A cytoplasmic escapee: desmin is going nuclear

Ecem KURAL MANGIT1,2, Niloufar BOUSTANABADIMARALAN DÜZ1, Pervin DINÇER1

1Department of Medical Biology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
2Laboratory Animals Research and Application Centre, Hacettepe University, Ankara, Turkey

Received: 18.07.2021 • Accepted/Published Online: 04.11.2021 • Final Version: 14.12.2021

Abstract: It has been a long time since researchers have focused on the cytoskeletal proteins' unconventional functions in the nucleus. Subcellular localization of a protein not only affects its functions but also determines the accessibility for cellular processes. Desmin is a muscle-specific, cytoplasmic intermediate filament protein, the cytoplasmic roles of which are defined. Yet, there is some evidence pointing out nuclear functions for desmin. In silico and wet lab analysis shows that desmin can enter and function in the nucleus. Furthermore, the candidate nuclear partners of desmin support the notion that desmin can serve as a transcriptional regulator inside the nucleus. Uncovering the nuclear functions and partners of desmin will provide a new insight into the biological significance of desmin.

Key words: Cytoskeleton, intermediate filament, desmin, nucleus, nuclear localization signal, nuclear export signal

1. Introduction

Intermediate filaments (IFs) are a protein superfamily of 10-nm fibrous polymers in eukaryotes. Together with microtubules and microfilaments, IFs form the basic structure of the cytoskeleton. IF family is formed by a large (>70 proteins) and diverse group of proteins, which are expressed in a tissue type-specific manner (Hesse et al., 2001; Rogers et al., 2004, 2005; Oshima, 2007). IFs are mainly take part in maintaining cell and tissue integrity, but, beyond the traditional functions, they play essential roles in organelle and protein distribution (Brunet et al., 2004; Toivola et al., 2005). According to Human Intermediate Filament Database (Szeverenyi et al., 2008), there are 119 diseases associated with mutations in IF proteins, which points out the importance of IFs in medicinal studies.

The “cytosolic” IF proteins are now starting to emerge as nuclear elements. Many different studies suggest that these proteins can localize and function in the nucleus and bring new insight into cellular events (Kumeta et al., 2012).

This review focuses on the functions and candidate nuclear binding partners of one particular cytoplasmic protein: desmin.

Desmin is a cytoplasmic muscle-specific type III IF. Through interaction with other cytoskeletal elements, desmin connects myofibrils to the nucleus, mitochondria, and sarcolemma and facilitates force transmission during muscle contraction (Lazarides, 1980; Fuchs and Weber, 1994) (Figure 1a). Desmin can act as a potential mechanosensor and transduce mechanical forces from the cytoplasm to the nucleus (Lockard and Bloom, 1993; Capetanaki et al., 2015). Mutations in the desmin gene (DES) cause skeletal and cardiac myopathies, collectively known as desminopathies.

2. Evidence of desmin localization in the nucleus

Except for type V IFs lamins, no IFs are expected to be localized in the nucleus. Yet, there are evidence from different studies implicating that the IFs other than lamins may localize in the nucleus. Desmin is one of the interesting examples. One of the oldest pieces of evidence about nuclear localization is the presence of desmin in the nucleus of BHK21 cells (Kamei, 1986). Not only it resides in the nucleus, but it has also been shown that desmin is a nucleic acid-binding protein in vitro (Traub and Shoeman, 1994; Tolstonog et al., 2000, Wang et al., 2001; Tolstonog et al., 2005). Furthermore, our studies have revealed that desmin can co-localize with lamin B at the nuclear periphery in the human skeletal muscle sections (Çetin et al., 2013). Finally, desmin has been found to be localized in the nucleus of differentiating embryonic stem cell-derived cardiac progenitor cells (Fuchs et al., 2016).

Unfortunately, there is a relatively small body of literature that is concerned with the nuclear localization of desmin (Kamei, 1986; Traub and Shoeman, 1994; Hartig et al., 1998; Tolstonog et al., 2000, Wang et al., 2001; Tolstonog et al., 2005; Fuchs et al., 2016).
What can a cytoskeletal protein do in the nucleus? The former far-fetched idea of cytoskeletal proteins being in the nucleus is now beginning to settle, and it is not too absurd to assume that they can take on important tasks at both compartments. Nonerythroid α-spectrin, a structural protein, is required to recruit DNA repair proteins (Sridharan et al., 2003). Myosin VI (MVI), an actin-based motor protein, is associated with proteins involved in nuclear/ribosomal processes (Majewski et al., 2018). α-actinin, an actin cross-linking protein, is actively transported between nucleus and cytoplasm and interacts with transcriptional regulators (Kumeta et al., 2010). There are also examples of intermediate filament proteins taking part in the nucleus. Vimentin, a type III IF like desmin, is suggested to be a part of a chromatin-modifying complex (Hartig et al., 1998). Type I IF keratin, has an impact on a transcriptional regulator’s nuclear localization and function (Hobbs et al., 2015). There are many other examples of cytoskeletal proteins localize in the nucleus (For review: Kumeta et al., 2012; Hobbs et al., 2016)). For IFs, it is not unusual to present in the nucleus considering they all originated from lamin-like predecessor (Weber et al., 1989). As a matter of fact, there is a belief that IFs might appear as nuclear-localized elements in primitive organisms (Peter and Stick, 2015). The distinguishing aspect of lamins from other IFs is that they have a nuclear localization signal (NLS) (Loewinger and McKeon, 1988) and a C-terminal CaaX-isoprenylation motif, which targets lamins to the nuclear envelope (Holtz et al., 1989; Peter and Stick, 2015). But are the lamins only IFs that have an NLS?

In the case of desmin, in silico analysis (La Cour et al., 2004; Kosugi et al., 2009) shows there are two potential NLSs one starting at the Arginine 10 and ending at Serine 42 (R10-S42), and a second one starting at Glutamate 282 and ending at Alanine 313 (E282-A313) and one nuclear export signal (NES) starting at Alanine 192 and ending at Leucine 200 (A192-L200) (Figure 2). Localization of these potential signals on desmin is very interesting. One might envision that these signals become ‘accessible’ depending on the assembly or polymerization status of the protein since they are located on amino-terminal and rod domain, which are responsible for the assembly and coiled-coil polymerization of desmin, respectively (La Cour et al., 2004; Hnia et al., 2015). The amino terminal of desmin is also a post-translational modification (PTM) site (Höllrigl et al., 2007; Mavroidis et al., 2008) (Figure 2) which indicates that the on/off status of the signal R10-S42 might be related to cell status since these PTMs are responsible for IF organization and structure through cell cycle and development (Mavroidis et al., 2008). The PTMs within NLSs and NES are illustrated in Figure 2. Among these PTMs, the amino-terminal phosphorylation might be specifically crucial for the subcellular localization of

![Figure 1. Functions of desmin in the cytoplasm (a) and the nucleus (b). (a) Desmin is mainly located at the Z-discs (Z) in the sarcoplasm and connects myofibrils to the nucleus and mitochondria (Lazarides, 1980; Fuchs and Weber, 1994). Through the Linker of Nucleoskeleton and Cytoskeleton Complex (LINC), desmin provides a mechanical link between the nucleus and the cytoskeleton (Stroud et al., 2014). (b) Inside the nucleus via lamin B association, desmin can provide static support to nucleoskeleton, involve in the nucleo-sarcoplasmic exchange, or affect the DNA structure and function (1) (Lockard and Bloom, 1993). Desmin can modulate chromatin conformation (2) (Li et al., 1994) or regulate gene expression with other transcription factors (3). Desmin-lamin B interaction and their association with Nup153 and Nup214 are highlighted in the red rectangular area.](https://example.com/figure1.png)
desmin. The phosphorylation status of the amino-terminal determines the polymerization-depolymerization status of desmin and other IFs (Geisler and Weber, 1988; Inagaki et al., 1988; Agnetti et al., 2021). According to a paper by Hobbs (2016), IFs destined to go to the nucleus — in this study, the referent IF is keratin — are expected to be small (newly synthesized or derived from existing IF network) and specified by PTMs or via interaction with other proteins (Hobbs et al., 2016). Considering the PTM sites along the amino-terminal NLS are responsible for the polymerization status of desmin; one can assume that NLS between R10-S42 might be activated during the polymerization-depolymerization cycle, and desmin filaments that are destined for nuclear transportation might be marked via phosphorylation. The investigation of the relationship between activation of NLS and phosphorylation would be interesting and valuable for understanding desmin localization. Other PTMs within the NLSs and NES are acetylation and ubiquitination. While ubiquitination is usually associated with proteasomal inhibition, acetylation is related to the protein solubility and insolubility depending on the location of this PTM (Snider and Omary, 2014).

3. Binding partners and potential functions of desmin in the nucleus

Fuchs (2016) discovered desmin occurs in the nuclei of differentiating cardiac progenitor cells and immature cardiomyocytes, presents in a transcription factor complex with nanog, brachyury, mesp1, and nkh2.5, and contributes to transcriptional regulation of cardiac-specific transcription factor nkh2.5 during cardiomyogenesis (Fuchs et al., 2016). This study does not only pointing out that desmin can localize in the nuclei of cardiomyocytes but also presents evidence pointing at the functions of desmin in modulating nuclear events. According to an earlier study by Li (1994), desmin displays significant similarity to the myogenic members of the helix-loop-helix (HLH) motif-containing family, particularly myoD, myogenin, and KE2-binding protein E12 (Murre et al., 1989; Li et al., 1994). Desmin also shows similarity to the basic and leucine zipper domains of jun, fos, and CREB transcription factors (Li et al., 1994). These similarities were associated with the functions of desmin in signal transduction and transport of myogenic factors to the nucleus or the modulation of chromatin conformation (Figure 1b). The study also shows that inhibition of desmin expression interferes with myoblast fusion and myotube formation. Moreover, desmin inhibition or reduction inhibits the expression of muscle-specific genes, namely myoD, myogenin, α-sarcomeric actin, and muscle creatine kinase (Li et al., 1994). Furthermore, mutations in desmin cause downregulation at the early expression of nkh2.5 and hamper the cardiomyogenesis (Höllrigl et al., 2002, 2007). All these data suggest that desmin could be a key molecule in the regulation of myogenesis as a nuclear element.

Another and the most curious partner in crime for desmin is the nuclear lamin. Lamins are bona fide nuclear proteins. They provide mechanical support to the nucleus, function in DNA repair, cell signaling, and transcription
methyltransferase protein: SET and MYND domain- (Lockard and Bloom, 1993).

The "interaction at NPC" hypothesis by Lockard (1993) supports assumptions from the earlier study by Lockard and Bloom (1993) (Figure 1b). Of special interest, to explore the binding partners for desmin and lamin B, and to understand the extent of this relationship, we have performed a mass spectrometry analysis. One of the interesting candidates as a binding partner for desmin is a histone methyltransferase protein: SET and MYND domain-containing 1a (smyd1a). In zebrafish, smyd1a localizes in the nucleus and is required for myofiber maturation and muscle contraction (Tan et al., 2006). Considering the functions, we postulate that these two proteins, desmin and smyd1a, might be involved in the development or differentiation of skeletal muscle tissue.

Tropomodulin (tmod4) is another candidate protein partner for desmin and the desmin-lamin B network. This actin minus-end protein has an NLS and possible function in the proliferation and differentiation of muscle cells (Kong and Kedes, 2004). It may seem that lack of hard evidence of interaction in literature lowers the probability of tmod4 being a part of the desmin-lamin B network; however, considering its functions in muscle cells, it would be interesting to think desmin-tmod4 interaction might somehow take part in the regulation of muscle development processes.

The final potential interactor of desmin acquired from our results is the phosphoglycerate mutase (pgam2), a glycolytic enzyme, which has critical effects on muscle fusion and development (Qiu et al., 2008; Tixier et al., 2013). Pgam2 has been shown to localize in the nucleus (Qiu et al., 2008). Furthermore, the study by Tixier (2013) on zebrafish shows knockdown of pgam2 causes thin muscle phenotype, and these results suggest a role for glycolysis on muscle growth based on myoblast fusion (Tixier et al., 2013). From these, we postulate that desmin and pgam2 might involve in muscle development.

These postulations and assumptions must be tested in a wet lab before jumping to any conclusion. Yet, it is still interesting to imagine the spectrum of different functions that desmin can undertake in the nucleus.

4. Protein localization, transport, and diseases
Mutations in the desmin gene causes skeletal and cardiac myopathies known as desminopathies. There is not a treatment for desminopathies thus far (Langer et al., 2020). The pathology caused by desmin mutations usually emerge from dysfunctional desmin network due to the desmin aggregation or myofibrillar degeneration, or the mutation interferes with PTMs or protein-protein interaction sites (Capetanaki et al., 2015). More than 70 mutations in the desmin gene have been associated with desminopathies (Capetanaki et al., 2015), and six of them (Ser12Phe, Ser13Phe, Arg16Cys, Ala285Val, Ser298Leu, Asp312Asn) are located within the NLSs on desmin (Szeverenyi et al., 2008) (Figure 2). These mutations are related to desmin aggregation (Ser12Phe, Ser13Phe, Ala285Val, Ser298Leu, Asp312Asn) (Bergman et al., 2007; Taylor et al., 2007; van Tintelen et al., 2009; Hong et al., 2011; Tse et al., 2013; Brodehl et al., 2018) and defects in network formation (Ser13Phe,Arg16Cys) (Pica et al., 2008; Sharma et al., 2009). Ser12Phe and Ser13Phe mutations also overlap with the phosphorylation sites on desmin (Figure 2). It
is postulated that the Ser12Phe and Ser13Phe mutations might affect desmin’s phosphorylation status and interfere with filament polymerization and depolymerization (Pica et al., 2008; Hong et al., 2011). However, none of these studies have focused on how (or if) desmin transport might be affected by these mutations. We believe there are two main reasons why the ‘how and if’ questions were not investigated: First, the researchers were focused on the cause of disease pathology and not the yet undiscovered nuclear function of desmin, and, secondly, since the primary pathology of the disease is right on the table, no need arises for a detailed further investigation. For desminopathies, there is an experimental study aim to reduce desmin aggregation (Cabet et al., 2015). Nonetheless, it is not clear how the information obtained from this study can be translated into the treatment of desminopathies, and these studies usually did not focus on the subcellular localization of desmin since the “nuclear desmin” concept is relatively new.

Besides the potential to understand the structure of NPC and transport mechanisms and function of a protein better, the cellular localization and how it is regulated might also reveal the targetability of a protein. The precise localization of a protein can control the accessibility of the interaction partners and molecules that regulate PTMs and allows the protein to integrate into the biological networks in the cell. Apart from causing aggregation and defects in filament formation, the mutations within the desmin NLSs and NES can alter the subcellular localization of desmin by blocking PTM sites and preventing desmin from entering the nucleus. It has been known for a long time that fault in subcellular localization or transport of a protein may result in diseases related to protein aggregation, biosynthesis, or cell metabolism (Kaiser et al., 2004; Sabherwal et al., 2004; Mendes et al., 2005; Mizutani et al., 2007; McLane and Corbett, 2009; Hoover et al., 2010; Shoubridge et al., 2010; Hung and Link, 2011). Hence, the clarification of the mechanism of transport of a protein has become a very attention-grabbing area. Understanding the transport not only indicates the controllability of protein activity but also allows revealing possible pathways associated with the biological processes of interest.

One other benefit that might arise from localization and transport studies is the broadening of our understanding of NLSs and NESs. There is a growing body of research on increasing the therapeutic targetability of the nucleus. For example, some researchers use modified NLSs to increase the efficiency of nuclear transport (Wilson et al., 1999; Escriou et al., 2003) and utilize the NLS characterization studies to understand the effects of modifications on delivery efficiency. Another therapeutic approach is based on the inhibition of nucleocytoplasmic transport mechanisms. There are many different and successful studies, especially in cancer research (Mahipal and Malafa, 2016; Kim et al., 2017). These studies clearly demonstrate the importance of the detailed analysis of basic biological processes.

5. Conclusions
The researchers studying the subcellular localization of proteins must ask: What is the biological significance of IF proteins in the nucleus? IFs act as a sensor and transmitter for extracellular signals in the cytoplasm, while nucleocytoplasmic transport of these proteins helps to regulate basal and adaptive cellular responses. The nucleocytoplasmic localization of the proteins that shuttle between cytoplasm and nucleus -shuttling proteins, changes perpetually to adapt to the extracellular environment. Thus, the subcellular localization of the shuttling proteins must be tightly controlled. Subcellular localization of the shuttling proteins can be affected by several factors such as interaction partners (for example, transport proteins) or the cellular state (proliferation, differentiation, etc.). This means that a change in the balance of the subcellular localization of the protein can cause either depletion or accumulation of the protein in the nucleus, which can result in impairment of the nuclear functions (Kumeta et al., 2012). All these suggest that the nuclear cytoskeletal proteins are as central for the nuclear responses as in the transduction of the signals from the plasma membrane. As for desmin, it is now known that desmin can occur and function inside the nucleus (Fuchs et al., 2016; Kural-Mangıt and Dinçer, 2021). Evidence on literature and our findings strongly suggest that desmin has a transcriptional regulatory role in the cell in addition to its cytosolic functions. Uncovering these functions, along with the binding partners and the network they generate, will contribute to the revelation of new roles of desmin in health and disease and how the nuclear transport may be involved and/or affected in facilitating highly orchestrated signaling processes.

Acknowledgments
These studies were funded by The Scientific and Technological Research Council of Turkey (TÜBİTAK), Project no. 214S174 and Hacettepe University Scientific Research Project Coordination Unit (HÜBAP), Project no.THD-17210 to P.R.D. The authors declare no conflicts of interest.
References

Aebi U, Chon J, Buble L, Geraca L (1986). The nuclear lamina is a meshwork of intermediate-type filaments. Nature 323 (9). doi: 10.1038/323560a0

Agnetti G, Herrmann H, Cohen S (2021). New roles for desmin in the maintenance of muscle homeostasis. FEBS Journal 1–16. doi: 10.1111/febs.15864.

Al-Haboubi T, Shumaker DK, Köser J, Wehnert M, Fahrenkrog B (2011). Distinct Association of the Nuclear Pore Protein Nup153 with A- and B-type Lamins. Nucleus 2 (5): 1–10. doi: 10.4161/nuc.2.5.179713

André V, González JM (2009). Role of A-type lamins in signaling , transcription , and chromatin organization. Journal of Cell Biology 187 (7): 945–957. doi: 10.1083/jcb.200904124

Bergman JEH, Veenstra-Knol HE, van Essen AJ, van Ravenswaaij CMA, den Dunnen WFA et al. (2007). Two related Dutch families with a clinically variable presentation of cardioelectrolytun muscle myopathy caused by a novel S13F mutation in the desmin gene. European Journal of Medical Genetics 50 (5): 355–366. doi: 10.1016/j.jmg.2007.06.003

Brodehl A, Gaertner-Rommel A, Milting H (2018). Molecular insights into cardiomyopathies associated with desmin (DES) mutations. Biophysical Reviews 10 (4): 983–1006. doi: 10.1007/ s12551-018-0429-0

Brunet S, Sardon T, Zimmerman T, Wittmann T, Pepperkok R et al. (2004). Characterization of the TPX2 Domains Involved in Microtubule Nucleation and Spindle Assembly in Xenopus nucleation around chromatin and functions in a network of other molecules , some of which also are regulated by. Molecular Biology of the Cell 15 (December): 5318–5328. doi: 10.1091/mbc.E04

Cabet E, Batonnet-Pichon S, Delort F, Gausséres B, Vicart P et al. (2015). Antioxidant treatment and induction of autophagy to cooper reduce desmin aggregation in a cellular model of desminopathy. PLoS ONE 10 (9): 1–26. doi: 10.1371/journal.pone.0137009

Capetanaki Y, Papatheonasiu S, Diokmetzidou A, Vatsellas G Tsikitis M (2015). Desmin related disease: A matter of cell survival failure. Current Opinion in Cell Biology 32 (Dcm): 113–120. doi: 10.1007/s11065-015-9294-9.Functional

Capetanaki Y, Milner DJ Weitzer G (1997). Desmin in muscle formation and maintenance : knockouts and consequences. Cell Structure and Function 22 (1): 103–116. doi: 10.1247/ csf.22.103

Çetin N, Balci-Hayta B, Gundesli H, Korkusuz P, Purali N et al. (2013). A novel desmin mutation leading to autosomal recessive limb-girdle muscular dystrophy: Distinct histopathological outcomes compared with desminopathies. Journal of Medical Genetics 50: 437–443. doi: 10.1136/jmedgenet-2012-101487

Costa ML, Escaleira R, Cataldo A, Oliveira F, Mermelstein CS (2004). Desmin: molecular interactions and putative functions of the muscle intermediate filament protein. Brazilian Journal of Medical and Biological Research 37 (12): 1819–1830.

La Cour T, Kiemer L, Molgaard A, Gupta R, Skriver K et al. (2004). Analysis and prediction of leucine-rich nuclear export signals. Protein Engineering, Design and Selection 17 (6): 527–536. doi: 10.1093/protein/gzh062

Escrivo V, Carrière M, Scherman D, Wils P. (2003). NLS bioconjugates for targeting therapeutic genes to the nucleus. Advanced Drug Delivery Reviews 55 (2): 295–306. doi: 10.1016/S0169-409X(02)00184-9

Fuchs C, Gawlas S, Heher P, Nikouli S, Paar H et al. (2016). Desmin enters the nucleus of cardiac stem cells and modulates Nkx2.5 expression by participating in transcription factor complexes that interact with the nkx2.5 gene. Biology Open 5 (2): 140–153. doi: 10.1242 bio.014993

Fuchs E, Weber K (1994). Intermediate Filaments: Structure, Dynamics, Function and Disease. Annual Review of Biochemistry 63: 345–382.

Geisler N, Weber K (1988). Phosphorylation of desmin in vitro inhibits formation of intermediate filaments; identification of three kinase A sites in the aminoterminal head domain. The EMBO Journal 7 (1): 15–20. doi: 10.1002/j.1460-2075.1988. tb02778.x

Georgatos SD, Webert K, Geisler N, Blobel G (1987). Binding of two desmin derivatives to the plasma membrane and the nuclear envelope of avian erythrocytes: Evidence for a conserved site-specificity in intermediate filament-membrane Interactions. Proceedings of the National Academy of Sciences of the United States of America 84: 6780–6784.

Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V (2008). Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. Journal of Cell Biology 183 (4): 653–666. doi: 10.1083/jcb.200805049

Hartig R, Shoeman RL, Janetzko A, Tolstonog G, Traub P (1998). DNA-mediated transport of the intermediate filament protein vimentin into the nucleus of cultured cells. Journal of Cell Science 111 (24): 3573–84.

Hesse M, Magin TM, Weber K (2001). Genes for intermediate filament proteins and the draft sequence of the human genome: Novel keratin genes and a surprisingly high number of pseudogenes related to keratin genes 8 and 18. Journal of Cell Science 114 (24): 2569–2575.

Hnia K, Ramspacher C, Vermot J, Laporte J (2015). Desmin in muscle and associated diseases: beyond the structural function. Cell and Tissue Research 360 (3): 591–608. doi: 10.1007/s00441-014-2016-4

Hobbs RP, Depianto DJ, Jacob JT, Han MC, Chung RM et al. (2015). Keratin-dependent regulation of Aire and gene expression in skin tumor keratinocytes. Nature Genetics 47 (8): 953–938. doi: 10.1038/ng.3355

Hobbs RP, Jacob JT, Coulombe PA (2016). Keratins Are Going Nuclear. Developmental Cell 38 (3): 227–233. doi: 10.1016/j. devcel.2016.07.022
KURAL MANGIT et al. / Turk J Biol

Höllrigl A, Puz S, Al-Dubai H, Kim JU, Capetanaki Y et al. (2002). Amino-terminally truncated desmin rescues fusion of des−/− myoblasts but negatively affects cardiomyogenesis and smooth muscle development. FEBS Letters 523 (1–3): 229–233. doi: 10.1016/s0014-5793(02)02995-2

Höllrigl A, Hofner M, Stary M, Weitzer G (2007). Differentiation of cardiomyocytes requires functional serine residues within the amino-terminal domain of desmin. Differentiation 75: 616–626. doi: 10.1111/j.1432-0436.2007.00163.x

Holtz D, Tanaka RA, Hartwig J, McKeon F (1989). The CaaX motif of lamin A functions in conjunction with the nuclear localization signal to target assembly to the nuclear envelope. Cell 59 (6): 969–977. doi: 10.1016/0092-8674(89)90753-8.

Hong D, Wang Z, Zhang W, Xi J, Lu J et al. (2011). A series of Chinese patients with desminopathy associated with six novel and one reported mutations in the desmin gene. Neuropathology and Applied Neurobiology 37 (3): 257–270. doi: 10.1111/j.1365-2990.2010.01112.x

Hoover B, Reed MN, Su J, Penrod RD, Kotilinek LA et al. (2010). Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron 68 (6). doi: 10.1038/nn.2471

Hornbeck PV, Zhang B, Murray B, Kornhauser JM, Latham V et al. (2015). PhosphoSitePlus, 2014: Mutations, PTMs and recalibrations. Nucleic Acids Research 43 (Database Issue). doi: 10.1093/nar/gku1267

Hung MC, Link W (2011). Protein localization in disease and therapy. Journal of Cell Science 124 (20): 3381–3392. doi: 10.1242/jcs.089110

Inagaki M, Gonda Y, Matsuyama M, Nishizawa K, Nishi Y et al. (1986). A Monoclonal Antibody to Chicken Gizzard capping protein tropomodulin. Journal of Biological Chemistry 261: 45–55. doi: 10.1016/s0021-9258(18)60661-1

Kaiser FJ, Brega P, Raff ML, Byers PH, Gallati S et al. (2004). Novel missense mutations in the TRPS1 transcription factor define the nuclear localization signal. European Journal of Human Genetics 12 (2): 121–126. doi: 10.1038/sj.ejhg.5201094

Kamei H (1986). A Monoclonal Antibody to Chicken Gizzard Desmin that Recognizes Intermediate Filaments and Nuclear Granules in BHK21 / C13 Intermediate filaments. Cell Structure and Function 11: 367–377.

Kim YH, Han ME, Oh SO (2017). The molecular mechanism for nuclear transport and its application. Anatomy & Cell Biology 50 (2): 77. doi: 10.5115/acb.2017.50.2.77

Kong KY, Kedes L (2004). Cytoplasmic nuclear transfer of the actin-capping protein tropomodulin. Journal of Biological Chemistry 279 (29): 30856–30864. doi: 10.1074/jbc.M302845200

Kosugi S, Hasebe M, Tomita M, Yanagawa H (2009). Systematic identification of cell cycle-dependent yeast nucleocytoplasmic shuttling proteins by prediction of composite motifs. PNAS 106 (25): 1–6. doi: 10.1073/pnas.0900604106

Kumeta M, Yoshimura SH, Harata M, Takeyasu K (2010). Molecular mechanisms underlying nucleocytoplasmic shuttling of actin-4. Journal of Cell Science 123 (7): 1020–1030. doi: 10.1242/jcs.059568

Kumeta M, Yoshimura SH, Hejna J, Takeyasu K (2012). Nucleocytoplasmic shuttling of cytoskeletal proteins: Molecular mechanism and biological significance. International Journal of Cell Biology 2012. doi: 10.1155/2012/494902

Kural-Mangıt E, Diçner PR (2021). Physical evidence on desmin–lamin B interaction. Cytoskeleton (December 2020): 1–4. doi: 10.1002/cm.21651

Kural E (2017). Desmin ve Lamin B Etikleșiminin Zebra Balığında Araştırılması. Hacettepe Üniversitesi. Ankara. Türkiye.

Langer HT, Mossakowski AA, Willis BJ, Grimsrud KN, Wood JA et al. (2020). Generation of desminopathy in rats using CRISPR-Cas9. Journal of Cachexia Sarcopenia and Muscle 11 (5): 1364–1376. doi: 10.1002/jscm.12619

Lazarides E (1980). Intermediate Filaments as Mechanical Integrators of Cellular Space. Nature 283: 249–256. doi: 10.1038/283249a0

Li H, Choudhary SK, Milner DJ, Munir MJ, Kuisk IR et al. (1994). Inhibition of desmin expression blocks myoblast fusion and interferes with the myogenic regulators myoD and myogenin. The Journal of Cell Biology 124 (5): 827–841. doi: 10.1083/jcb.124.5.827

Liu B, Wang J, Chan KM, Tjia WM, Deng W et al. (2005). Genomic instability in laminopathy-based premature aging. Nature Medicine 11 (7): 780–785. doi: 10.1038/nm1266

Lockard VG, Bloom S (1993). Trans-cellular desmin-lamin B intermediate filament network in cardiac myocytes. Journal of Molecular and Cellular Cardiology 25: 303–309.

Loewinger L, McKeon F (1988). Mutations in the nuclear lamin proteins resulting in their aberrant assembly in the cytoplasm. The EMBO Journal 7 (8): 2301–2309. doi: 10.1002/j.1460-2075.1988.tb03073.x

Mahipal A, Malafa M (2016). Importins and exportins as therapeutic targets in cancer. Pharmacology and Therapeutics 164: 135–143. doi: 10.1016/j.pharsrbera.2016.03.020

Majewski L, Nowak J, Sobczak M, Karatsai O, Havrylov S et al. (2018). Myosin VI in the nucleus of neurosecretory PC12 cells: Stimulation-dependent nuclear translocation and interaction with nuclear proteins. Nucleus doi: 10.1002/cm.21651

Malhas AN, Lee CF. Vaux DJ (2009). Lamin B1 controls oxidative stress responses via Oct–1. Journal of Cell Biology 184 (1): 45–55. doi: 10.1083/jcb.200804155

Manju K, Muralikrishna B. Parnaik VK (2006). Expression of disease-related missense mutations in the desmin gene. Neuropathology and Applied Neurobiology 32 (45–55). doi: 10.1083/jcb.200804155

Mavroidis M, Panagopoulou P, Kostavasilis I, Weisleder N, Capetanaki Y (2008). A missense mutation in desmin tail domain linked to human dilated cardiomyopathy promotes cleavage of the head domain and abolishes its Z-disc localization. The FASEB Journal 22 (9): 3318–3327. doi: 10.1096/fj.07-086724

717
McLane LM, Corbett AH (2009). Nuclear localization signals and human disease. IUBMB Life 61 (7): 697–706. doi: 10.1002/iub.194

Mendes HF, Van Der Spuy J, Chapple JP, Cheetham ME (2005). Mechanisms of cell death in rhodopsin retinitis pigmentosa: Implications for therapy. Trends in Molecular Medicine 11 (4): 177–185. doi: 10.1016/j.nano.2005.02.007

Mizutani A, Matsuzaki A, Momoi MY, Fujita E, Tanabe Y et al. (2007). Intracellular distribution of a speech/language disorder associated FOXP2 mutant. Biochemical and Biophysical Research Communications 353 (4): 869–874. doi: 10.1016/j.bbrc.2006.12.130

Murre C, Schonleber P, Baltimore D (1989). A New DNA Binding and Dimerization Motif in Immunoglobin Enhancer Binding, daughterless, MyoD, and myc Proteins. Cell 56: 777–783.

Oshima RG (2007). Intermediate filaments: A historical perspective. Experimental Cell Research 313 (10): 1981–1994. doi: 10.1016/j.yexcr.2007.04.007

Peter A, Stick R (2015). Evolutionary aspects in intermediate filament proteins. Current Opinion in Cell Biology 32: 48–55. doi: 10.1016/jceb.2014.12.009

Pica EC, Kathirvel P, Pramono ZAD, Lai PS, Lee WC (2008). Characterization of a novel S13F desmin mutation associated with desmin myopathy and heart block in a Chinese family. Neuromuscular Disorders 18 (2): 178–182. doi: 10.1016/j.nmd.2007.09.011

Qiu H, Zhao S, Xu X, Yerle M, Liu B (2008). Assignment and expression patterns of porcine muscle-specific isoform of phosphoglycerate mutase gene. Journal of Genetics and Genomics 35 (5): 257–260. doi: 10.1016/S1673-8527(08)60036-3

Rogers MA, Winter H, Langbein L, Bleiler R, Schweizer J (2004). The human type I keratin gene family: Characterization of new hair follicle specific members and evaluation of the chromosome 17q21.2 gene domain. Differentiation 72 (9–10): 527–540. doi: 10.1111/j.1432-0436.2004.07209006.x

Rogers MA, Edler L, Winter H, Langbein L, Beckmann I et al. (2005). Characterization of new members of the human type II keratin gene family and a general evaluation of the keratin gene domain on chromosome 12q13.13. Journal of Investigative Dermatology 124 (3): 536–544. doi: 10.1111/j.0022-202X.2004.23530.x

Sabherwal N, Schneider KU, Blaschke RJ, Marchini A, Rappold G (2004). Impairment of SHOX nuclear localization as a cause for Léri-Weill syndrome. Journal of Cell Science 117 (14): 3041–3048. doi: 10.1242/jcs.01152

Sharma S, Mücke N, Katus HA, Herrmann H, Bär H (2009). Disease mutations in the ‘head’ domain of the extra-sarcomeric protein desmin distinctly alter its assembly and network-forming properties. Journal of Molecular Medicine 87 (12): 1207–1219. doi: 10.1007/s00109-009-0521-9

Shoubridge C, Tan M, Fullston T, Cloosterman D, Coman D et al. (2010). Mutations in the nuclear localization sequence of the Aristaless related homeobox; Sequestration of mutant ARX with IPO13 disrupts normal subcellular distribution of the transcription factor and retards cell division. Patho Genetics 3 (1): 1–15. doi: 10.1186/1755-8417-3-1

Snider NT, Omary MB (2014). Post-translational Modifications of Intermediate Filament Proteins: Mechanisms and Functions. Nature Reviews. Molecular Cell Biology 15 (3): 163–177. doi: 10.1016/j.jbiotechadv.2011.08.021.Secreted

Sridharan D, Brown M, Lambert C, McMahon L, Lambert M (2003). Nonerythroid alphaH1 spectrin is required for recruitment of FANCA and XPF to nuclear foci induced by DNA interstrand cross-links. Journal of Cell Science 116 (5): 823–835. doi: 10.1242/jcs.00294

Stroud MJ, Banerjee I, Veevers J, Chen J (2014). Linker of Nucleoskeleton and Cytoskeleton Complex Proteins in Cardiac Structure. Function and Disease Circulation Research 114: 538–48. doi: 10.1161/CIRCRESAHA.114.301236

Szeverenyi I, Cassidy AJ, Cheuk WC, Lee BTK, Common JEA et al. (2008) The human intermediate filament database: Comprehensive information on a gene family involved in many human diseases. Human Mutation 29 (3): 351–360. doi: 10.1002/humu.20652

Tan X, Rotllant J, Li H, Deyne PD, Du SJ (2006). SmyD1, a histone methyltransferase, is required for myofibril organization and muscle contraction in zebrafish embryos. PNAS 103 (8): 2713–2718.

Taylor MRG, Slavov D, Ku L, Di Lenarda A, Sinagra G et al. (2007). Prevalence of desmin mutations in dilated cardiomyopathy. Circulation 115 (10): 1244–1251. doi: 10.1161/CIRCULATIONAHA.106.646778

van Tintelen JP, Van Gelder IC, Asimaki A, Suurmeijer AJH, Wieselfeld ACP et al. (2009). Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm 6 (11): 1574–1583. doi: 10.1016/j.heart.2009.07.041

Tixier V, Bataille L, Etard C, Jagla T, Weger M et al. (2013). Glycolysis supports embryonic muscle growth by promoting myoblast fusion. Proceedings of the National Academy of Sciences of the United States of America 110 (47): 18982–18987. doi: 10.1073/pnas.1301262110

Toivola DM, Tao GZ, Hattezon A, Liao J, Omary MB (2005). Cellular integrity plus: Organelle-related and protein-targeting functions of intermediate filaments. Trends in Cell Biology 15 (11): 608–617. doi: 10.1016/j.tcb.2005.09.004

Tolstonog GV, Wang X, Shoeman R, Traub P (2000). Intermediate filaments reconstituted from vimentin, desmin, and glial fibrillary acidic protein selectively bind repetitive and mobile DNA sequences from a mixture of mouse genomic DNA fragments. DNA and Cell Biology 19 (11): 647–677. doi: 10.1089/10445490050199054
Tolstonog GV, Li G, Shoeman RL, Traub P (2005). Interaction In Vitro of Type III Intermediate Filament Proteins with Higher Order Structures of Single-Stranded DNA, Particularly with G-Quadruplex DNA. DNA and Cell Biology 24 (2): 85–110. doi: 10.1089/dna.2005.24.85

Traub P, Shoeman RL (1994). Intermediate Filament Proteins: Cytoskeletal Elements with Gene-Regulatory Function?. International Review of Cytology 154: 1–103. doi: 10.1016/S0074-7696(08)62198-1

Tse HF, Ho JCY, Choi SW, Lee YK, Butler AW et al. (2013). Patient-specific induced-pluripotent stem cells-derived cardiomyocytes recapitulate the pathogenic phenotypes of dilated cardiomyopathy due to a novel DES mutation identified by whole exome sequencing. Human Molecular Genetics 22 (7): 1395–1403. doi: 10.1093/hmg/dds556

Ünsal Ş (2019). Limb - Girdle Kas Distrofisi 2R (LGMD2R)de mekanotransdüksiyonun rolünün araştırılması. Hacettepe Üniversitesi, Ankara, Türkiye.

Wang Q, Tolstonog GV, Shoeman R, Traub P (2001). Sites of Nucleic Acid Binding in Type I - IV Intermediate Filament Subunit. Biochemistry 40: 10342–10349. doi: 10.1021/bi0108305

Weber K, Plessmann U, Ulrich W (1989). Cytoplasmic intermediate filament proteins of invertebrates are closer to nuclear lamins than are vertebrate intermediate filament proteins; sequence characterization of two muscle proteins of a nematode. EMBO Journal 8 (11): 3221–3227. doi: 10.1002/j.1460-2075.1989.tb08481.x

Wilson GL, Dean BS, Wang G, Dean DA (1999). Nuclear Import of Plasmid DNA in Digitonin-permeabilized Cells Requires Both Cytoplasmic Factors and Specific DNA Sequences. Journal of Biological Chemistry 274 (31): 22025–22032.