiation [30], oxidation [31], deamidation [32], and proteolysis [33], results in the formation of protein aggregates that scatter the incident light in the lens. Numerous studies have also demonstrated that the abnormal levels of essential elements (calcium, copper, and zinc) and heavy metals (divalent lead, cadmium, and mercury) are the important sources of destructive damages to crystallin proteins and, under some circumstances, can be considered as potential causative factors in cataract development [34-37]. For example, diseases that increase the level of essential metals in eye lenses (e.g., diabetes) also cause structural damage to lens proteins and induce their aggregation, which further facilitates the development of cataract complications [38, 39]. Although, the only currently available treatment is surgical removal of cataract lenses, scientific and medical community has long sought for the non-destructive treatments as well. In this regard, therapies based on the use of natural products [40], modulators of oxidation processes [41], protein aggregation inhibitors (e.g., chemical chaperones) [42], homoeopathic remedies [43], and lens regeneration using endogenous stem cells [44] have been proposed.

Below, I will briefly introduce the articles of this special issue [51, 53, 57, 58, 60]. Over the years, Professor Boris Kurganov's research team has developed methods for evaluating the effect of molecular and chemical chaperones, as well as the effects of their combined application on the kinetics of protein aggregation [45-50]. In continuation of these studies, Chebotareva et al. [51] investigated the effect of trehalose as a chemical chaperone, on the quaternary structure and chaperone activity of αB-crystallin. Mature fiber cells contain extremely high concentrations of crystallin proteins that make up approximately 90% of the dry weight of human lens [52]. While lens proteins are continuously exposed to physical and chemical damage, lens cells have developed protective systems to counteract the harmful effects of environmental factors on lens proteins. However, in the case of diseases, such as diabetes or aging, the dominance of the damaging factors over two important levels of natural protections (chaperone and antioxidant defense systems) can have serious destructive effects on the structure and function of lens proteins. Various approaches for preventing lens opacity, in particular, combined use of antioxidants and chemical molecules, have been reviewed by Muranov and Ostrovsky [53]. Diabetes mellitus is one of the causes of rapid cataract development. Beside oxidative stress, this metabolic disorder is characterized by the elevated concentrations of reactive metabolites, such as glucose, fructose, phosphorylated sugars (glycolytic intermediates), methylglyoxal, peroxynitrite, and sorbitol, in the lenticular tissues [54]. The oxidative stress typical for diabetes promotes the reaction between sugars or sugar derivatives and eye lens proteins [55]. The osmotic stress created by the increased sorbitol accumulation in eye lenses in hyperglycemia is one of the mechanisms of diabetic cataract [56]. Therefore, the effect of different concentrations of sorbitol on the structure and chaperone-like activity of rat α-crystallin has been studied by Reddy et al. [57]. The impact of peroxynitrite (an important source of oxidative stress in diabetes), methylglyoxal (diabetes-associated reactive carbonyl compound), and their simultaneous action on the structure and function of human recombinant αA-crystallin (αA-Cry) and the protective role of ascorbic acid and glutathione (main components of lens antioxidant defense system) have been investigated by Yousefi et al. [58]. Many mutations that found in the crystallin protein

genes are associated with diseases such as cataracts and myopathy [59]. Finally, the role of genetic mutations of α-crystallins on their structural unfolding and aggregation is discussed by Rao et al. [60].

This issue was initiated by and until recently created with a significant contribution from Professor Kurganov, and now it had to be finished in his absence. This is why we dedicate it to the memory of Professor Boris Ivanovich Kurganov, whose relentless efforts over the past decades and his valuable and influential scientific legacy have paved the way for other researchers to the unknown frontiers of knowledge.

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