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μ-Crystallin: A thyroid hormone binding protein

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Abstract

μ-Crystallin is a NADPH-regulated thyroid hormone binding protein encoded by the *CRYM* gene in humans. It is primarily expressed in the brain, muscle, prostate, and kidney, where it binds thyroid hormones, which regulate metabolism and thermogenesis. It also acts as a ketimine reductase in the lysine degradation pathway when it is not bound to thyroid hormone. Mutations in *CRYM* can result in non-syndromic deafness, while its aberrant expression, predominantly in the brain but also in other tissues, has been associated with psychiatric, neuromuscular, and inflammatory diseases. CRYM expression is highly variable in human skeletal muscle, with 15% of individuals expressing ≥13 fold more *CRYM* mRNA than the median level. Ablation of the *Crym* gene in murine models results in the hypertrophy of fast twitch muscle fibers and an increase in fat mass of mice fed a high fat diet. Overexpression of *Crym* in mice causes a shift in energy utilization away from glycolysis towards an increase in the catabolism of fat via β-oxidation, with commensurate changes of metabolically involved transcripts and proteins. The history, attributes, functions, and diseases associated with *CRYM*, an important modulator of metabolism, are reviewed.

Keywords

CRYM; μ-Crystallin; mu-crystallin; thyroid hormone; T_3; T_4; ketimine reductase

Thyroid hormones (THs) are essential regulators of gene expression and metabolism and their precise control is therefore crucial to maintaining homeostasis and adapting to different environmental conditions. TH regulation is achieved at many levels and through multiple means, including synthesis, secretion, uptake into tissues, intracellular processing by deiodinases, and potentially binding to proteins involved in intracellular storage. Here, we review the TH binding protein, μ-crystallin (*CRYM*), that may play a key role in the latter process, intracellular sequestration and storage.

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T_3 and T_4 thyroid hormone (TH) are produced in the thyroid, though the thyroid primarily produces T_4 and less than 20% of the TH it releases is T_3 (Abdalla and Bianco 2014). Triiodothyronine (T_3) is primarily produced peripherally in the body via the monodeiodination of thyroxine (T_4) (Chopra 1977). THs typically act as transcription factors by binding to thyroid hormone receptors (TRs). T_3 has a 10-fold higher affinity for TRs than T_4 and therefore, it is a more potent transcription factor (Abdalla and Bianco 2014). Liganded and unliganded TRs act as strong regulators of metabolism and thermogenic homeostasis (Larsen et al. 1981) primarily by affecting transcription of genes containing thyroid response elements (Brent 2012).

The ability to bind TH with high affinity suggests that μ-crystallin may play a role in regulating TH levels by controlling the availability of TH to interact with receptors, with possible downstream consequences to physiology and metabolism. Reed et al. (2007) have observed on a 2D proteomic gel of skeletal muscle biopsies taken from 3 individuals with FSHD and 2 healthy individuals that μ-crystallin showed increased expression and was the only differentially expressed protein in comparing individuals with facioscapulohumeral muscular dystrophy (FSHD) to healthy individuals (Reed et al. 2007). In order to study increased levels of skeletal muscle μ-crystallin, which was at that time a candidate for the then unknown pathological protein in FSHD, they constructed a transgenic mouse specifically overexpressing μ-crystallin in skeletal muscle, the *Crym* tg mouse. At the time, little was known about the pathological agent in FSHD, although Double Homeobox 4 (DUX4) is now widely believed to determine disease pathology (Tawil et al. 2014).

Crym tg mice were created to specifically overexpress μ-crystallin in skeletal muscle by placing the mouse *Crym* open reading frame under the control of the human skeletal actin promoter (*ACTA1*) and the human slow troponin I enhancer (*TNNI1*). The transgenic plasmid incorporated randomly into intron 12 of the *Cntn6* gene after oocyte injection. The resultant transgenic mice were bred to homozygosity to be used to measure the effects of high μ-crystallin expression in skeletal muscle (Kinney et al. 2021).

Discovery of μ-Crystallin

μ-Crystallin was first identified in 1957 by Tata who called the protein a thyroxine-binding protein (Tata 1958). Hashizume et al. subsequently showed the same protein that they called Factor b, could bind T_3 and T_4 in the presence of NADH or preferably NADPH (Hashizume et al. 1986), the latter dinucleotide causing the increased binding capacity of cytosolic 3,5,3'-triiodo-L-thyronine (T_3)-binding protein (CTBP), the next name for μ-crystallin (Hashizume et al. 1989a). NADP bound to CTBP (μ-crystallin) enhanced the presence of T_3 in the nucleus of rat kidney cells at sites that differed from other nuclear T_3 sites (Hashizume et al. 1989b), whereas NADPH diminished the amount of nuclear T_3 (Hashizume et al. 1989c). Maximal activation by NADP or NADPH was at concentrations of 0.1 μM and 25 μM respectively, 20 and 4 times less, respectively, than physiological levels (Hashizume et al. 1989d), suggesting that μ-crystallin in cells was likely to be bound to both NADP and NADPH. CTBP was shown to increase cellular and nuclear uptake of T_3 as well as decrease cellular and nuclear efflux of T_3 in addition to suppressing expression of thyroid hormone responsive genes (Mori et al. 2002). Kobayashi et al. (1991) further characterized

μ-crystallin as a dimer of two identical 38,000 Da subunits. At the time, it was referred to as p38CTBP, to distinguish it from a 58 kDa thyroxine-binding protein, p58CTBP (Hashizume et al. 1989a). Wistow and Kim (1991) gave μ-crystallin its current name after they found the protein highly expressed in the lens of some marsupials. More recently, μ-crystallin has been shown to function as a ketimine reductase in addition to its activity as a NADPH-regulated thyroid hormone binding protein (Hallen et al. 2011; Hallen et al. 2015a, b; Hallen and Cooper 2017).

Temporospatial expression of CRYM

μ-Crystallin is predominantly expressed in the cerebral cortex, heart, skeletal muscle, prostate, and kidney (Thul et al. 2017). Temporally, *Crym* expression in mice gradually increases from embryonic day 10.5 until its zenith at embryonic day 14.5, when the brain and inner ear have the highest expression. Expression subsequently decreases gradually and falls sharply postnatally in most tissues. Some *Crym* expressing organs such as the renal medulla of the kidney increase in expression of *Crym* postnatally while other organs continue to express *Crym*, albeit at lower levels than *in utero* (Smith et al. 2019). *CRYM* mRNA in humans is expressed at its highest levels in the basal ganglia of the brain followed by the heart; at the protein level, μ-crystallin is most highly expressed in the basal ganglia, cerebral cortex, kidney and prostate (data obtained from the normalized Consensus Dataset of the Human Protein Atlas) (Uhlen et al. 2015). Subcellularly, μ-crystallin localizes to the cytosol (Kobayashi et al. 1991). In humans, μ-crystallin is also expressed in the inner ear where two, rare mutations, X315Y and K314T, cause Deafness, Autosomal Dominant 40 (Abe et al. 2003). There are no other illnesses in which *CRYM* has been implicated, although it's aberrant expression has been associated with amyotrophic lateral sclerosis (Fukada et al. 2007; Daoud et al. 2011; Hommyo et al. 2018), facioscapulohumeral muscular dystrophy (FSHD) (Reed et al. 2007; Vanderplanck et al. 2011), endotoxin-induced uveitis (Imai et al. 2010), schizophrenia (Middleton et al. 2002; Miklos and Maleszka 2004), and Huntington's Disease (Francelle et al. 2015).

Thyroid hormones and their receptors

THs are crucial affecters of metabolism and thermogenesis, with 30% of resting energy expenditure under their control (Silva 2005). Significant changes in the levels of THs lead to illness. Hypothyroidism can cause depression, cardiovascular disease, fatigue and lethargy, and weight gain, among other consequences (Bello and Bakari 2012). Conversely, hyperthyroidism results in a wide range of largely distinct maladies, such as heart palpitations, fatigue, weight loss, and muscle weakness, among others (Mansourian 2010). Given their centrality to biological systems, the production of THs is under tight regulation.

Regulation and synthesis of thyroid hormones.

TH production is governed by the Hypothalamic-Pituitary-Thyroid axis (Mendoza and Hollenberg 2017). Thyrotropin-releasing hormone neurons located in the paraventricular nucleus of the hypothalamus control secretion of thyrotropin releasing hormone (TRH) in response to THs (Morley 1979; Yarbrough 1979), Agouti Related Peptide (AgRP) (Fekete et al. 2002), Neuropeptide Y (NPY) (Fekete et al. 2001), cocaine and amphetamine-regulated

transcript (Serrano et al. 2014; Fekete et al. 2000), norepinephrine (Zimmermann et al. 2001), and leptin (Harris et al. 2001). These factors are directly and indirectly regulated by environmental stimuli such as cold exposure (Sotelo-Rivera et al. 2017), teat suckling (Sanchez et al. 2001), and shortage of food (Legradi et al. 1997; Mihaly et al. 2000) and the TH feedback loop, among other factors (Rodriguez-Rodriguez et al. 2019).

Upon secretion of TRH by the hypothalamus, the hormone enters fenestrated primary portal capillaries connected to the anterior pituitary pars distalis (Rodriguez-Rodriguez et al. 2019). TRH binding to its receptor (TRH receptor 1) in the anterior pituitary induces the synthesis and release of thyroid stimulating hormone (TSH) (Snyder and Utiger 1972; Heuer et al. 2000). TSH then travels via the bloodstream to the thyroid gland where it binds TSH receptors (Schaefer and Klein 2011). This binding promotes the synthesis and release of the THs, T_3 and T_4. Approximately 80% of THs produced by the thyroid gland are T_4 (Pirahanchi et al. 2000) while 80% of T_3 comes from the peripheral deiodination of T_4 (Schimmel and Utiger 1977), with the remaining T_3 fraction generated by the intrathyroidal deiodination of T_4 and by the direct synthesis of T_3 within the thyroid gland itself (Deme et al. 1975; Kubota et al. 1984). T_3 and T_4 then travel via the bloodstream to peripheral organs, where they are taken up.

Thyroid hormone transport.

THs are transported into cells primarily by *SLC16A2* (MCT8), *SLC16A10* (MCT10), and *SLCO1C1* (OATP1C1) which are largely specific transporters for T_3 and T_4 (Visser et al. 2011). THs are also transported through more broadly acting transporters as well, such as *SLC10A1* (Friesema et al. 1999; Visser et al. 2010), *ABCB1* (efflux) (Mitchell et al. 2005), *SLC7A5* and *SLC3A2* (LAT1 and 4F2hc respectively, acting as a heterodimer), *SLC7A8* and *SLC3A2* (LAT2 and 4F2hc respectively, acting as a heterodimer) (Jansen et al. 2005), and thirteen organic anion transporting polypeptides (OATP) (Jansen et al. 2005). Once in the cell, deiodinases remove one or more iodine atoms from T_4 or T_3 to convert T_4 into T_3 or reverse T_3 (rT_3). T_3 and rT_3 can be converted into T_2. Deiodinase 1 (*DIO1*) is responsible for the production of T_3, rT_3, and T_2. Deiodinase 2 (*DIO2*) produces T_3 from T_4, and T_2 from rT_3. Finally, deiodinase 3 (*DIO3*) is capable of producing rT_3 and T_2 from T_4 and T_3 respectively (Pihlajamaki et al. 2005; Williams and Bassett 2011). rT_3 and T_2 are largely inactive biologically (Beckett and Arthur 1994; Senese et al. 2014).

Thyroid receptors.

In mammals, THs, primarily in the form of T_3, bind to nuclear TRs α1 (Sap et al. 1986; Weinberger et al. 1986), β1 (Jhanwar et al. 1985), β2 (Hodin et al. 1989), β3 [rodent only] (Williams 2000), and β4 (Tagami et al. 2010). T_3 can also bind to mitochondrial TRs p43 (Casas et al. 1999) and p28 (Sterling et al. 1984), and to the plasma membrane TR p30 TRα1 (Kalyanaraman et al. 2014). A number of additional isoforms of the TR subunits can be generated through alternative splicing of the *THRA* and *THRB* genes, including Δα1, Δα2 (Chassande et al. 1997), α2, α3, αΔE6 (Pantos and Mourouzis 2018), and Δβ3 [rodent only] (Williams 2000). These do not bind TH and most instead act in a dominant negative fashion, competing against TH bound TRs for TRE sites in the genome (O'Shea and Williams 2002; Casas et al. 2006; Raparti et al. 2013; Watanabe and Weiss 2018).

T_3 binds to TRs with a K_D = 0.06 nM. T_4 can also bind to thyroid hormone receptors, though with a much lower affinity, K_D = 2 nM (Sandler et al. 2004). TH binding to TRs alters the conformation of the protein affecting its ability to bind DNA (Apriletti et al. 1998). TRs act as transcriptional regulators as ligand-bound or unbound monomers, homodimers, heterotrimers, homotrimers (Mengeling et al. 2005), or most commonly as heterodimers with retinoid X receptors (RXR) (Velasco et al. 2007). TRs bind to thyroid hormone response elements (TREs), sequences in the genome that regulate transcription of associated genes. There are three consensus TRE sequences: direct repeat 4 (DR4) AGGTCAnnnnAGGTCA, a palindrome AGGTCATGACCT, and an inverted palindrome with a 6 base pair gap (IP6) TGACCTnnnnnnAGGTCA (Liu et al. 2020). Both unliganded and ligand-bound TRs can bind TREs to repress or promote transcription (Graupner et al. 1989). Some TRE sites are bound by unliganded TR and prevent transcription until TH binds to the receptor, while some TRE sites are repressed by TH-bound TR. The same is true with TRs acting as transcriptional activators (Eckey et al. 2003). There are many different ways activation or repression of gene expression can occur through the multitude of THs, TRs, RXRs, TREs, and various combinations thereof. The diversity of mechanisms by which THs can act through TRs, RXRs and TREs may help explain its ability to regulate so many different cellular and bodily functions and physiology, and why regulation of the unifying factor, TH, is so important.

μ-Crystallin (*CRYM*).

CRYM, the gene encoding CRYM mRNA and the μ-crystallin protein, is located at 16p12.2 in the human genome. The gene is 64.2 kb long, encoding a protein of 314 amino acids with a calculated molecular mass of 33.8 kD. Similarly, in mice, the *Crym* gene is located at 7qF2, is 15.7 kb long, and encodes a 313 amino acid protein, with a calculated molecular mass of 33.5 kD. μ-Crystallin binds strongly to T_3 with a K_D = 0.3 nM (Beslin et al. 1995) [see also Hallen et al. 2015a]. The crystal structure of mouse μ-crystallin has been solved to 1.75 Å. Five residues in the protein form a potassium ion binding pocket: Leu130, Gly219, Cys283, Lys285, and Thr287 (Borel et al. 2014). T_3 binds to murine μ-crystallin through the hydrophobic interactions of Phe58, Phe79, and Val49 as well as Arg229. Ser228 and Arg47 form hydrogen bonds with T_3. Finally, Lys75, Arg118, Ser228, and Leu292 interact with T_3 through water molecules (Borel et al. 2014).

μ-Crystallin in animals.

μ-Crystallin may play a role in adapting metabolism to meet the specific energetic requirements determined by genetic and environmental factors. Joshi et al. showed in 2017 that the sleeping breath rate of female *Crym* knockout (KO) mice was higher than controls (Joshi et al. 2019). Serum T_3 and T_4 concentrations are decreased while influx and efflux of T_3 is increased in *Crym* KO mice (Suzuki et al. 2007). It's possible that *Crym* KO mice have higher levels of anaerobic glycolysis due to lower levels of free cytoplasmic TH, causing an increased buildup of lactate, which may be indirectly cleared by a higher breath rate (Ducros and Trippenbach 1991). Indeed, *Crym* KO mice had hypertrophy of glycolytic fast twitch Type IIb muscle fibers (Seko et al. 2016) and when *Crym* KO mice were placed on a high fat diet they had increased fat mass as assayed by computer tomography compared to control mice on the same diet (Ohkubo et al. 2019).

μ-Crystallin appears to play an important role in environmental and metabolic adaptation in other mammals as well. *CRYM* levels in the hypothalamus of dogs are significantly lower than in the hypothalami of wolves and coyotes (Saetre et al. 2004). This may be a difference in regulation of TRH production since TRH is produced in the hypothalamus which ultimately causes the production of TH. TH in the hypothalamus acts in a negative feedback loop to inhibit the production of TRH (Fekete and Lechan 2007). Lower levels of *CRYM* in the hypothalami of dogs may allow for greater inhibitory effects of TH on TRH production, reflecting adaptation to differences in food availability and shelter of domesticated dogs versus wolves and coyotes. Mukai et al. (2009) used microarrays and qPCR to measure decreased levels of *CRYM* in the hypothalamus of song sparrows in autumn compared to spring, possibly implicating μ-crystallin again in controlling metabolic rate in relation to seasonal changes and the availability of food. Hinaux noted polymorphisms present in *crym* in *Astyanax mexicanus* surface fish compared to the same species of fish that dwell in caves devoid of any light and plentiful food sources (Hinaux et al. 2015). Curiously, the skeletal muscles of the cavefish are resistant to insulin, and the fish have a lower metabolic rate and higher percent of body fat than their surface-dwelling cousins (Ojha and Watve 2018). Chinese Erhualian pigs express 16-26 times more *CRYM* in their subcutaneous fat than in their visceral fat (intramuscular, retroperitoneal, and mesenteric adipose tissue) and *CRYM* is one of only seven genes specifically enriched in subcutaneous fat compared to visceral fat pads (Liu et a. 2019). Similarly, humans express 2.6-3.0 times more *CRYM* in their subcutaneous fat compared to their visceral fat (Serrano et al. 2014). Taken together, these observations suggest that μ-crystallin may play a role in the metabolic adaptation of organisms to the energy requirements and food availability in their environments.

μ-Crystallin as a ketimine reductase.

Although μ-Crystallin accounts for approximately a quarter of total lens protein in some Australian marsupials, the protein does not share sequence homology with other crystallins (Wistow and Kim 1991). Rather, mammalian μ-crystallin shares 31–33% amino acid sequence identity with bacterial ornithine cyclodeaminases (Kim et al. 1992) and 30% sequence identity with archaeal AF1665 AlaDH (Gallagher et al. 2004), suggesting a potential role for μ-crystallin in amino acid metabolism. Consistent with this, μ-crystallin is a ketimine reductase and uses both NADH and NADPH as a cofactor (Hallen et al. 2011). μ-Crystallin acts on naturally occurring ketimines present in lysine degradation, Δ^1-piperideine-2-carboxylate (P2C) and an analog of P2C, Δ^1-pyrroline-2-carboxylate (Pyr2C), at neutral pH (7.2) and more efficiently at an acidic pH (5.0) (Hallen et al. 2011; Hallen et al. 2015a, b; Hallen and Cooper 2017). Interestingly, μ-crystallin's activity as a ketimine reductase is competitively inhibited by sub-nanomolar concentrations of T_3 and T_4, with K_I= 0.60 nM and K_I= 0.75 nM, respectively (compared to T_3, which binds with a K_D = 0.3 nM) (Beslin et al. 1995). T_2 and rT_3 only minimally inhibit μ-crystallin (Hallen et al. 2015). μ-Crystallin has been proposed to play a role in the pipecolate pathway, the dominant lysine degradation pathway in the brain, as opposed to the saccharopine pathway, which breaks down lysine in the rest of the body (Hallen and Cooper 2017).

CRYM and disease

CRYM expression in the brain.

Crym is highly specific to certain regions and cell types in the brain. Kim et al. (1992) were the first to measure μ-crystallin in the brain of kangaroo and humans in 1992. Arlotta et al. (2005) identified μ-crystallin expression in some corticospinal motor neurons and subcerebral neurons of layer V of the cerebral cortex. There is increased staining of μ-crystallin in the hippocampus with higher expression distal to the dentate gyrus of mice, and gradually diminishing proximally (Lein et al. 2007). Fink et al. (2015) showed μ-crystallin expression in the cortex to be limited to spinally projecting corticospinal motor neurons, and not in layer V neurons sending projections either intracortically or corticofugally. They also documented μ-crystallin in the dorsal, lateral, and ventral funiculi of the cervical and lumbar spinal cord and spinal gray matter of mice.

CRYM mRNA in man is expressed in most areas of the brain assessed by GTEx (amygdala, anterior cingulate cortex, caudate, cerebellar hemisphere, cerebellum, cortex, frontal cortex, hippocampus, nucleus acumbens, putamen) but not in the substantia nigra or the spinal cord (GTEx Consortium 2013). The absence of *CRYM* mRNA in human spinal cord does not agree with the findings of Fink et al. (2015) in mice. This incongruency may be due to a difference in species, condition, or due to temporal expression of mRNA versus protein. At the mRNA level the nucleus acumbens expresses the most *CRYM* (GTEx Consortium 2013). Because labeling for μ-crystallin can clearly delineate the neuronal structures in the brain many researchers use its expression as a regional marker.

Huntington's disease.

μ-Crystallin's increased presence and function in the brain may have implications for disease. *CRYM* expression is significantly decreased in human caudate nucleus and cerebellum in individuals with Huntington's disease (Hodges et al. 2006). *Crym* also shows decreased expression in the brains of R6/2, BACHD, and Knock-In 140 CAG mice (Brochier et al. 2008; Francelle et al. 2015), murine models of Huntington's disease, and may play a neuroprotective role in striatal medium-size spiny neurons in Huntington's disease (Francelle et al. 2015).

Amyotrophic Lateral Sclerosis.

μ-Crystallin has also been associated with amyotrophic lateral sclerosis (ALS). In a mouse model of familial ALS, $SOD1^{L126delTT}$, *Crym* shows an approximately 26-fold increase in expression in the spinal cord from pre-symptomatic to post-symptomatic mice (Fukada et al. 2007). Two mutations, R169C and H16P, in *CRYM* have been associated with sporadic ALS (Daoud et al. 2011); a recurrent mutation has also been identified in a mixed pool of familial and sporadic ALS patients (Pensato et al. 2020). The human *CRYM* gene is approximately 2.7 Mb away from a 37.8 Mb locus with genetic linkage to familial ALS (Sapp et al. 2003). μ-Crystallin progressively decreases in expression in the pyramidal tracts in ALS patients, in a mosaic expression pattern and leading to its total absence in the distal regions of the pyramidal tract (e.g., lateral and anterior corticospinal tracts of the spinal cord). Hommyo et al. (2018) suggest that this expression pattern may reflect the "dying back" phenomenon, in

which progressive neurodegeneration begins with more distal tissues and axons. In addition, miR-155 and miR-142, predicted to be regulators of *CRYM*, are increased in the spinal cord of individuals with sporadic ALS (Figueroa et al. 2016).

Schizophrenia.

Individuals with schizophrenia show decreased *CRYM* in Brodmann area (BA) 9 of the dorsal prefrontal cortex (PFC) (Middleton et al. 2002; Arion et al. 2007), as well as BA 46 of the PFC at the mRNA (Martins-de-Souza et al. 2009a) and protein level (Martins-de-Souza et al. 2009b). Martins-de-Souza et al. (2010) reported the decreased expression of μ-crystallin in the mediodorsal thalamus of the brain in individuals with schizophrenia as well as a negative correlation between μ-crystallin levels and duration of the disease. By contrast, Hakak et al. (2001) reported increased levels of *CRYM* in BA 46 of the PFC in individuals with schizophrenia. μ-Crystallin also increases in the corpus callosum of individuals with schizophrenia (Sivagnanasundaram et al. 2007).

CRYM is not implicated broadly in many neurologic disorders, however. For example, no associations between major depressive disorder or bipolar disorder have been observed (Johnston-Wilson et al. 2000; Beasley et al.2006).

CRYM as a potential therapeutic for psychiatric disorders.

CRYM appears to play an important, though yet unknown, role in the brain. Walker et al. (2020) show that *Crym* overexpression in the medial amygdala of adult mice can recapitulate the transcriptional and behavioral effects of adolescent social isolation. Amazingly, social isolation of adult mice does not result in these same changes, suggesting that *Crym* overexpression in the medial amygdala of adult mice can revert the brain to a more plastic state associated with adolescence (Walker et al. 2020). This raises the eventual possibility, though technically still unachievable, that overexpressing *CRYM* in human medial amygdala could be used to reprogram individuals to become more resilient to some psychiatric disorders (Walker et al. 2020).

CRYM and non-syndromic deafness.

Autosomal dominant deafness-40 (DFNA40), a non-syndromic deafness in man, is the only disease that is currently known to be caused by mutations in *CRYM*. It is not associated with any intellectual, structural or other dysfunctions. Two heterozygous mutations were identified at the C-terminus of μ-crystallin, X315Y and K314T. The K314T mutation segregated in an autosomal dominant fashion, while the X315Y mutation was a *de novo* change (Abe et al. 2003). A third heterozygous mutation, P51L was later found to associate with DFNA40. This mutation also segregates in an autosomal dominant fashion, further confirming the inheritance pattern of DFNA40 (Wang et al. 2020). The severity of hearing loss varies with the mutations noted above. Moderate bilateral hearing impairment (50–60 dB) has been observed in the individual with the X315Y mutation, starting at 19 months of age and progressing to a hearing loss of 70 dB by age 13. Individuals with the K314T show severe bilateral hearing loss (80–90 dB) starting at 1 year old, with no further progression (Abe et al. 2003). Individuals with the P51L mutation have moderate to severe hearing

loss (50–110 dB) without progression, though only one individual was followed for 4 years (Wang et al. 2020).

Correlating these auditory changes with changes in the activities of μ-crystallin is challenging. The X315Y mutation in μ-crystallin showed a similar binding affinity to T_3 as wild type μ-crystallin, but the K314T mutation in μ-crystallin was unable to bind to T_3 at all (Oshima et al. 2006). When expressed in COS-7 cells, the X315Y mutation in μ-crystallin localizes to vacuoles and the K314T mutation in μ-crystallin localizes perinuclearly, in contrast to the wild type protein, which is cytoplasmically distributed (Abe et al. 2003). Although CRYM-X315Y can bind T_3, its sequestration in vacuoles may reduce its access to cytoplasmic THs. Alternatively, these μ-crystallin mutants may affect potassium ion recycling of the endolymph, a function of lateral fibrocytes of the spiral ligaments and the spiral limbus fibrocytes, where *Crym* is highly expressed (Abe et al. 2003)

Genetics of *CRYM*

CRYM has a mutation rate of $10^{-4.9127}$ mutations per chromosome (Samocha et al. 2014), which is outside of the definition of a constrained gene (Samocha et al. 2014), i.e. a gene in which mutations are likely deleterious and result in their negative selection and removal from the gene pool. Congruent with the mutation rate, there are 209 “common” mutations (variants with a minor allele frequency [MAF] of at least 1%) in the 1000 Genomes Phase 3 dataset (www.internationalgenome.org/data). However, there is only one common exonic variant, rs34045013, a synonymous mutation in exon 8. Rs34045013 is only a common variant in African populations; its MAF does not rise to a frequency of 1% in European, East Asian, South Asian, or American populations in the 1000 Genomes Phase 3 dataset, though it is a common variant in the African American population examined in the GO Exome Sequencing Project (Tennessen et al. 2012). To the best of our knowledge, there are no *CRYM* null individuals. One individual has been identified with copy number loss of one chromosome [GRCh37/hg19 16p12.2(chr16:21313377-21947230)x1] where exon 1 of *CRYM* transcript variant 1 (RefSeq ID: NM_001888.5), the longer of the two *CRYM* variants observed in humans, is lost. A second individual shows a homozygous deletion [GRCh37/hg19 16p12.2(chr16:21300997-21308651)x0] of either intron 1 of *CRYM* transcript variant 1, or the putative promoter/upstream region of *CRYM* transcript variant 2 (RefSeq ID: NM_001376256.1). In contrast to the absence of *CRYM* null individuals, there are 22 individuals with a *CRYM* copy number gain (3 copies as opposed to the normal 2 [diploid] copies) and one individual with maternal uniparental disomy without copy number change in NCBI ClinVar.

Rs3848259 is a “common” variant that occurs in the 5’ untranslated region (UTR) of *CRYM* transcript variant 1 and is upstream of *CRYM* transcript variant 2. Rs3848259 is present in approximately 24.8% of the European population while being present in only 5.0% of the African population according to data from the ALFA Project (Phan et al. 2020). Furthermore, rs3848259 is located in a DNase hypersensitive region (Miga et al. 2015), a ZIC3 and ZNF341 transcription factor binding site (Fornes et al. 2020), and a CpG island (Gardiner-Garden and Frommer 1987). Rs3848259 alters one of the two most conserved base pairs in the DNA binding sequence motif of ZIC3, C<u>C</u>(C/T)GCTGGG (Ahmed et al.

2020) (underlined), from a cytosine to a guanine. This may inhibit the transcription factor ZIC3 from binding to the 5'UTR/genic upstream region potentially affecting transcription of *CRYM*. In one of the two consensus DNA binding motifs in ZNF341, rs3848259 affects a non-conserved base pair in the sequence, TGGAACAGCCNC (underlined) (Beziat et al. 2018; Frey-Jakobs et al. 2018).

Because it is located in an epigenetically active region in the 5'UTR of *CRYM* transcript variant 1 and upstream of *CRYM* transcript variant 2, rs3848259 and its effects on ZIC3 and ZNF341 binding may alter transcription of *CRYM* in the approximately 25% of individuals of European descent and 5% of individuals of African descent in whom this common variant is found. Humans display a wide range of expression of *CRYM* in skeletal muscle. In 803 transcriptomes in GTEx Analysis V8, *CRYM* levels vary from 0 transcripts per million (TPM) to 39.1 TPM with a median of 0.1584 TPM. Most people express little to no *CRYM* in their skeletal muscle, yet 15.44% express 2 TPM of *CRYM* or more, and 5.85% of people express *CRYM* at levels of 10 TPM or greater (GTEx Consortium 2013). SNPs like rs3848259 as well as other factors may play a role in the large degree of heterogeneity of *CRYM* expression seen skeletal muscle.

Effects of high Crym expression

μ-Crystallin has been shown to modulate TH levels. Precise control of TH levels is crucial to physiology and metabolism. Serious diseases can arise from inadequate or overabundant levels of TH. Nevertheless, the most abundant tissue in humans, skeletal muscle, displays a wide range of *CRYM* levels (GTEx Consortium 2013). What effects does μ-crystallin have in individuals who express high levels of μ-crystallin? Kinney et al. explored this question with a transgenic murine model that specifically overexpresses *Crym* in skeletal muscle (Kinney et al. 2021).

Along with a 27.5- to 154-fold increase of *Crym* mRNA and a 2.6-to 147.5-fold increase of μ-crystallin protein, depending on which skeletal muscle was assayed, Kinney et al. (2021) observed a 192-fold increase in T_3 in extracts of tibialis anterior (TA) muscle and a 1.2-fold decrease of serum T_4 in *Crym* tg mice compared to control mice. Both changes were significant. The large increase in intramuscular T_3 due to the increased expression of *Crym* may be the cause for some of the phenotypes they observed in *Crym* tg mice.

Crym tg mice have a decreased respiratory exchange ratio (RER), a metric that can be used to discriminate between carbohydrates and fat as energy sources (Lusk 1924). This decreased RER in *Crym* tg mice corresponds to a 13.7% shift towards increased utilization of fat as an energy source compared to controls. Consistent with this, gene ontology (GO) enrichment analysis of RNA-seq transcriptomic and LC.MS/MS proteomic data revealed significantly enriched ontological terms involving metabolism and muscle contraction. Kinney et al. (2021) found that almost all fiber types in *Crym* tg mouse soleus (but not TA) muscle had a smaller minimum Feret's diameter. Other groups have shown that slow twitch muscles like the soleus (Close 1965) mostly utilize β-oxidation of fat as opposed to fast twitch muscles that primarily utilize glycolysis of carbohydrates (Kalmar et al. 2012) and have smaller fiber sizes (Schiaffino and Reggiani 2011). Thyrotoxic doses of TH cause

shifts in slow twitch mouse soleus, but not in fast twitch extensor digitorum longus (Freake and Oppenheimer 1995) muscle towards faster twitch characteristics such as shortened isometric twitch duration and increased rate of tension development (Fitts et al. 1984). By these metrics, TH has a greater impact on slow twitch muscle than fast twitch muscle. Taken together, the shift in metabolism from glycolytic towards β-oxidative in *Crym* tg mice, the concomitant GO terms at the transcriptomic and proteomic level, and the smaller soleus muscle fibers and the unchanged fiber sizes in fast twitch TA in the TH rich muscle of *Crym* tg mice all point towards μ-crystallin shifting the metabolic and morphologic state of the muscle through the regulation of TH. Although this is difficult to reconcile with the fact that most muscle fibers in mice are fast twitch, a large proportion of them are also oxidative (i.e., Type IIA) and thus may be subject to the same shifts in gene regulation and morphology induced by *Crym* and T_3 as soleus.

Although *Crym* tg mice show significant alterations in metabolism, transcripts and proteins expressed, and fiber size of slow twitch muscle, *Crym* tg mice do not show significant differences compared to controls in a number of physiologic tests including: specific isometric force of contraction, maximal rate of twitch force contraction/relaxation, grip strength, maximum treadmill running speed, and voluntary distance run. Fiber type as assayed by immunohistochemistry of myosin heavy chains, weight of most muscles and fat pads, diameter of TA muscle, percent of centrally nucleated fibers, voltage-induced Ca^{2+} transients, maximal amplitudes of transients and transient decay rates, total number of muscle fibers, and intramuscular fat were also unchanged compared to control mice (Kinney et al. 2021). *Crym* therefore appears to play an important but subtle role in skeletal muscle, through a mechanism that remains unknown.

Conclusions

μ-Cystallin binds thyroid hormones and can act as a ketimine reductase in the brain when unbound by TH. As demonstrated by a number of studies, μ-crystallin plays a crucial role in regulating the availability and level of thyroid hormone. Consequently, it's of no surprise that μ-crystallin expression is tightly regulated both temporally and spatially. When mutated at particular moieties, μ-crystallin becomes less active or mislocalized, leading to nonsyndromic deafness, DFNA40. Inappropriate expression of *CRYM* may be involved in several neurologic disorders as well. Despite this tight regulation in many tissues, men and women can express a wide range of *CRYM* in their skeletal muscle. The regulatory elements that lead to this difference are still unknown, and the physiological consequences to humans with high *vs.* low levels of muscle *CRYM* are still unclear. Our studies of transgenic mice that express high levels of muscle μ-crystallin suggest that the physiological consequences are significant but subtle, with perhaps the most intriguing result indicating a change in the use of fat *vs.* carbohydrate as an energy source. For now, however, *CRYM's* physiological role in man remains to be determined. Future studies will help define its function at the cellular, tissue and system levels.

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