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Myotonic Dystrophy Protein Kinase: Structure, Function and Its Possible Role in the Pathogenesis of Myotonic Dystrophy Type 1

Jonathan J. Magaña¹, Rocío Suárez-Sánchez¹,
Norberto Leyva-García¹, Bulmaro Cisneros²
and Oscar Hernández-Hernández¹

¹*Department of Genetics, National Rehabilitation Institute, Mexico City,*

²*Department of Genetics and Molecular Biology, Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV-IPN), Mexico City, Mexico*

1. Introduction

Myotonic dystrophy protein kinase (DMPK) is a member of the AGC super family of serine/threonine protein kinases (Caenepeel et al., 2004; Manning et al., 2002). The *DMPK* human gene encodes several alternative spliced protein products believed to be involved in remodeling of the actin cytoskeleton, mitochondrial dynamics, ion homeostasis and nuclear envelope stability. DMPK and its isoforms are mainly expressed in skeletal, heart and smooth muscle, and brain, the main targets of myotonic dystrophy type 1 (DM1) (Groenen et al., 2000; Ueda et al., 2000). DM1 is the most common form of muscular dystrophy in adults with a frequency of 1 in 8,000 individuals worldwide. It is a multisystem dominantly inherited disorder characterized by myotonia, progressive muscular weakness and wasting, cardiac defects, cataracts and frontal balding, as well as several central nervous system (CNS) manifestations (Harper et al., 2002). The disease is caused by the expansion of an unstable (CTG)_n repeat in the 3'-untranslated region (3'-UTR) of the *DMPK* gene (Brook et al., 1992; Fu et al., 1992; Mahadevan, M. et al., 1992). In healthy population the CTG tract is polymorphic with alleles ranging from 5 to 37 in length. Individuals carrying the DM1 premutation, a tract between 38 and 49 CTG repeats, generally are asymptomatic but are at risk of transmitting a pathological expanded mutation. In contrast, a CTG expansion between 50 and 4000 CTG repeats results in DM1 disease. Affected families show the phenomenon of anticipation; longer expansions correlate with an earlier age of onset and more severe course in subsequent generations. Based on their clinical presentation DM1 is classified into four subtypes: late onset, classic DM1, childhood onset and congenital DM1 (CDM) (Harley et al., 1992). An RNA-mediated dominant gain-of-function is currently accepted as the pathogenic mechanism to explain features of the DM1. *DMPK* toxic transcripts accumulate as nuclear foci (Davis et al., 1997; Taneja et al., 1995), interfering with the activity of RNA-interacting proteins and altering RNA metabolism, notably the splicing programme (Ranum & Day, 2004). Although reduced DMPK protein levels in DM1 tissues

are well described (Fu et al., 1993; Hofmann-Radvanyi et al., 1993; Krahe et al., 1995; Novelli et al., 1993), the specific role of DMPK in the pathogenesis of the disease is not completely understood. Studies focused on the biology of this protein had received little attention, as protein product of *DMPK* gene seemed to have no direct role in the disease. Identification of novel DMPK targets, and comparative differences of DMPK isoforms have started to emerge (Groenen et al., 2000; Kaliman & Llagostera, 2008; Mulders et al., 2011; Oude Ophuis et al., 2009a; van Herpen et al., 2005). This chapter offers the current knowledge about the structure, expression patterns and function of DMPK and its isoforms. A better understanding of DMPK biology will enable us to speculate how this protein could be involved in the pathophysiology of DM1.

2. Myotonic Dystrophy Protein Kinase gene

2.1 Localization and structure of the *DMPK* gene

The *DMPK* human gene is located on the long (q) arm of chromosome 19 at position 13.3 covering 13 kb in length. The gene is composed of 15 exons coding a full-length protein of 692 amino acids with a composite domain structure. The *DMPK* gene is transcribed in the telomere-to-centromere orientation, giving rise to a set of primary transcripts that are subject to extensive alternative splicing (Figure 1). The (CTG)_n repeat lies within the 3'-UTR of the gene, in the exon 15 downstream of the translation stop signal, and approximately 500 bp upstream of the poly (A) signal (Groenen et al., 2000; Jansen et al., 1992; Mahadevan, M.S. et al., 1993).

Characterization of the promoter region has showed that *DMPK* gene contains a conserved GC box to which the transcription factor Sp1 binds. Four E-box elements within the first intron mediate interactions with upstream promoter elements to up-regulate its transcription in myoblast (Storbeck et al., 1998). The (CTG)_n repeat tract is located in a gene-dense region; in fact the expansion overlaps with the promoter region of the downstream neighboring *SIX5* gene. *SIX5* expression is needed for eye development in the fruit fly and regulates distal limb muscle development in the mouse (Otten & Tapscott, 1995; Ranum & Day, 2004; Wang et al., 1994). In DM1 an anti-sense *DMPK* transcript is originated from *SIX5* regulatory region. This transcript extends into an insulator element on the 3'UTR of *DMPK* regulating the environmental chromatin structure of the region (Cho et al., 2005).

2.2 Alternative splicing and DMPK isoforms

Initial bioinformatic analysis of the *DMPK* gene, and subsequent expression studies have demonstrated that six major *DMPK* isoforms can arise in both humans and mice as a result of extensive alternative splicing. In the full-length polypeptide, four distinct domains can be distinguished: a leucine-rich N terminus comprised by 40 amino acid that are shared by all DMPK isoforms, a serine/threonine protein kinase domain specified by exons 2 to 8, an α -helical coiled-coil region encoded by the exons 9 to 12, the VSGGG motif and a the C terminus. The presence of VSGGG motif and the nature of the C-terminus, the most important distinction among DMPK isoforms, are both determined by alternative splicing (Groenen et al., 2000; Jansen et al., 1992; Mahadevan, M.S. et al., 1993) (Figure 1).

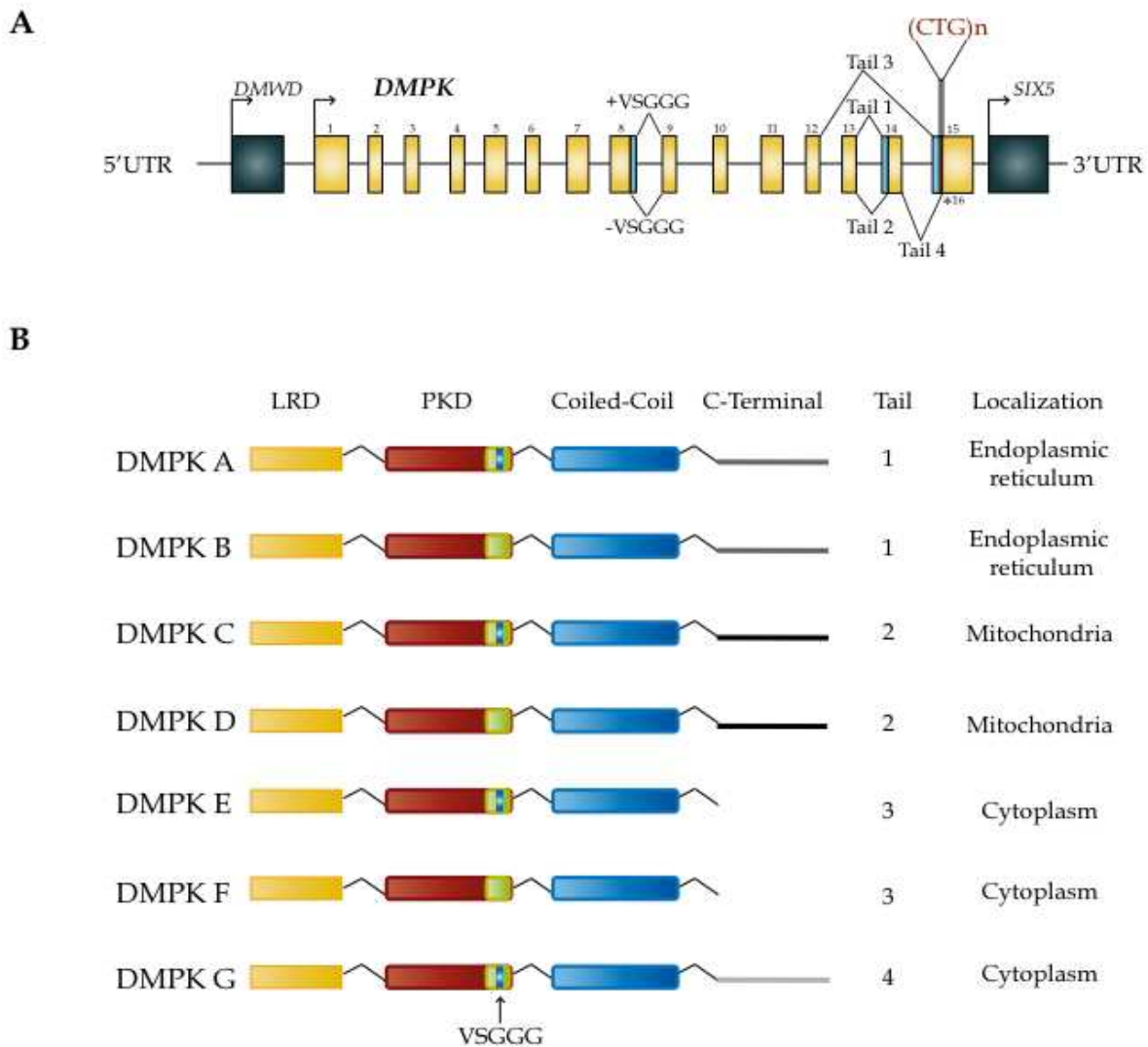


Fig. 1. The human *DMPK* gene and its splicing isoforms. (A) *DMPK* gene is composed of 15 exons, represented by rectangles. The $(CTG)_n$ expansion mutation over exon 15 is shown. Exons that are subject to alternative splicing are also indicated. (B) Schematic representation of the protein domain organization of the *DMPK* isoforms. All isoforms have a leucine-rich N-terminus domain (LRD), a serine/threonine protein kinase domain (PDK), a VSGGG motif, and an α -helical coiled-coil domain. C-terminal tail is specific to each isoform and determines their subcellular localization.

It can be distinguished *DMPK* isoforms with (A to D isoforms) or without a C-terminal extension (DMPK E and F). The alternative splice of the first four nucleotides of exon 14 produces two different open reading frames (ORFs) encoding proteins with C-terminal tail 1 or 2. An additional C-terminal with tail 3 is originated by the direct joining of exons 12 and 15 sequences, due to the splicing of exons 13-14. In this case, an ORF with stop codon at the beginning of exon 15 is generated. Altogether, the six distinct isoforms constitutes the *DMPK* profile in different cell types and tissues.

As predicted, the alternative splicing of *DMPK* pre-mRNA determines the structure and function of *DMPK* products. For instance, the inclusion of exon 14 generates ~ 70-kDa

proteins with a hydrophobic C terminus carrying the tail 1 (isoforms A and B), whereas exclusion of the first four nucleotides from this exon results in the production of ~ 70-kDa proteins with less hydrophobic C terminus carrying the tail 2 (isoforms C and D). The presence of both tail 1 and tail 2 confers to the protein the capacity to anchor into membranes of endoplasmic reticulum and mitochondria. In contrast, isoforms with tail 3 as C terminus (isoforms E and F) adopt a cytosolic localization (van Herpen et al., 2005; Wansink et al., 2003). Interestingly, a tissue-specific expression pattern of DMPK isoforms have been showed in brain and smooth, cardiac and skeletal muscle.

There is a cryptic splice acceptor site in exon 15 of the human *DMPK* gene that defines the inclusion of an additional exon (exon 16). The fusion between exons 14 and 16 results in removal of the 5' part of exon 15, including the (CUG)_n repeat, generating the so-called *DMPK G* isoform. This transcript encodes a ~ 69-kDa protein with a unique C-terminal tail (tail 4). Because of the absence of the (CUG)_n repeat, *DMPK G* transcripts can freely exit the nucleus, which might result in efficient *DMPK G* expression in DM1 cells (Tiscornia & Mahadevan, 2000; Wansink et al., 2003).

3. The DMPK family of proteins

DMPK belongs to the AGC super family of related serine/threonine protein kinases (Caenepeel et al., 2004; Manning et al., 2002). *DMPK* shows higher homology with myotonic dystrophy kinase-related Cdc42-binding kinases (MRCKs), comprise by MRCK α , MRCK β and MRCK γ proteins (Figure 2). Regarding to the *DMPK* kinase domain, there is a 60% of sequence identity between *DMPK* and MRCKs (Leung et al., 1998; Ng et al., 2004). *DMPK* is closely related to the Rho-associated kinases I and II (ROCK1/ROCK2), with 45 and 43% identity respectively (Riento & Ridley, 2003), as well as to citron kinase (CRIK), with about 41% sequence identity (Madaule et al., 1998). *DMPK* is also related in a lower degree to the NDR family (consisting of NDR1, NDR2) and Lat's proteins (Lat 1 or Lat 2), and more distantly, to PKA, PKB (Akt), and PKC, the archetypes of the AGC group (Caenepeel et al., 2004; Manning et al., 2002).

3.1 Structural domains of DMPK

All *DMPK* family members are composed of the four following domains: an N terminal leucine-rich domain, a kinase domain, an α -helical coiled-coil region, and the C-terminal domain (Groenen et al., 2000; Mahadevan, M.S. et al., 1993) (Figure 1). *DMPK* and other family members have important differences among them, mainly in their size and overall protein domain composition. MRCKs, ROCKs and CRIK contain a number of additional domains with distinct functions, such as the GTPase binding domain, the pleckstrin homology domain (PH), the cysteine-rich domain and the citron homology domain (CNH), as shown in the Figure 2 (Riento & Ridley, 2003; Zhao & Manser, 2005). Both *DMPK* and ROCKs are able to form dimers. Structural studies on *DMPK*, ROCKs, and MRCK have shown that dimerization depends on the regions N- and C-terminal immediately adjacent to the kinase domain (Doran et al., 2004; Garcia et al., 2006; Jacobs et al., 2006; Tan et al., 2001). *DMPK* is regulated by activation loop phosphorylation, dimerization and trans-autophosphorylation (Elkins et al., 2009). Although specific sites have not yet been identified, the residues Ser234, Thr240 and Thr403 conserved in *DMPK* and MRCKs, are

probably implicated in DMPK activation (Tan et al., 2001; Wansink et al., 2003). In the following sections, the structural domains that comprise DMPK are described in detail.

3.1.1 Lucine-Rich Domain

In DMPK, the Leucine-Rich Domain (LRD) encodes a peptide of approximately 70 amino acids, in which, almost every fourth amino acid is a leucine. This domain constitutes a highly non-polar amino-terminal region that is constant in all DMPK isoforms, and presents 93% of sequence identity between human and mouse forms. This high degree of interspecies conservation suggests a potential role for this domain in DMPK activity (van der Ven et al., 1993; Waring et al., 1996). A segment of this region conforms the leucine zipper motif, which is conserved in all DMPK family members. Although the MRCK α and ROCK-II leucine zipper motifs mediate the dimerization, or even oligomerization, of GTPase-regulated kinases, the DMPK leucine zipper motif seems not to be involved in multimerization (Bush et al., 2000; Zhang & Epstein, 2003). Then, the specific role played by the DMPK N-terminal leucine-rich domain remains to be revealed. In many cases, protein kinase activity is modulated by domains flanking the catalytic domain (Manning et al., 2002). Therefore, it is thought that the leucine-rich domain may regulate the DMPK kinase activity, due to its proximity to the serine/threonine protein domain. The leucine-rich domain might link DMPK to signaling modules, or alternatively may help DMPK to localize to specific subcellular compartments (Manning et al., 2002). Further studies are necessary to clarify the functional activity of this domain.

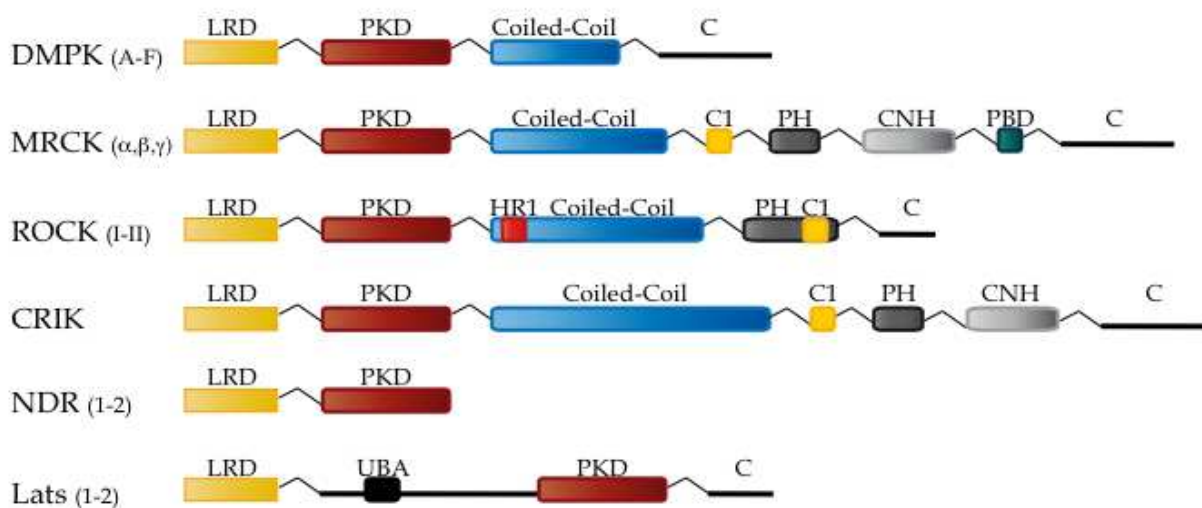


Fig. 2. Domain organization of DMPK and five major AGC proteins closely related. All proteins present a N-terminal leucine-rich domain (LRD), a protein kinase domain (PKD) and a C-terminal domain (C); most of them present also a coiled coil domain. AGC proteins have some domains that are distinctive of certain members, such as protein kinase C conserved region 1 domain or cysteine-rich domain (C1), pleckstrin homology domain (PH), citron homology domain (CNH), P21 Rho binding domain (PBD), Rho effector domain (HR1) and ubiquitin-associated domain (UBA).

3.1.2 Protein kinase domain

The catalytic domain between residues 70 and 349 carries out the kinase function. This domain transfers the gamma phosphate from nucleoside triphosphate (ATP) to the hydroxyl group of serine or threonine residues on the target protein, which results in a conformational change that affects protein function. Serine/Threonine protein kinase domain has eleven major conserved subdomains, separated by regions of lower conservation (Hanks & Hunter, 1995). In the active conformation, the kinase domain folds in a structure of two lobes: an N-terminal lobe formed by β sheets with a single α helices (α B and α C helices) and a larger C-terminal lobe containing mainly α helices and the activation loop (Huse & Kuriyan, 2002; Krupa et al., 2004; Nolen et al., 2004). Activation loop phosphorylation and autophosphorylation of DMPK induce a conformational change that stabilizes the kinase domain in an open conformation permissive for substrate binding. The ATP binding site is situated in the cleft at the interface of the N-terminal and C-terminal lobes. This highly conserved region creates the phosphate-binding loop site (P-loop), that is a glycine-rich GXGX Φ G consensus sequence (with Φ usually being phenylalanine or tyrosine) (Hanks & Hunter, 1995). DMPK is also known as a Lys/Arg-directed kinase. An invariant lysine (Lys100) in the ATP binding region makes contact with the α - and β -phosphates of ATP, promoting in coordination with the P-loop the phosphotransfer from ATP (Wansink et al., 2003).

It is generally accepted that, in the nonphosphorylated state, activation loop folds into the active site blocking the binding of ATP and peptide substrate (Adams, 2003; Hanks & Hunter, 1995; Johnson et al., 1996). However, mass spectrometry of crystallized recombinant DMPK (unphosphorylated) has showed that activation loop occupies a well-ordered conformation that does not impede access to the nucleotide or substrates binding sites, resembling an active conformation (Elkins et al., 2009). A conserved structure in DMPK and ROCK1, the α EF/ α F loop, interact with the activation loop to stabilize this active conformation. Also important for catalysis is the position of helix α C in close proximity to the active site. This helix is highly structured, unlike the structures of several inactive kinases, and formation of a bridge between α C and β 3 (residues Glu119 and Lys100 of DMPK) is an indicator of the active kinase conformation. This suggests that DMPK could be active without phosphorylation, however there is still the question of what the structural impact of phosphorylation at the conserved phosphorylation sites (Ser234, Thr240 and Thr403) would be (Elkins et al., 2009).

3.1.3 The VSGGG Motif

The VSGGG motif is unique among DMPK-related kinases. As previously mentioned, the presence of this pentapeptide is defined by alternative splicing, and is found in A, C, E and G DMPK isoforms (Figure 2) (Wansink et al., 2003). It has been shown that VSGGG motif modulates DMPK autophosphorylation activity, an event that is usually required to regulate activity of many protein kinases (Johnson et al., 1996; van Herpen et al., 2005). The presence of Serine 379 in the VSGGG motif has a marked effect on the conformational state of the protein but it is not clear whether the presence of the motif increases the kinase activity by stabilization of the active conformation, or if the motif makes a turn-motif serine/threonine more available for autophosphorylation. Interestingly, it has been showed that DMPK isoforms lacking the VSGGG motif (B, D, and F) are also phosphorylated in this region.

Adjacent sequences the VSGGG motif may be used as phosphoracceptors (residues Thr375 or Thr379) or a different conformational regulation is possibly taking place.

3.1.4 Coiled-coil region

The coiled-coil domain is a common structural motif, formed by approximately 5% of all amino acids in proteins (Wolf et al., 1997), including transcription factors, signaling enzymes and motor proteins. Typically, it consists of two to five α -helices wrapped around each other into a left-handed helix to form a supercoil. Whereas regular α -helices go through 3.6 residues for each complete turn, the distortion imposed upon each helix within a left-handed coiled-coil in DMPK lowers this value to around 3.5 residues. Thus a heptad repeat (seven residues) occurs every two turns of the helix (Landschulz et al., 1988; Lupas, 1996).

The most commonly observed type of coiled-coil is left-handed, with anywhere from two (in designed coiled-coils) to 200 of these repeats in a protein (Burkhard et al., 2001; Kohn et al., 1997). The heptad repeat is commonly denoted (a-b-c-d-e-f-g)_n in one helix, and (a'-b'-c'-d'-e'-f'-g')_n in the other one (Lupas, 1996; Mason & Arndt, 2004). In this model, a and d are typically nonpolar core residues found at the interface of the two helices, whereas e and g are solvent exposed polar residues that give specificity between the two helices through electrostatic interactions. Interactions between a-a' and d-d' helices drive the "hydrophobic collapse" and formation of the supercoil, whereas e-g' and g-e' ionic interactions determine the specificity of the interhelical interaction (Mason & Arndt, 2004).

In DMPK the coiled-coil domain consist of only ~9 heptad repeats, containing approximately 65 amino acids. The DMPK coiled-coil domain is smaller than that of other AGC family members (Figure 2). DMPK isoforms could form high-molecular-weight complexes, due to homo- and heteromultimerization of up to 10 DMPK molecules (Bush et al., 2000; Zhang & Epstein, 2003). This multimerization is mediated by coiled-coil interactions, and occurs independently of alternatively spliced protein segments or DMPK activity (van Herpen et al., 2005). When a coiled-coil heptad repeat is mutated to glycines, the coiled-coil mutants are still capable of autophosphorylation and transphosphorylation, but the rates of their kinase activities are significantly lowered. Furthermore, it has been shown that the coiled-coil domain is important for the cellular localization of DMPK mitochondrial isoforms (van Herpen et al., 2005). In summary, the coiled-coil domain is involved in DMPK multimerization, substrate binding, kinase activity and subcellular localization.

3.1.5 C-terminal domain

The C-terminal domain appears to play an autoinhibitory role as C-terminally truncated DMPK activity is increased by 3-fold for MBP and 10-fold for myosin phosphatase target subunit (MYPT1). This inhibitory activity is mapped in the residues 550 to 629, which has also been implicated in oligomerization (Bush et al., 2000; Wansink et al., 2003).

Interestingly, alternative splicing affecting the C-terminal domain appears to determine the subcellular localization of DMPK isoforms (Groenen et al., 2000). DMPK isoforms with long C-terminal domain (DMPK A to D) anchor into membranes of the endoplasmic reticulum or mitochondria, whereas isoforms with no C-terminal extension (DMPK E and F) adopt a cytosolic localization.

The structure of DMPK illustrates that the most varied part of AGC proteins is the long C-terminal domain, compared with the structure of the closely related ROCKs, MRCKs and CRICK. Long C-terminal domain containing 96 and 97 amino acids, are named as tail 1 and tail 2, respectively. These tails are characterized by unique structures without homology to any other protein and by a single C-terminal hydrophobic stretch. The presence of tail 1 anchored DMPK A and DMPK B into membranes of the endoplasmic reticulum, whereas tail 2 is responsible for DMPK association with the mitochondrial outer membrane (van Herpen et al., 2005; Wansink et al., 2003) (Figure 2). Interestingly, presence of the coiled-coil region in DMPK C and DMPK D is essential for tail 2 to target isoforms to the mitochondrial membrane. Not much is known about the relationship between tail anchor structure and membrane specificity, and its avidity for lipid composition. A specific role of the signal recognition particle for targeting of similar proteins to the ER has been reported (Abell et al., 2004), but detailed insight on the mechanism of membrane insertion is currently lacking. Data from various studies suggest that shared structural elements in the C terminal reflect the only critical features implicated in membrane selectivity. For instance, the fact that amino acids in the DMPK A tail are all neutral is consistent with this observation, and may determine binding strength. Taking these data together, we can conclude that the strong hydrophobic character of the DMPK A isoform constitutes the endoplasmic reticulum targeting signal. This is compatible with other studies showing that artificially engineered stretches of hydrophobic amino acids of different lengths can be sufficient for endoplasmic reticulum targeting (Whitley et al., 1996; Yang et al., 1997). On the contrary, targeting of DMPK C to the mitochondrial outer membrane seems to be more elaborate, and additional structural information is necessary to make conclusions.

On the other hand, as showed figure 2, DMPK E and DMPK F isoforms do not contain the C-terminal domain. They present only two amino acids long segment, named tail 3, without any targeting information (Mulders et al., 2011; Whitley et al., 1996; Yang et al., 1997). Although the coiled-coil domain confers by itself no targeting properties, as evidenced from the cytosolic localization of DMPK E, the amino acid information in this domain seems to be a critical component for the correct association of DMPK C to the mitochondrial outer membrane. Finally, the minor human isoform DMPK G, which shows a cytosolic localization, has a C-Terminal domain with a function still unknown. Some authors have named this C-terminal domain as tail 4 (Wansink et al., 2003). Further studies are necessary to known in depth the impact of the C-terminal domain on DMPK isoforms cellular localization.

4. Expression pattern of DMPK

4.1 Tissue distribution of DMPK

Expression data based on mRNA analysis (*in-situ* hybridization, northern blot and RT-PCR) have showed a wide expression profile of *DMPK* in mouse and human tissue samples. *DMPK* mRNA is highly expressed in skeletal, cardiac, and smooth muscle and at lesser extent in different brain areas. Others tissues and organs that express *DMPK* mRNA include bone, testis, eye, skin, thymus, lung and liver. In contrast, no expression of *DMPK* transcript is found in ovary, pancreas and kidney (Jansen et al., 1992; O'Coirlain et al., 2004; Sarkar et al., 2004). The production of DMPK antibodies by using peptides or recombinant DMPK protein as immunogen has made possible the detection of DMPK at protein level (Lam et al.,

2000; Pham et al., 1998; Ueda et al., 2000). DMPK antibodies recognize protein products varying in size from ~42- to 84-kDa, being the smaller proteins (42- to 50-kDa) not real products of the DMPK gene (Lam et al., 2000; van der Ven et al., 1993). In general, mRNA and DMPK protein expression appear strongly correlated. Highest levels of *DMPK* gene products are found in smooth muscle (Jansen et al., 1992; O'Coilain et al., 2004; Sarkar et al., 2004), heart and skeletal muscle (Groenen et al., 2000; Lam et al., 2000; O'Coilain et al., 2004; Sarkar et al., 2004). DMPK at protein level has also been identified in several brain regions (van der Ven et al., 1993) both in neurons and glia. Interestingly astrocytes from brain cortex show higher DMPK levels compared with neurons (Oude Ophuis et al., 2009a). DMPK transcripts and protein products are also detected in fetal eyes, adult retina, corneal epithelia and optic nerve (Winchester et al., 1999).

Expression of DMPK during development has also been explored. DMPK expression is significantly increases in skeletal muscle between 9 and 16 weeks of human muscle development. The large increase in protein accumulation correlates with the formation of second-generation muscle fibers, and the major period of muscle formation. Increase in DMPK expression is also observed during *in vitro* myogenic differentiation (Furling et al., 2003). In other studies, DMPK protein expression has been revealed in eye, skin and intestine chick embryos as well as in heart and skeletal muscle, specifically in postmitotic myocytes, where it activates myotubes formation (Harmon et al., 2008). In brain and spinal cord of rat, DMPK begins to be expressed after birth and increases gradually to peak at postnatal day 21 in many regions. After that and proceeding to the adult stage, DMPK expression becomes more restricted to certain cell groups like spinal motor neurons (Balasubramanyam et al., 1998). Immunoreactive neurons have been observed in the early fetal frontal cortex and cerebellar granule cell layer before 29 weeks of gestation (Endo et al., 2000).

Regarding the DMPK isoforms expression pattern, it has been showed that long membrane-anchored isoforms are expressed in heart, diaphragm and skeletal muscle while short cytosolic isoforms are highly expressed in bladder and stomach. Interestingly, both long- and short-isoforms are expressed in diverse brain regions (Oude Ophuis et al., 2009a). Other reports have demonstrated that the four different ~74-kDa full-length DMPK isoforms are present in heart, skeletal muscle and brain, in contrast to the two C-terminally truncated ~68-kDa isoforms that are restricted to smooth muscle and to a lesser extent at heart (Groenen et al., 2000).

4.2 Differential subcellular localization

Detailed analyses of the subcellular localization of DMPK isoforms carrying distinct C termini have been performed. By applying electron and confocal microscopy and immunodetection approaches after overexpressing individual isoforms in several cell types, it has been demonstrated that unique sequences arrangement in the C terminus tail of DMPK control the specificity of anchoring into intracellular membranes. DMPK E and F mouse isoforms carrying a truncated tail present an evident cytosolic localization. In contrast, DMPK A, B, C and D mouse isoforms carrying a hydrophobic tail are associated specifically with either the endoplasmic reticulum or the mitochondrial outer membrane. In agreement with this, the corresponding human DMPK A and C proteins localized to mitochondria. Furthermore, the expression of mouse and human DMPK A, but not DMPK C

isoforms in mammalian cells caused clustering of ER or mitochondria. That means that DMPK has a possible role in organelle distribution and dynamics (van Herpen et al., 2005; Wansink et al., 2003). Subcellular localization of the DMPK protein during cardiac myocytes differentiation has been analyzed in chicken and mouse cardiac myoblast, and in C2C12 cells transfected with a vector expressing the DMPK fused to the reporter protein GFP. The analysis revealed a shift in the DMPK subcellular localization during myogenesis, from the perinuclear region to the cellular membrane, suggesting the possibility that DMPK performs different roles during this process (Reddy et al., 1996). Electron microscopy analyses in adult rat spinal motor neurons reveal a localization of DMPK in the endoplasmic reticulum and dendritic microtubules, suggesting a function in membrane trafficking and secretion within neurons associated with cognition, memory, and motor control (Balasubramanyam et al., 1998). In addition, multiple subcellular localizations have been assigned to DMPK, including neuromuscular and myotendinous junctions (Berul et al., 1999; Berul et al., 2000; Shimokawa et al., 1997) and terminal cisternae and intercalated discs of skeletal muscle sarcoplasmic reticulum (Benders et al., 1997; Pall et al., 2003; Saba et al., 1999). Furthermore, DMPK localization to gap junctions of the intercalated discs has been reported in the heart and Purkinje fibers (Kaliman et al., 2005; Mounsey et al., 2000b).

5. DMPK function

5.1 Transgenic and knockout mice

In order to elucidate the DMPK function and its possible involvement in DM1 pathogenesis, several transgenic and knockout mice had been created. DMPK totally deficient (DMPK^{-/-}) mice develop a late-onset and progressive skeletal myopathy showing variation in muscle fiber size, increased fiber degeneration and fibrosis with ultra structural changes, and a 50% decrease in force generation. Inconsistent and minor changes in head and neck muscle fibers in adult mouse are also shown (Jansen et al., 1996; Reddy et al., 1996). In addition, the DMPK^{-/-} mouse shows cardiac conduction defects, which include first-, second-, and third-degree atrioventricular (A-V) block in His-Purkinje regions. This effect demonstrates that conduction system is specifically compromised; supporting the idea that loss of DMPK plays a significant role in the cardiac DM1 phenotype (Berul et al., 1999; Berul et al., 2000). DMPK deficit also cause an enhanced basal contractility of single cardiomyocytes with associated increase in intracellular Ca²⁺, suggesting that DMPK has a modulator role in the control of intracellular Ca²⁺ concentration (Benders et al., 1997; Pall et al., 2003). In addition, hypophosphorylation of phospholamban (PLN), a muscle-specific sarcoplasmic reticulum Ca²⁺-ATPase (SERCA2a) inhibitor, causes a deregulation of Ca²⁺ uptake in sarcoplasmic reticulum vesicles of ventricular homogenates from DMPK^{-/-} mice (Kaliman et al., 2005). An effect on Na⁺ current amplitude in DMPK^{-/-} myocytes because of reduced channel number is also observed (Mounsey et al., 2000b; Reddy et al., 2002). Supporting this result, multiple late re-opening of Na⁺ channels is observed when DMPK is absent in both cardiac and skeletal muscles. This is reflected in a plateau of non-inactivating macroscopic Na⁺ current and prolongation of cardiac action potentials (Lee et al., 2003). Altogether these findings suggest the existence of a regulatory DMPK pathway for cardiac contractility, and provide a suitable molecular mechanism for DM1 heart pathology. A common feature in DM1 is insulin resistance, which is a major factor in the development of type 2 diabetes (Biddinger & Kahn, 2006). DMPK^{-/-} mice exhibit impaired insulin signalling in muscle tissues but not in

adipocytes and liver. These mice also display metabolic derangements such as abnormal glucose tolerance, reduced glucose uptake and impaired insulin-dependent GLUT4 trafficking in muscle. Altogether, these data indicate that reduced DMPK expression may directly influence the onset of insulin resistant in DM1 patients and suggest that DMPK could represent a gene of susceptibility to type 2-diabetes (Llagostera et al., 2007).

A transgenic murine line overexpressing the complete human DMPK gene (Tg26-hDMPK) has been generated. In this animal model, skeletal muscle shows myopathy with myotonic discharges coupled with deficit in sarcolemmal chloride channels. Deficient exercise endurance, fiber degeneration and smooth muscle tone deficit with systemic hypotension are also present in the Tg26-hDMPK mouse. Heart from these mice develops cardiomyopathic remodeling and propensity for dysrhythmia, characterized by overt intracellular calcium overload that promotes nuclear translocation of transcription factors responsible for maladaptive gene reprogramming. The cumulative stress induced by permanent overexpression of DMPK gene products increases the risk of some distinctive muscle traits of DM1 (O'Coilain et al., 2004). Additional overexpression studies using different transgenic lines show enhanced neonatal mortality in addition to hypertrophic cardiomyopathy (Jansen et al., 1996). In DM1, membrane inclusions accumulate in lens fiber cells producing cataracts. Overexpression of DMPK with enzymatic activity in epithelial lens cells led to apoptotic-like blebbing of plasma membrane and reorganization of the actin cytoskeleton. This may be relevant to the removal of membrane organelles, a necessary process during normal lens differentiation (Jin et al., 2000).

5.2 DMPK function in muscle and brain tissues

The function of DMPK protein is not completely understood yet, however, several reports have described the participation of this protein in different cellular processes notably in both muscle and brain tissues.

DMPK has been described as an important factor during myogenesis. The differentiation process begins with the exit of the proliferating myoblast from the cell cycle and activation of the differentiation program throughout the expression of myogenic factors, such as MyoD and myogenin. Additionally, morphological changes are needed for myotube formation. Overexpression of DMPK in BC3H1 cells (Bush et al., 1996) or its depletion in C2C12 cells (Harmon et al., 2008) have demonstrated the role of DMPK as a regulator of myogenin expression during muscle differentiation. Overexpression of DMPK in chick cardiac and skeletal myocytes, and C2C12 cells provoked rounding cells that are brought to apoptosis, which suggest a pro-apoptotic role for DMPK. In addition, depletion of DMPK in C2C12 cells prevented cell fusion, a necessary step for myotube formation (Harmon et al., 2008). As mentioned previously, DMPK knockout transgenic mice have been employed to study the function of DMPK. Disruption of normal muscle function both in muscle and heart is attributed to altered DMPK expression (Jansen et al., 1996; Reddy et al., 1996). CDM, the most severe form of DM1, is associated with several developmental defects that include delayed muscle development. Myoblasts from CDM embryos have a reduced capacity to differentiate, and interestingly, produce less than 50% of DMPK protein levels, implying a specific role for DMPK in embryonic myocyte development (Furling et al., 2001; Furling et al., 2003). Overall, these data suggest that DMPK is crucially involved in myogenesis.

Ion homeostasis is a determinant mechanism regulated by membrane permeability to cations (Na^+ , Ca^{2+} , K^+) or anions (Cl^-). Transmembrane ion flux is the predominant factor in controlling the excitation–contraction coupling mechanism. Alteration in the function of voltage-dependent L-type Ca^{2+} (the dihydropyridine receptor DHPR) and Na^+ channels has been shown in DMPK mice models (Benders et al., 1997), which evidences the importance of DMPK in the maintenance of this homeostasis. That is consistent with the fact that DHPR is a target of DMPK and that its activity is altered in DMPK^{-/-} cells (Benders et al., 1997). Reduction in Na^+ current amplitude in DMPK^{-/-} mice muscle has also been demonstrated (Mounsey et al., 2000b; Reddy et al., 2002). Furthermore, activity and membrane localization of chloride channel phospholemman (PLM), which regulates Cl^- currents, is also modulated by DMPK (Mounsey et al., 2000a). All these data suggest that DMPK is involved in regulating the initial events of excitation–contraction coupling in skeletal muscle, and controlled then, ion homeostasis. In the other hand, proteins involved indirect or directly with the cytoskeleton (MYPT1 and SRF) and nuclear envelope (Lamin A/C) integrity were reported as DMPK partners (Harmon et al., 2011; Iyer et al., 2003; Muranyi et al., 2001), suggesting the participation of DMPK in these cellular processes.

One of the most common DM1 alterations, the atrioventricular conduction block, was shown to be dependent on DMPK levels in a mechanism not yet understood (Berul et al., 2000; Saba et al., 1999). In addition, DMPK^{-/-} mice with cardiac contractility deregulation exhibit an impaired SERCA2a function. This ATPase is regulated by PLN protein, which is phosphorylated by DMPK (Kaliman et al., 2005). Furthermore, cardiac dysfunction, hypertrophic cardiomyopathy, propensity for dysrhythmia and enhanced neonatal mortality has been reported in the DMPK mice (O’Cochlain et al., 2004). Altogether, these findings delineate a feasible molecular mechanism for DM1 heart pathology.

Participation of DMPK in DM1 brain physiology has also been reported. Mis-localization of DMPK occurs in DM1, and even at higher extent in the CDM (Endo et al., 2000). In the CNS an involvement of DMPK in important physiological processes has been suggested, including membrane trafficking and neuro-secretion. DMPK is expressed in a subpopulation of neurons associated with cognition, memory, and motor control. It is localized in the endoplasmic reticulum and dendritic microtubules within adult spinal motor neurons (Balasubramanyam et al., 1998). DMPK has been also associated with intracellular communication functions, due to its synaptic localization in cerebellum, hippocampus, midbrain and medulla (Whiting et al., 1995). DMPK might contribute to synaptic plasticity and cognitive function via cytoskeletal remodeling. Long-term potentiation (LTP) is a use-dependent form of synaptic plasticity that contributes to the cellular basis of memory storage and other cognitive functions. Changes in the actin cytoskeleton are important for mechanisms underlying LTP including changes in synaptic and dendritic spine shapes (Engert & Bonhoeffer, 1999; Fischer et al., 2000; Kim & Lisman, 1999). Phosphorylation of myosin phosphatase by DMPK promotes an increase in the phosphorylation state of myosin, which supports the assembly and contractility of the actin cytoskeleton (Muranyi et al., 2001). Thus, deregulation of DMPK expression could influence directly on actin cytoskeleton remodeling (Jin et al., 2000). These data together with abnormal LTP measures in a DMPK null mice (Schulz et al., 2003) suggest that DMPK have a key role in synaptic plasticity in such a way that DMPK depletion might contribute to the cognitive dysfunction associated with CDM, which is characterized by strong motor function and brain disability.

5.3 DMPK-protein interactions and function

DMPK protein is a serine/threonine kinase with preference for substrates with an arginine residue upstream of the phosphoacceptor site (serine or threonine), followed by a hydrophobic residue (usually leucine or valine), and another arginine (Bush et al., 2000). The consensus recognition motif on substrates -RxxS/TL/VR- is similar to that of PKC and CaMKII. DMPK has the capability to form multimeric complexes among individual molecules, as revealed by gel-filtration experiments on cell lysates expressing DMPK A, C, E or F isoforms (van Herpen et al., 2006). As remarked previously, coiled-coil domain mediates multimerization, which in turn modulates DMPK binding to substrate and phosphorylation. Multimerization also influences subcellular targeting properties of individual DMPK isoforms (van Herpen et al., 2006; Zhang & Epstein, 2003). On the other hand, DMPK targets are involved in important cell functions notably ion homeostasis and actin cytoskeleton remodeling (Table 1).

<i>PROTEIN</i>	<i>NORMAL FUNCTION</i>	<i>DM1 ASSOCIATED PHENOTYPE</i>	<i>REFERENCES</i>
<i>PLN</i>	Ion (Ca ²⁺) homeostasis	Cardiac contractility alterations	(Kaliman et al., 2005)
<i>PLM</i>	Ion (Cl ⁻) homeostasis	Myotonia	(Mounsey et al., 2000b) (Mounsey et al., 2000a)
<i>DHPR</i>	Ion (Ca ²⁺) homeostasis	Deregulation of excitation-contraction coupling	(Benders et al., 1997) (Timchenko, L. et al., 1995)
<i>MYPT</i>	Calcium sensitization Regulation of the cytoskeletal structure	Calcium desensitization Cytoskeleton rearrangement defects	(Muranyi et al., 2001) (Mulders et al., 2011)
<i>SRF</i>	Alpha-actin gene transcription regulator	Synaptic plasticity abnormalities Cataracts	(Iyer et al., 2003) (Schulz et al., 2003) (Jin et al., 2000)
<i>Lamin A/C</i>	Nuclear envelope integrity	Muscle wasting	(Harmon et al., 2011)
<i>CUG-BP</i>	Alternative splicing regulator	Splicing alteration	(Roberts et al., 1997)
<i>ATP synthase a and β Trifunctional enzyme β</i>	Mitochondrial proteins	Mitochondrial morphology (?)	(Forner et al., 2010) (Oude Ophuis et al., 2009b)

Table 1. Partners and phosphorylation targets of DMPK implicated in the DM1 phenotype.

Cardiac contractility dysfunction is an alteration commonly present in DM1 patients and DMPK^{-/-} mouse model. Cardiac contraction and relaxation cycle is an important cell process regulated by intracellular calcium levels. In cardiac sarcoplasmic reticulum, SERCA2a regulates the cytoplasmic levels of Ca²⁺, and SERCA2a in turn is tightly controlled by the sarcoplasmic reticulum membrane protein PLN. Hence, nonphosphorylated PLN inhibits

SERCA2a function, whereas phosphorylated PLN reverse such inhibition (Frank et al., 2003; MacLennan & Kranias, 2003). It has been reported that PLN is a target of PKA kinase and CaMKII. However, Kaliman and co-workers reported that DMPK colocalizes and interacts with PLN promoting its phosphorylation. In fact, PLN protein is found under a nonphosphorylated state in DMPK^{-/-} mice, where Ca²⁺ uptake is highly reduced. Disruption of the interaction between PLN and DMPK and/or loss of the PLN activity regulatory mechanism, due to DMPK downregulation, might explain at least in part the cardiac pathology observed in DM1 patients (Kaliman et al., 2005).

Interestingly, the splicing regulator CUGBP, member of the CELF family, is also a DMPK target. CUGBP was described as a CUG-binding protein with high avidity to single-strand RNA containing CUG repeats (Ladd et al., 2001). It has been shown in DM1 patients and DMPK knockout mice that phosphorylation and intracellular localization of CUGBP is regulated by DMPK. By using immunoprecipitation and kinase activity assays, the interaction between CUGBP-DMPK and the subsequent CUGBP phosphorylation were demonstrated (Roberts et al., 1997). DMPK phosphorylates CUGBP thereby decreasing its nuclear levels, which is consistent with the augment of CUGBP nuclear levels found in cultured cells from DM1 patients (Roberts et al., 1997). A plausible interpretation of these findings is that DMPK downregulation results in increased levels of the nonphosphorylated form of CUGBP, which might cause an increase in the nuclear levels of CUGBP, thereby adversely affecting the processing of pre mRNAs. Several reports have described alteration in the RNA processing of CUGBP targets genes in DM1 patients, including human cardiac troponin T (cTNT) (Philips et al., 1998), transcription factor CCAAT/ enhancer-binding protein b (C/EBPb) (Timchenko, N.A. et al., 2001), and insulin receptor (IR) (Dansithong et al., 2005; Savkur et al., 2001). On the other hand, an increase in the steady-state levels of CUGBP was revealed in DM1 tissues. This increase is due to an augmentation in the stability of the protein, which is mediated by PKC phosphorylation (Kuyumcu-Martinez et al., 2007; Timchenko, N.A. et al., 2001). Further studies are necessary to identify specific serine/threonine residues on CUGBP that could be phosphorylated in a PKC-or DMPK-dependent manner. The complete understanding of the two pathways concurring in CUGBP phosphorylation would help to better know DM1 pathogenesis.

PLM is a major membrane substrate for PKA and PKC. In oocytes from *Xenopus*, PLM induces hyperpolarization-activated non-inactivating chloride current ($I_{Cl(PLM)}$) (Moorman et al., 1992; Palmer et al., 1991). By *in vitro* assays Mounsey and co-workers showed that PLM is a substrate for DMPK, and that co-expression of both PLM and DMPK reduces $I_{Cl(PLM)}$ by about half (Mounsey et al., 2000b). Site-directed mutagenesis has demonstrated that reduced $I_{Cl(PLM)}$ is provoked by decreased PLM expression at the plasma membrane, as a consequence of its phosphorylation by DMPK. Furthermore, electrophysiological studies have evidenced reduced muscle chloride conductance and membrane depolarization in myotonic muscles. On the other hand, mutations in CLCN1 have been reported in the myotonia congenital disease condition. As myotonia can be induced by reducing chloride conductance, at the plasma membrane, the exploration of PLM phosphorylation state and intracellular localization in the mouse model Tg2-hDMPK mouse, which shows reduced chloride channel expression (O'Coilain et al., 2004), would provide insights into the development of DM1-associated myotonia (Mounsey et al., 2000a).

Another target for DMPK is the MYPT1, a component of the myosin phosphatase (MP). MP phosphatase activity is inhibited by phosphorylation mediated by Rho-kinase (Hartshorne et al., 1998), and such inhibition increases the levels of myosin light chain phosphorylation, which in turn leads to Ca^{2+} sensitization in smooth muscle (Hartshorne et al., 1998). At subcellular level, phosphorylation of MYPT1 by DMPK produces cytoskeletal rearrangements in non-muscle cells (Muranyi et al., 2001), whereas *in-vitro* DMPK can phosphorylate MYTP1 in the same way that Rho-kinase, suggesting a regulatory role for DMPK in myosin function (Muranyi et al., 2001).

It has been described that deregulation of ion influxes is a key factor for development of the DM1 phenotype. Particularly, Ca^{2+} conductance abnormalities may contribute to hyperexcitability of sarcoplasmic membrane in DM1. DHPR, the voltage gating L-type Ca^{2+} channel, shows an altered activity in differentiated myotubes derived from DMPK^{-/-} mice (Benders et al., 1997). By applying *in-vitro* approaches it was demonstrated that DMPK phosphorylates the β -subunit of DHPR in a serine residue. These data demonstrate that DHPR is substrate for DMPK, and suggest that DMPK is involved in the initial events of excitation-contraction coupling in skeletal muscle, a mechanism regulated by ion homeostasis (Timchenko, L. et al., 1995). DMPK has also been associated with SRF, the serum response transcription factor. SRF is a phosphoprotein that regulates skeletal and cardiac α -actin gene transcription. DMPK phosphorylates the Thr159 residue localized in the α 1 coil of the DNA-binding domain on a MADS box. By using site-directed mutagenesis it has demonstrated that phosphorylation on Thr159 regulates cardiac α -actin expression at promoter level (Iyer et al., 2003).

By using high-resolution mass spectrometry, a new group of proteins associated with DMPK has been reported (Forner et al., 2010). Authors identified 15 putative partners of DMPK grouped as follows: mitochondrial proteins (ATP synthase subunit α , ATP synthase subunit β , trifunctional enzyme subunit β), contractile and myofibrillar proteins (myosin heavy chain 7, myosin regulatory light chain 2-skeletal muscle isoform, myosin light chain 1-skeletal muscle isoform, myosin light chain 3), heat shock proteins (HSP) (α -crystallin B chain, heat shock protein β -1, heat shock protein β -6) and other proteins (adenylate kinase isoenzyme 1, carbonic anhydrase 3, peroxiredoxin-1, peroxiredoxin-2, similar to glyceraldehyde-3-phosphate dehydrogenase). To study in detail some of these DMPK interactions, these authors used immunoprecipitation and pull-down assays, and showed direct interaction of DMPK with α B-crystallin/HSPB5 and HSP25/HSPB1. These findings suggest that DMPK isoforms might modulate some HSPs functions at diverse subcellular localizations (i.e. mitochondrial membrane rather than cytoplasm) or under different physiological conditions (i.e. oxidative stress opposed to heat production) (Forner et al., 2010).

Finally, the participation of DMPK in the integrity of the nuclear envelope (NE) has recently been disclosed. NE is an important actor that determines the nuclear structure and regulates gene expression. Key structural elements of NE are the nuclear type-A and type-B lamins. Lamin A/C and lamin B1 proteins interact with proteins of the inner nuclear membrane and chromatin (Hetzer, 2010). Mutations in inner NE proteins are the genetic cause of Emery-Dreifuss muscular dystrophy (EDMD) and limb girdle muscular dystrophy 1b (LGMD1B) (Roux & Burke, 2007). Thus, NE defects may represent a common mechanism of muscle wasting in muscular dystrophies. DMPK localizes to the NE forming a protein complex with

lamin A/C, and importantly, overexpression or depletion of DMPK disrupts the nuclear envelope localization of both lamin A/C and lamin B1, and causes ultimately nuclear fragmentation. Thus, DMPK expression seems to be critical to maintain NE stability. As nuclear instability is a common mechanism of muscle wasting in muscular dystrophies (Harmon et al., 2011), DMPK misexpression may be an important contributor to skeletal muscle wasting in DM1.

6. DMPK contribution to DM1 phenotype

6.1 Mechanisms of pathogenesis in DM1

DM1 is a multisystemic neuromuscular disease characterized by a wide range of clinical manifestations, including myotonia, muscle weakness and wasting, cardiac abnormalities, cognitive and behavioural alterations, and lens opacities (Harper et al., 2002). Cumulative experimental evidence has demonstrated that several DM1 manifestations are the result of the nuclear accumulation of CUG repeat-containing transcripts, which interfere with the alternative splicing, and gene expression programs (Ranum & Day, 2004). Besides the RNA gain-of-function mechanism, additional pathways might contribute to DM1, including chromatin rearrangements at the DM1 locus, interference RNA pathways and DMPK haploinsufficiency (Figure 3) (Sicot et al., 2011).

RNA gain-of-function mechanism: Mutated *DMPK* RNA expression results in decreased muscle-blind (MBNL) and increased CUGBP/Elav-like family member 1 (CELF1) activities. CUG repeat-containing transcripts form alternative secondary RNA structures that bind to and sequester MBNL in nuclear foci altering its normal distribution in the nucleoplasm (Jiang et al., 2004; Lin et al., 2006; Mankodi et al., 2005). In addition, CELF1 overexpression due to PKC phosphorylation has been described in DM1 cells (Kuyumcu-Martinez et al., 2007). Deregulation of the splicing transcription factors MBNL and CELF1 disrupts a tightly regulated developmental program, leading to altered expression of embryonic splicing isoforms in adult tissues (Osborne & Thornton, 2006; Ranum & Day, 2004). Muscle specific chloride channel (*CLC1*), insulin receptor (IR), cardiac troponin T (*cTNT*), myotubularin related protein 1 (*MTMR1*), microtubule binding protein Tau (*MAPT*), and NMDA glutamate receptor (*NR1*), are examples of genes affected at the alternative splicing level in DM1 (Du et al., 2010; Ranum & Day, 2004).

Leaching of transcription factors mechanism: It has been reported that mutant *DMPK* RNA interferes with the function of selected transcription factors, depleting them from the active chromatin by an RNA leaching mechanism. In fact, altered expression of *CLCN1* by leaching of Sp-family transcription factors was found in DM1 cells (Ebralidze et al., 2004). It is predicted that massive derangement at transcription level, due to leaching of transcript factors, is present in DM1 cells.

Chromatin rearrangements at the DM1 locus, and interference RNA (iRNA) pathways mechanism: *DMPK* gene is transcribed into sense and anti-sense transcripts (Cho et al., 2005). iRNA pathways might be activated by processing of dsRNA structures that could be formed due to folding of CUG-containing transcripts into hairpin structures, or due to complementary hybridization between complementary sense and anti-sense *DMPK* transcripts. MicroRNA (miRNA) deregulation appears to be an additional mechanism

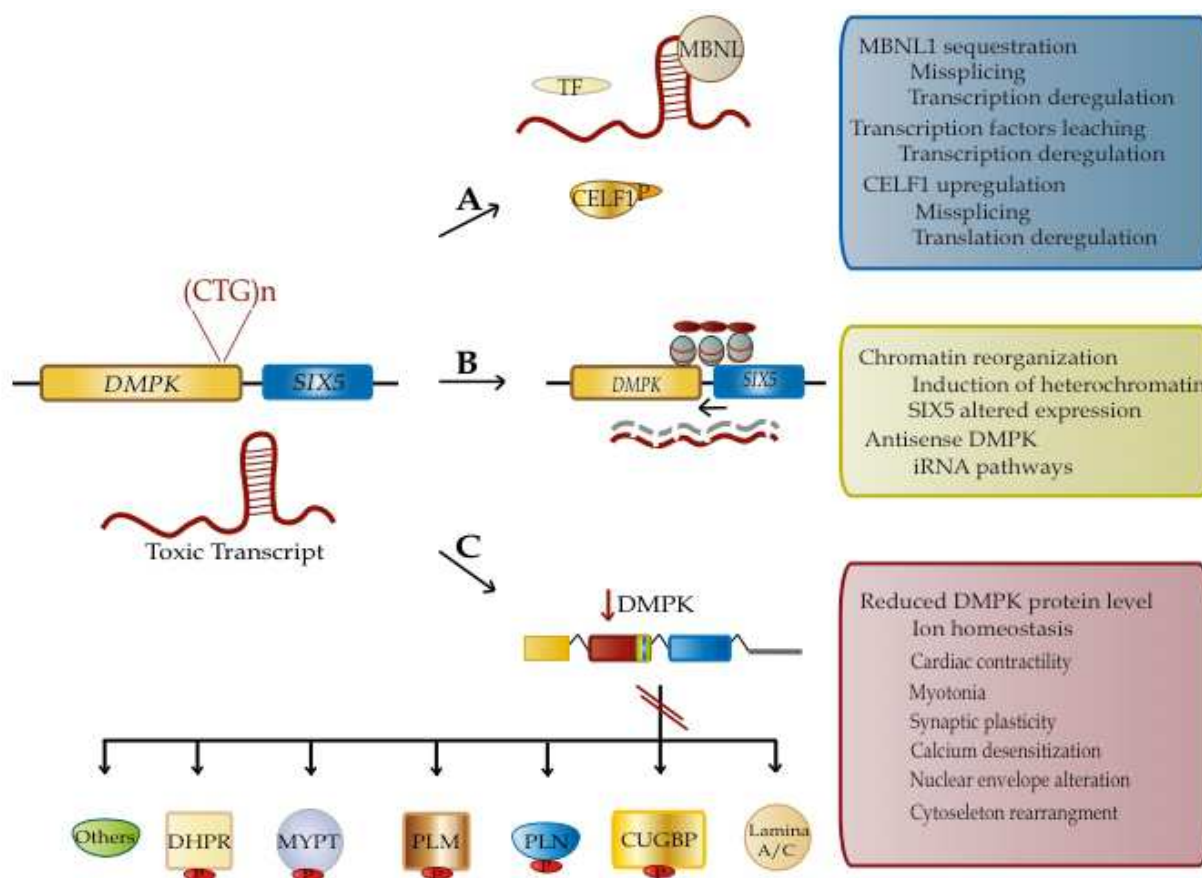


Fig. 3. Mechanisms of pathogenesis in DM1. Toxic CUG-containing transcripts form secondary structures and accumulate in the nucleus of DM1 cells, causing the multisystemic effects of DM1 throughout RNA gain-of-function mechanism (A), chromatin rearrangements at the DM1 locus (B) and DMPK haploinsufficiency (C). See text for details.

involved in DM1 biogenesis; in fact, the miRNAs pathway was found to be altered in DM1 skeletal muscle and heart. Interestingly, mi-R1 downregulation is mediated by MBNL1 depletion in cardiac DM1 tissue, which results in misprocessing of pre-miR-1 (Perbellini et al., 2011; Rau et al., 2011). On the other hand, processing of anti-sense transcript might be involved in chromatin ultrastructure regulation. It is known that anti-sense *DMPK* transcript extends into an insulator element located between *DMPK* and *SIX5* genes (Cho et al., 2005). CTCF-binding sites have been described on each side of the CTG repeat within the *DMPK* gene, restricting the extent of anti-sense RNA expression. Remarkable, the expanded mutant allele impairs CTCF binding, and induces spread of heterochromatin and regional CpG methylation in CDM cells. It is hypothesised that barrier function of the insulator is missing in DM1 due to disruption of CTCF binding, inducing higher *DMPK* expression in late embryogenesis, as a consequence of a high *SIX5* enhancer activity, thereby contributing to the earlier disease onset in CDM (Sicot et al., 2011).

6.2 The possible role of DMPK and its isoforms in the pathogenesis of DM1

Although debated, many studies indicate that CTG expansion causes a decrease in the amount of DMPK protein by ~ 50%, with greatly reduced expression from the mutant allele

and normal expression from the unaffected allele, a phenomenon known as haploinsufficiency (Bhagavati et al., 1996; Furling et al., 2001; Narang et al., 2000). Mice model generated to study the effects of DMPK deficiency have revealed an important contribution of DMPK to the development of myopathy and cardiac abnormalities (Berul et al., 1999; Jansen et al., 1996; Reddy et al., 1996). CDM is an entity of the disease that evidences the importance of DMPK expression; because, delayed muscle development and reduced capacity for muscle differentiation correlate with a decrease of more than 50% in DMPK levels. As stated above, it was recently reported that DMPK is a structural component of the nuclear envelope, forming a protein complex with lamin A/C (Harmon et al., 2011). In fact, alteration of DMPK expression disrupts the localization of lamins A/C and B1, causing nuclear fragmentation. Thus, deficient expression of DMPK in DM1 cells might contribute to nuclear instability, a common mechanism of muscle wasting in muscular dystrophies.

In skeletal muscle, the study of DMPK individual isoforms has provides insights into their potential contribution to the DM1 phenotype. In DMPK $-/-$ mice myoblasts, exogenous expression of the cytosolic DMPK E isoform results in the presence of stress fibers, significant changes in myoblast polarity and delay myogenesis progression (Mulders et al., 2011). It is known that DMPK gene is expressed early in muscle development, but alternative splicing down-regulates DMPK E expression during myogenesis (Jansen et al., 1996; Oude Ophuis et al., 2009a). In contrast, membrane-anchored DMPK splice isoforms remain equally abundant between myoblast and myotubes, indicating that expression of these isoforms is not differentially regulated during myogenesis. Stress fibers formation induced by DMPK E is enhanced by myosin II light chain (MLC2) phosphorylation (Mulders et al., 2011). The phosphorylation status of MLC2 is dependent on myosin phosphatase (PP1) activity, which is inactivated by phosphorylation of its subunit MYPT1, a DMPK substrate. Hence, MCL2 phosphorylation levels are determined by the interplay between kinase and phosphatase activities, in which DMPK is involved. Exogenous expression of DMPK E causes also changes in cell shape and cell motility, which may be due to the abnormally rigid cytoskeletal organization caused by the high content of phosphorylated MLC2, which ultimately may impact myogenesis.

As mentioned previously, brain dysfunction is prominently implicated in DM1. Mental manifestations in CDM and adult-onset DM1 include mental retardation, cognitive and emotional disturbances, and hypersomnia (de Leon & Cisneros, 2008; Meola & Sansone, 2007). DMPK transcripts aggregated in foci were observed in brain of postmortem DM1 tissue (Jiang et al., 2004), suggesting that the RNA-gain of-function mechanism is involved in the development of DM1-associated brain dysfunction. With respect to DMPK, it was recently demonstrated that both long and short DMPK isoforms are expressed across many brain regions, including brainstem, olfactory bulb, and striatum. In addition, DMPK protein was identified in astrocytes and U373 glioblastoma cells (Oude Ophuis et al., 2009a). Therefore, involvement of DMPK isoforms in DM1-mediated mental retardation can not be ruled out.

Finally, overexpression of human DMPK A in various cell lines causes abnormal mitochondrial morphology, mitochondrial clustering in the perinuclear region, loss of the mitochondrial membrane potential, increased autophagy activity, mitochondrial fragmentation, and eventually apoptosis (Oude Ophuis et al., 2009b). Interestingly, an

abnormal mitochondrial morphology and mitochondrial dysfunction has been described in DM1 patients (Siciliano et al., 2001; Ueda et al., 1999). Furthermore, ATP synthase subunit α , ATP synthase subunit β , and trifunctional enzyme subunit β , three mitochondrial important components, have been described as possible partners of DMPK (Forner et al., 2010). Supporting the participation of DMPK isoforms in the DM1 phenotype and mitochondria morphology, overexpression of tail-anchored human DMPK isoforms in heart and skeletal muscles of Tg26-hDMPK mice causes accumulation of mitochondria in the subsarcolemmal space, disorganization of the mitochondrial cristae structure, and importantly, the appearance of DM1-like symptoms, including reduced workload tolerance, atrophy, cardiomyopathy, and myotonic myopathy (O'Coilain et al., 2004). Oude Ophuis and cols. propose that expression and activity of DMPK isoforms should be tightly controlled, both in time and place. Thus, any alteration in the balance of DMPK isoforms expression due to changes in mRNA synthesis or pre-mRNA splicing, might contribute to the DM1 pathophysiology.

In addition, DMPK deficiency could be involved in specific process of DM1 biogenesis, according to its interaction with different protein partners and targets (Table 1).

7. Conclusion

DM1 is a neuromuscular multisystemic disease caused by the expansion of the CTG repeats in the 3'UTR of the *DMPK* gene. *DMPK* primary transcript gives rise to 6 isoforms with activity of serine/threonine kinase that differ each other in their capacity to anchor organelle membranes. DMPK is expressed mainly in heart, skeletal and smooth muscles, and brain, the most compromised tissues in DM1. Current knowledge indicates that clinical manifestations of DM1 are not due to a unique molecular mechanism; instead, it appears that different mechanisms operate in the development of the disease. In addition to the toxic RNA gain-of-function, the best-described mechanism, chromatin rearrangements of the DM1 locus, leaching of transcription factors, interference RNA pathways and altered expression of DMPK protein should be considered as contributors to DM1 biogenesis. Importantly, several partners and targets of DMPK have been reported, suggesting the involvement of DMPK in the specific cellular pathways affected in DM1. Although the physiological function of DMPK and its isoforms is not yet fully understood, growing body of experimental evidence strongly suggests a role for DMPK in DM1 pathophysiology. Future studies in different groups of DM1 patients (CDM versus classic DM1), as well as in animal and cells models with DMPK deficiency are required to define the participation of DMPK in DM1 biogenesis.

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9. References

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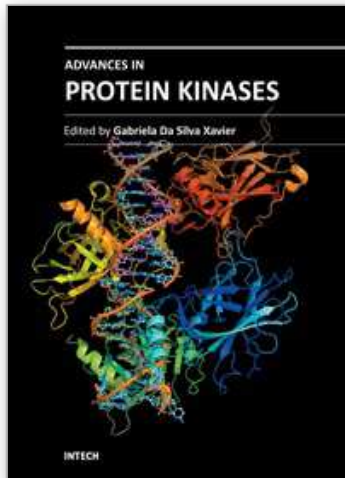
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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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