Minireview

What does desmin do: A bibliometric assessment of the functions of the muscle intermediate filament

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Impact Statement

More than 50 years after the identification of intermediate filaments, there is still a debate about their functions. While on one hand, several knockouts and genetic variants have been studied, on the other hand, there is still a tendency to mix together functions that are related to all intermediate filaments, dismissing the fact that desmin is specific to muscle cells. The present review uses a bibliometric approach to assess the research on desmin, and to compare its alleged functions. Based on the interpretation of the comparative list of functions we organized, we propose a new approach to interpret the function of desmin. This review should be useful to those interested in cytoskeleton, particularly in intermediate filaments, and in myogenesis and muscle structure and function, by providing a comprehensive view of the research on desmin.

Abstract

Intermediate filaments were first described in muscle in 1968, and desmin was biochemically identified about 10 years afterwards. Its importance grew after the identification of desminopathies and desmin mutations that cause mostly cardiopathies. Since its characterization until recently, different functions have been attributed to desmin. Here, we use bibliometric tools to evaluate the articles published about desmin and to assess its several putative functions. We identified the most productive authors and the relationships between research groups. We studied the more frequent words among 9734 articles (September 2021) containing "desmin" on the title and abstract, to identify the major research focus. We generated an interactive spreadsheet with the 934 papers that contain "desmin" only on the title that can be used to search and quantify terms in the abstract. We further selected the articles that contained the terms "function" or "role" from the spreadsheet, which we then classified according to type of function, organelle, or tissue involved. Based on the bibliographic analysis, we assess comparatively the putative functions, and we propose an alternative explanation for the desmin function.

Keywords: Desmin, intermediate filaments, cytoskeleton

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Introduction

The cytoskeletal component "intermediate filament" (IF) has been characterized by Holtzer in 1968[1] because of its diameter of 10 nm, based on his observation of chick muscle cells in culture. He pointed out that other similarly sized filaments have been described in other cell types, and he assumed that these structures were related. Later it was shown that, while IFs form the nuclear lamina in all cell types, not all cell types have cytoplasmic IFs. Furthermore, IFs are composed of different proteins in different tissues.[2] Here, we will focus on the muscle- (and endothelial) specific filament protein desmin. The first purification of muscle IF protein has been reported by Cooke in 1976,[3] followed by Lazarides,[4] who suggested the name "desmin" for its ability to join structures, and Small, who suggested the name "skeletin."[5] This sequence of events, from structure to biochemistry, is the opposite of what happened to microfilaments, where the biochemical identification of actin and myosin took place around 50 years before the visualization of contractile filaments, and similar to microtubules, that were first identified by electron microscopy and only biochemically purified 20 years afterwards. Yet the fundamental role of actin and myosin in contraction and tubulin in chromosome movement during mitosis, in all eukaryotic cells, appeared quite early in research, explaining why all cell types express actin and tubulin. The most obvious function assigned to IF is vaguely categorized as "mechanical integration."[6] While this

mechanical function can be undoubtedly observed in epithelial cells, the concept that all cell types have the same IF function is somewhat contradictory with the fact that each cell type has a different set of IF proteins.

Contrary to actin and tubulin, which are compact globular proteins that have to undergo an extra chaperone processing step before they assume their final form,[7] IF proteins are elongated molecules, with two varying globular domains and a conserved central rod domain. Polymerization of actin and tubulin involves a smaller region of the subunit than IFs, which first assemble as antiparallel dimers throughout their central domain.[2] While the polymerization of actin and tubulin involves nTP hydrolysis, the polymerization of IF is regulated by phosphorylation. In the immunofluorescence image of cultured cells (Figure 1), desmin filaments spread in every direction of the muscle cells, contrary to actin filaments which are mostly oriented in the direction of contraction along the major axis of the cell. We used the radiality-based processing (SRRF[8]) to better visualize both desmin and actin filaments. This method is based on the direction of changes in brightness among several images of the same field, much like the stochastic position determining microscopies such as STORM. Actin in these embryonic chicken primary cultures of skeletal myotubes[9] is still distributed in non-periodical stress fibers, while desmin is clearly distributed around the nuclei (visible in the interference contrast figure).

Many diseases have been related to mutations in IFs.[10] The hereditary disease epidermolysis bullosa simplex (EBS) is caused by alterations on the genes of cytokeratins.[11] The pathophysiology of EBS has been clearly established, with the symptoms of skin fragility combining to the loss of structural continuity between the cytokeratin network of adjacent skin cells. The disease is well modeled by cytokeratins K5 and K14 knockout mice, and a similar phenotype can be observed in alterations in desmosomes (IF-related cell–cell adhesion structures), such as pemphigus. Desminopathy has been characterized as a disease caused by alterations in the desmin gene or alterations that lead to the abnormal distribution and/or accumulation of desmin inside the cells.[12] As it happens to many other diseases, there is a gap between medical and basic cell biology knowledge,[13] and the desmin-related physiopathological mechanisms are not clearly characterized: it is still not clear whether the disease is caused by the lack of function of altered desmin or to the accumulation of unprocessed molecular aggregates.

Here, we used bibliometrics, the quantitative study of publications, to review desmin function. Until September 2021, 10,570 articles have been published in PubMed citing desmin on the title or abstract, and 970 articles cite desmin on the title (Figure 2). Among the first category, 797 articles were classified as "review," and about 7.5% of the total also mentioned the words "role" or "function." The annual number of articles on desmin has been growing sharply, and there is a change in the total number of articles concerning "function" since 2005, at about the same time when the field of desminopathies became better investigated. The growth in the number of articles, however, should be kept in perspective because when we compared with the whole PubMed production, the proportion of articles about desmin actually became smaller over time (blue line on graph). Since there are numerous excellent reviews on several aspects of desmin, we decided to concentrate on the putative function(s) of desmin.

Patients

The quest for the function of desmin is ever more important because the identification of new cases of desminopathies that are being frequently identified and can have severe consequences for patients. In these cases, the literature either focuses on medical case-descriptions or on trying to establish details of each mutation at the cellular and molecular levels. From the medical point of view, the lack of awareness regarding desminopathies may represent a serious bias in determining the prevalence of desminopathies in different countries. Indeed, there is a huge difference in the number of diagnosed cases in different countries, which suggests an under-notification of cases and that the number of cases reported per country is more dependent on the local medical expertise than on the country's human development index (data not shown) or possibly the population's genetic background. Assuming that all the desmin mutation cases in the world should be registered in the Leiden Open Variation Database (LOVD, https://databases.lovd.nl/shared/genes/DES, maintained by the University of Leiden at https://www.dmd.nl/), we analyzed the worldwide incidence of desmin mutations (Figure 3). There is a large variation in the incidence from country to country, even considering the differences in population size. For instance, we could find only two descriptions of desminopathy in Brazil, which are not listed on the Leiden database nor on PubMed. Based on the average incidence of 0.25 cases per million habitants (calculated from the sum of cases in the LOVD database), we should expect about 53 cases in Brazil.

Researchers

One of the questions that can be analyzed bibliometrically is who the main researchers in the desmin field are, and how the research groups are related. We built from PubMed (September 2021) a database of 9731 articles with the word "desmin" in the title or abstract (including "skeletin" and excluding the dermatan sulfate "Desmin 370"). Using the software Vosviewer, we assembled a diagram showing the number of publications per authors and their relationship on Figure 4 (the files that allow interactive visualization with Vosviewer app: https://app.vosviewer.com can be provide upon request). While more than 72% of the 39,450 authors published less than five articles about desmin, 175 authors published more than 10 articles. The five authors with most papers are: Christopher Fletcher (Brigham and Women's Hospital, US), Markku Miettinen (Nat Cancer Inst, US), Denise Paulin (Université Pierre et Marie Curie Paris 6, FR), Zhenlin Li (Université Pierre et Marie Curie Paris 6, FR), and Giulio Gabbiani (Université de Genève, SW), with more than 50 articles published each. While Fletcher and Miettinen publish mostly on tumor pathology, the others

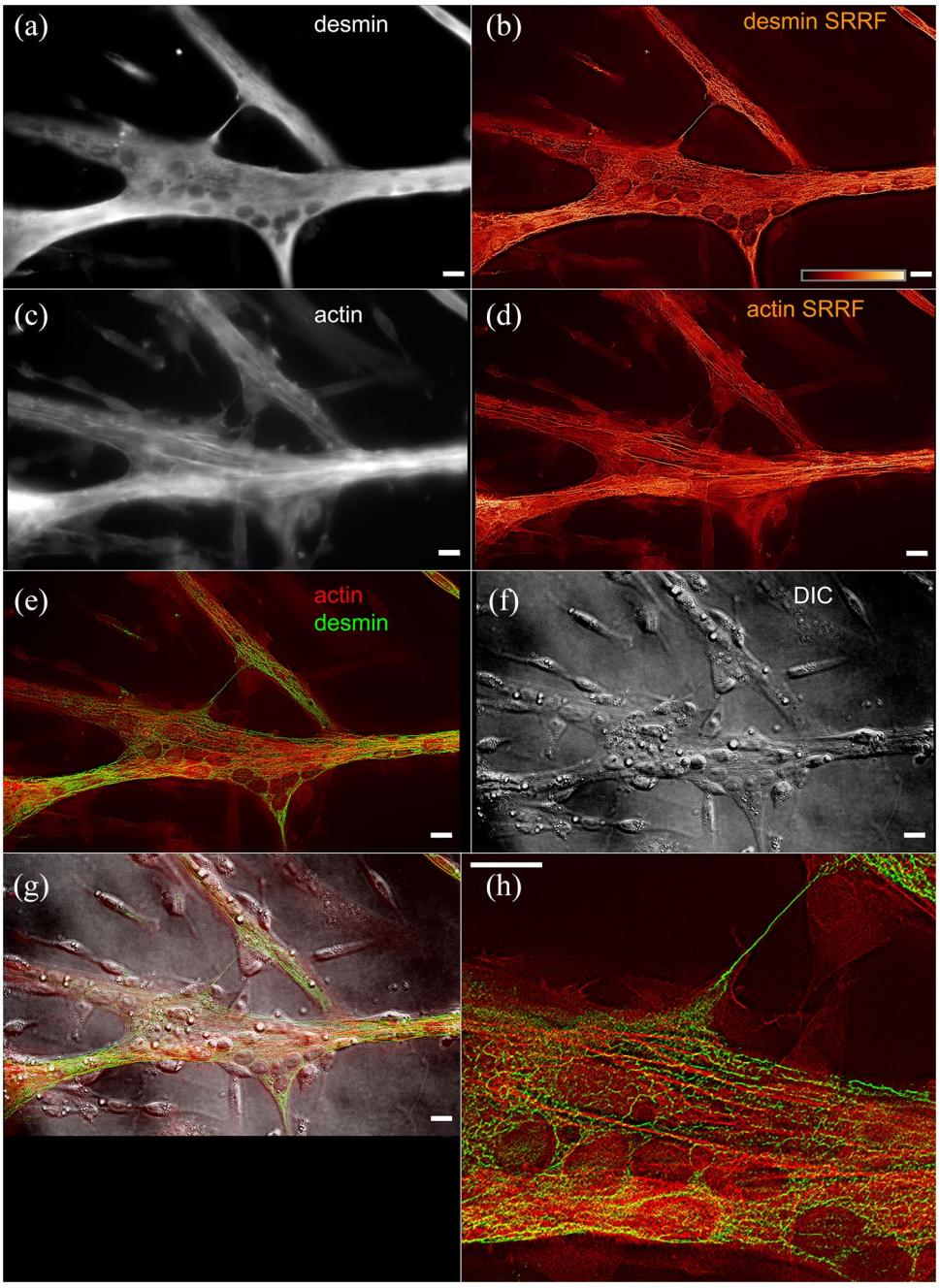

Figure 1. Immunofluorescence labeling of chick primary culture myoblasts for desmin (a) and actin (c), and images processed with SRRF for desmin (b) and actin (d). The merged image (e) shows desmin labeled in green and actin labeled in red, compared with the interference contrast image (f) and (g)—the superposition of immuno and contrast. In the inset (h), it is interesting to note how the distribution of the processed image of actin and desmin mostly exclude each other. Scale bars 10 μm. (A color version of this figure is available in the online journal.)

usually publish on basic cell biology science: the major focus of the articles will be discussed in the next section.

Research themes

Bibliometric analysis also allows the visualization of the most frequent words, which can be assumed to represent the main subjects in a field. The software Vosviewer identified the most frequent words in the desmin PubMed database, organized them according to their relationship (co-occurrence), and displayed them in a map (Figure 5, the files that allow interactive visualization with Vosviewer app: https://app.vosviewer.com can be provide upon request). From the association between these words, we can try to identify the major research areas (marked in the diagram): (1) articles that use desmin as a tumor marker, (2) articles on desmin-related diseases, (3) articles on the cell biology of desmin, and (4) articles on desmin biochemistry. The first group includes several medical cases and other articles in which desmin is used as a marker for the identification of a given cell type. Frequent words in this group are "expression," "immunohistochemistry," "staining" and "marker," and

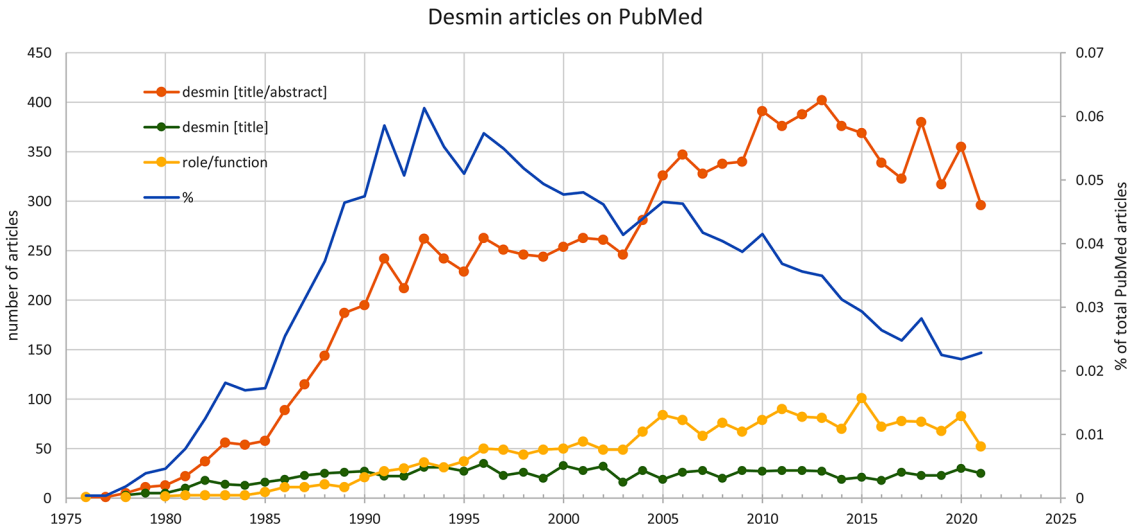

Figure 2. Number of articles with desmin on title or desmin on title and abstract, compared to the total number of articles on PubMed. (A color version of this figure is available in the online journal.)

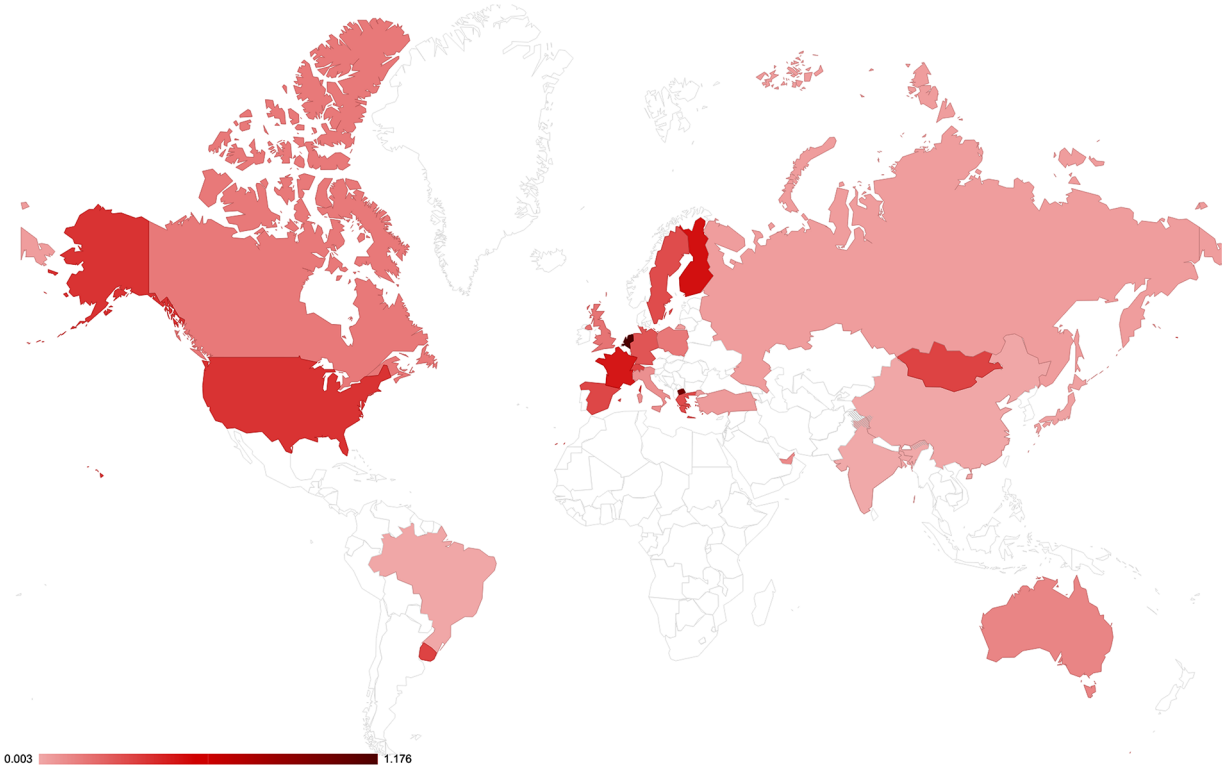

Figure 3. Worldwide distribution of desmin cases in each country relative to the size of the population, based on the LOVD database, with additional information for Brazil. Several countries do not have any cases reported and are left without color. (A color version of this figure is available in the online journal.)

medical terms such as "diagnosis," "case," and "treatment." The second group (mostly colored in blue) includes articles on desmin-related diseases, with words such as "myopathy," "cardiomyopathy," "patient," "mutation," and "desmin gene" highly frequent. The third group (mostly colored in green) has been tentatively composed of words related to cell biology, with high frequency of words such as "cell," "differentiation," "vimentin," and "keratin." Interestingly, words related to immunostain ("monoclonal antibody," "antibody," and "immunofluorescence") are also frequently used, but distinct from the first cluster. Finally, the fourth cluster (mostly colored in red) is tentatively associated with biochemistry, centered in the word "protein," and including as frequent words "intermediate filament," "filament" but also "myotube" and "myoblast." In the center of the figure there are some words colored in yellow, which are linked to all the groups, such as "muscle," "heart," and "function." Since these words link to words in all clusters, we considered

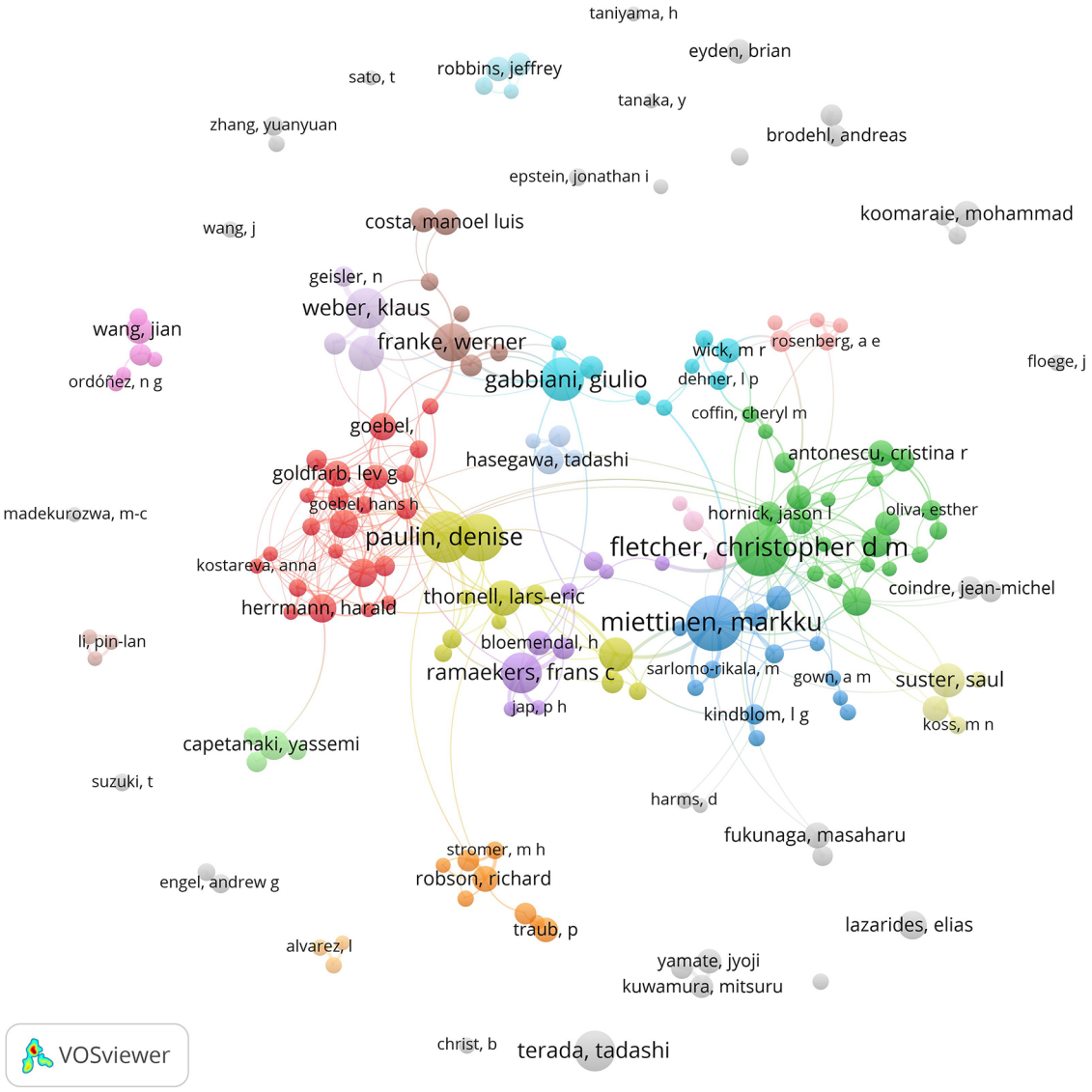

Figure 4. Diagram showing the number of publications per author and the relationship between authors in the database of articles with "desmin" in title/abstract in PubMed. The size of each author (circle) is proportional to the number of articles from the database we retrieved from PubMed (September 2021) with 9731 articles containing the word "desmin" in the title or abstract (including "skeletin" and excluding the dermatan sulfate "Desmin 370"), and the thickness of the connecting lines to the number of articles in co-authorship. (A color version of this figure is available in the online journal.)

them to be in an intersection between all groups and to not constitute an independent cluster.

Functions

Since the classification of all 10-nm filaments previously observed in several tissues as intermediate filaments, there has been a tendency to assume that they all have similar functions. The central core of all the IFs proteins, through which they polymerize, is conserved and they can be considered quite similar. However, it should be kept in mind that the head and tail of each of the tissue-specific IFs proteins are different, which must confer different properties to the filaments themselves, which in turn enable them to have different functions.[14] There should be a reason for the cell-type specificity of the IF proteins. Here we used a bibliographic protocol to select articles on desmin to comparatively assess the putative functions. First, based on the EuropePMC search for articles with "desmin" on the Title, we manually assembled a spreadsheet including the abstract of each article that can be made available upon request. The spreadsheet can be used to search and quantify terms in the abstract or authors fields, and spreadsheet cells can be classified according to the desired criteria, such as number of citations or publication year. Using this spreadsheet, we could observe that the impact of articles with "function" or "role" on the abstract is significantly higher than the rest of the papers: the average number of citations of "desmin" + "function" articles is 34.4, while the average number of "desmin" articles is 26.4. This difference could be justified because the scientific community has been emphasizing research focused on mechanisms of action rather than description of cases or observations.[13]

We then used the spreadsheet to further analyze the articles that contained "function" or "role" in their abstract and

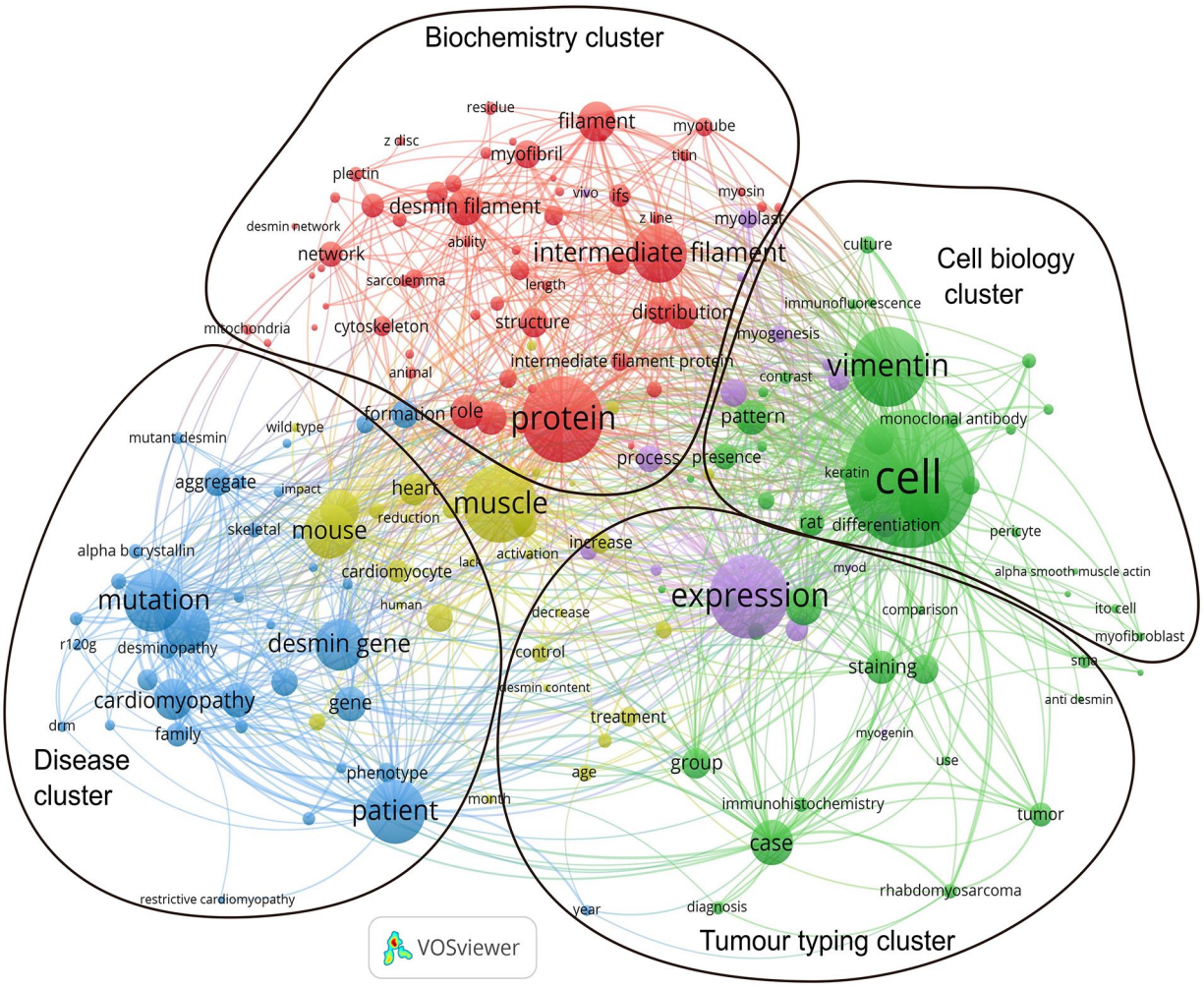

Figure 5. Diagram showing the most frequent words in the database of articles with "desmin" in title/abstract in PubMed and their relationship. The size of each circle is proportional to the frequency of word from the database we retrieved from PubMed (September 2021) with 9731 articles containing the word "desmin" in the title or abstract (including "skeletin" and excluding the dermatan sulfate "Desmin 370"), and the thickness of the connecting lines to their co-occurrence. Clusters are automatically colored. The overlay represents our interpretation of each cluster characteristic. The yellow words in the center interact with words in all other clusters, and therefore are not classified in a separate group. (A color version of this figure is available in the online journal.)

that were not Reviews. We extracted the papers listed on Table 1 among those 164 articles. We classified each article according to: (1) alleged function, (2) conceptual approach (pathological, physiological, or structural), (3) level (subcellular, cellular, or tecidual), (4) model had a genetic modification such as knockouts, mutant (naturally occurring), and variant (experimentally constructed), (5) biological model, and (6) tissue type.

The long list of functions of Table 1 suggests some interpretations.

1. There are important differences among the cell types that express desmin, the three muscle types and endothelial cells. In the table, we can observe that most (61%) of the alleged functions are described only in a single muscle cell type: 45% on cardiac muscle, 34% on skeletal muscle, and only 3% on smooth muscle. Since the muscles are quite different, should we expect that the same desmin molecule performs the same function(s) in the different muscle types? It should be kept in mind that desmin can have several post-translational modifications, related to several circumstances in the cell, but there are no tissue-specific isoforms in the desmin molecule among the various muscle cell types.[85] It is worth mentioning that among several desmin partners, some are tissue-specific, such as cardiac muscle troponin I (TNNI3) and skeletal muscle nebulin (NEB), which could be an indication of tissue-specific desmin functions. Several desmin-interacting molecules have been previously discussed by us[14] and by others, such as Klymkowsky,[86] and can be identified with automated databases such as STRING (https://string-db.org/), and therefore will not be further discussed here. Furthermore, some of the functions that could be attributed to desmin, like mechanical resistance, are in fact attributed to IFs in general, sometimes from observations in other cell types such as epithelia. Our previous bibliographic search method did not analyze articles on IF, but a PubMed search for IF on title/abstract selected 11,052 papers, among them 3329 (30%) containing "function" or "role."

Table 1. List of desmin functions, with the respective articles, classified according to alleged function, conceptual approach, structural level, genetic modification, biological model, and tissue type.

#	Authors	Function	Type	Level	Genetic modification	Biological model	Tissue
1	Alam *et al.*[15]	Regulates mitochondrial fission	Pathological	Mitochondria	Mutant	Mouse	Cardiac muscle
2	Balogh *et al.*[16]	Regulates sarcomere alignment	Structural	Myofibril	KO	Mouse	Cardiac muscle
3	Boriek *et al.*[17]	Regulates stiffness and force production	Structural	Myofibril	KO	Mouse	Skeletal muscle
4	Bouvet *et al.*[18]	Induce toxic aggregates formation	Physiological	Degradation systems	Variant molecule	Rat	Cardiac muscle
5	Cao *et al.*[19]	Regulates intercellular electrical coupling	Physiological	Gap junctions	–	Human/rat	Cardiac muscle
6	Capetanaki *et al.*[20]	Regulates cellular structural and functional integrity	Physiological/ structural	Myofibril	Variant molecule	Mouse	Skeletal, cardiac and smooth muscle
7	Charrier *et al.*[21]	Regulates myoblast stiffness	Physiological	Cell stiffness	–	Mouse	Skeletal muscle
8	Chaurasia *et al.*[22]	Remodeling of chorneal myofibroblasts	Physiological	Myofibroblast	–	Rabbit	Other
9	Chen *et al.*[23]	Regulates mechanoelectric feedback	Physiological	Cell signaling	Variant molecule	Rat	Cardiac muscle
10	Conover *et al.*[24]	Regulates actin microfilament and nebulin size	Pathological	Myofibril	Mutant	Chicken/rat	Skeletal and cardiac muscle
11	Dagvadorj *et al.*[25]	Support respiration	Physiological	Respiratory system	Mutant	Human	Skeletal muscle
12	D'Amati *et al.*[26]	Allows contraction	Physiological	Myofibril	–	Human	Cardiac muscle
13	Datta *et al.*[27]	Prevent cytoskeletal remodeling	Pathological	Heart	–	Rat	Cardiac muscle
14	Di Somma *et al.*[28]	Regulates cardiac function	Physiological	Heart	–	Human	Cardiac muscle
15	Diermeier *et al.*[29]	Regulates stiffness	Pathological	Myofibril	Mutant	Mouse	Skeletal muscle
16	Diguet *et al.*[30]	Regulates mitochondrial function	Physiological	Mitochondria	KO	Mouse	Cardiac muscle
17	Eiber *et al.*[31]	Regulates cellular structural and functional integrity	Physiological/ structural	Neuromuscular junction	KO	Mouse	Skeletal muscle
18	Galata *et al.*[32]	Interferes with laminopathy phenotype severity	Pathological	Nucleus	Variant molecule	Mouse	Cardiac muscle
19	Gard and Lazarides[33]	Regulates myofibril lateral organization	Structural	Myofibril	–	Chicken	Skeletal muscle
20	Gard *et al.*[34]	Prevents cardiac arrhythmogenesis	Physiological	Heart	Variant molecule	Mouse	Cardiac muscle
21	Heckmann *et al.*[35]	Allows contraction	Physiological	Myofibril	KO	Mouse	Cardiac muscle
22	Hijikata *et al.*[36]	Stabilizes the subsarcolemmal cytoskeleton	Structural	Cytoskeleton	–	Rat	Skeletal muscle
23	Hofner *et al.*[37]	Regulates mesodermal differentiation into cardiomyoblast	Physiological	Heart	Variant molecule	Mouse	Cardiac muscle
24	Höllrigl *et al.*[38]	Regulates myoblast fusion, but hampers cardiomyogenesis and blocks smooth muscle development	Physiological/ pathological	Myoblast fusion	KO	Mouse	Cardiac and smooth muscle
25	Huang *et al.*[39]	Regulates myofibril alignment	Pathological	Myofibril	Mutant	Hamster	Cardiac muscle
26	Joanne *et al.*[40]	Interferes with myofibril, mitochondria and autophagy	Physiological	Myofibril	KO	Mouse	Skeletal muscle
27	Kayman *et al.*[41]	Regulates calcium flux in myofibers	Physiological	Calcium homeostasis	KO	Zebrafish	Skeletal muscle
28	Kostareva *et al.*[42]	Interferes with heart remodeling	Pathological	Heart	Mutant	Human	Cardiac muscle
29	Kouloumenta *et al.*[43]	Regulates lysosome positioning	Structural	Lysosome and endoplasmic reticulum	Variant molecule	Yeast/ mouse	Cardiac muscle
30	Lapouge *et al.*[44]	Regulates cytoarchitecture in cardiomyocytes	Structural	Cell adhesion	Variant molecule	Yeast	Cardiac muscle
31	Lazarides[45]	Regulates nuclei positioning	Structural	Nucleus	–	Chicken	Cardiac muscle
32	Li *et al.*[46]	Prevent idiopathic dilated cardiomyopathy	Pathological	Heart	Mutant	Human	Cardiac muscle
33	Liu *et al.*[47]	Impairs proteolytic function if aggregated	Physiological	Degradation systems	Variant molecule	Rat	Cardiac muscle
34	Loufrani *et al.*[48]	Regulates vascular tone and blood flow	Physiological	Arteries	KO	Mouse	Other
35	Loufrani *et al.*[49]	Regulates arteries diameter and flow	Structural	Endothelial cells	KO	Mouse	Other
36	Lovering *et al.*[50]	Regulates muscle tension	Pathological	Myofibril	Mutant/KO	Mouse	Skeletal muscle
37	Mackiewicz *et al.*[51]	Regulates heart contractile function	Physiological	Heart	Variant molecule	Mouse	Cardiac muscle
38	Maloyan *et al.*[52]	Regulates mitochondrial function	Pathological	Mitochondria	Mutant	Mouse	Cardiac muscle
39	Mavroidis *et al.*[53]	Induces Z disk alterations	Pathological	Myofibril	Mutant	Mouse	Cardiac muscle
40	Mermelstein *et al.*[54]	Regulates myoblast cell shape	Physiological	Calcium homeostasis	–	Mouse	Skeletal muscle

(Continued)

Table 1. (Continued)

#	Authors	Function	Type	Level	Genetic modification	Biological model	Tissue
41	Meyer *et al.*[55]	Regulates Z disk stabilization	Structural	Myofibril	–	Theoretical prediction	Skeletal muscle
42	Milner *et al.*[56]	Regulates cellular structural and functional integrity	Physiological/ structural	Myofibril	Variant molecule	Mouse	Skeletal, cardiac and smooth muscle
43	Milner *et al.*[57]	Regulates mitochondrial function and positioning	Physiological/ structural	Mitochondria	KO	Mouse	Skeletal and cardiac muscle
44	Mitsui *et al.*[58]	Regulates contraction	Physiological	Myofibril	–	Rabbit	Skeletal muscle
45	Mohamed *et al.*[59]	Regulates smooth muscle hypertrophy	Physiological	Bronchi	KO	Mouse	Smooth muscle
46	Nag *et al.*[60]	Regulates organelle positioning	Structural	Nucleus	–	Rat	Cardiac muscle
47	Oliveira *et al.*[61]	Regulates decidualization of endometrial cells	Physiological	Nucleus	–	Mouse	Other
48	Otten *et al.*[62]	Regulates intercalated disk maintenance	Pathological	Myofibril	Mutant	Human	Cardiac muscle
49	Panagopoulou *et al.*[63]	Regulates ventricular wall thickness	Physiological	Heart	Variant molecule	Mouse	Cardiac muscle
50	Ralston *et al.*[64]	Regulates nuclei positioning	Structural	Nucleus	KO	Rat	Skeletal muscle
51	Russ and Grandy[65]	Regulates muscular function	Physiological	Muscle	–	Rat	Skeletal muscle
52	Sam *et al.*[66]	Increases vulnerability to mechanical injury	Structural	Myofibril	Variant molecule	Rat	Cardiac muscle
53	Schultheiss *et al.*[67]	Not necessary for myofibril organization	Structural	Myofibril	Variant molecule	Chicken	Skeletal muscle
54	Shah *et al.*[68]	Prevents respiratory problems	Pathological	Respiratory system	Variant molecule	Human	Skeletal muscle
55	Shah *et al.*[69]	Regulates sarcomere arrangement	Structural	Myofibril	KO	Mouse	Skeletal muscle
56	Shah *et al.*[70]	Regulates myofibrillar mobility	Structural	Myofibril	KO	Mouse	Skeletal muscle
57	Shah *et al.*[71]	Regulates nuclei positioning	Structural	Nucleus	KO	Mouse	Skeletal muscle
58	Sheng *et al.*[72]	Regulates blood pressure	Physiological	Myofibril	Variant molecule	Mouse	Cardiac muscle
59	Singh *et al.*[73,a]	Protects muscle from damage	Physiological	Degradation systems	–	–	–
60	Smythe *et al.*[74]	Regulates myoblast proliferation and fusion	Physiological	Myoblast fusion	KO	Mouse	Skeletal muscle
61	Tao and Ip[75]	Regulates myoblast fusion	Physiological	Myoblast fusion	Variant molecule	Chicken/ quail	Smooth muscle
62	Tassin *et al.*[76]	Not necessary for myofibril organization	Pathological	Myofibril	Mutant	Mouse	Skeletal muscle
63	Tokuyasu *et al.*[77]	Regulates myofibril organization	Structural	Myofibril	–	Chicken	Skeletal and cardiac muscle
64	Tolstonog *et al.*[78]	Contributes to genomic integrity	Physiological	Gene expression	–	Mouse	Other
65	Vermeer *et al.*[79]	Regulates cellular structural and functional integrity	Pathological	Mitochondria	Mutant	Human	Cardiac muscle
66	Wang *et al.*[80]	Regulates myofibril assembly	Structural	Myofibril	–	Chicken	Cardiac muscle
67	Wede *et al.*[81]	Regulates tension in micro arteries	Structural	Myofibril	KO	Mouse	Smooth muscle
68	Wieneke *et al.*[82]	Necessary for myofiber activation	Physiological	Myofibril	KO	Mouse	Skeletal muscle
69	Woolstenhulme *et al.*[83]	Regulates force generation	Physiological	Myofibril	–	Human	Skeletal muscle
70	Yamamoto *et al.*[84]	Regulates myosin maturation	Physiological	Myofibril	–	Human	Cardiac muscle

[a]OBS: Although this article is a review, it does propose a new function for desmin.
KO: knockout.

Comparatively, there are 9737 papers with desmin on the title/abstract and among them only 1803 papers (18%) containing "function" or "role." Just to compare, there are 5512 papers with "GFAP" and "function" and 7,427 with "vimentin" and "function" on PubMed.

2. Papers investigate at different levels: some focus on human physiology such as respiration, others focus on a single organ, like the heart, others in general cell behavior, other at subcellular level for instance in myofibrils. It is therefore difficult to compare these results.
3. Several (68%) of the articles rely on genetic modifications of desmin, either engineered or naturally occurring (mutations), assuming that the comparison with normal will highlight the (lack of) functions. Two groups constructed desmin mice knockouts: Capetanaki[20] and Paulin.[87] Desmin KO are viable and have somewhat subtle phenotypes. More recently, a zebrafish knockout model has been created using CRISPR: fish are also viable but with a subtle phenotype of calcium sensitivity.[41] These results contrast the previous results obtained with zebrafish morpholino-based desmin knockdown[88] or with knockins,[89] which

showed a highly damaged phenotype. Some of the alterations could be attributed to the morpholinos because they are known to disturb development. On the contrary, it is not possible to discard putative gene compensations in the CRISPR models because they are checked only for the affected genes: it is not unusual to have divergent results with morpholinos and CRISPR. Several papers study mutants, and many of them actually try to relate the affected part of the molecule with a specific function or phenotype.

4. Several (23%) of the alleged functions actually describe pathological situations, either using naturally occurring mutants or experimentally created modifications. As we mentioned before, in all these cases, the observed pathological alterations could be due to the loss of function of desmin, and their study can contribute to the identification of the desmin function. Alternatively, abnormal processing or mutant molecules could lead to the formation and accumulation of molecular aggregates which are pathological by themselves. Aggregates can be formed by changes in desmin sequence, in patients/mutants, by changes in desmin processing molecules, such as calpain and caspases or by changes in associated proteins, such as the heat-shock protein alphaBcrystallin.[90] It has been shown that some regions of the desmin molecules (which include regions where mutations have been reported) are prone to aggregation. Furthermore, there are already studies on the structural alterations caused by specific mutations.[12]

One interesting type of alteration in muscle development are the electric organs of fish. These muscle-derived organs specialized to produce electric discharges, and they lose their contractile filaments during development. They are related to the Purkinje fibers in the heart of large mammals, which also are muscle-derived cells specialized to conduct electricity, and which also have several desmin isoforms. We could show that the intermediate filaments of electric organs of the electric eel *Electrophorus electricus* are composed of desmin.[91] Desmin was also identified in the electric organs of the ray *Torpedo marmorata*.[92] Recently, proteome analysis of the electric eel confirmed the biochemical identification and demonstrated that there are about 78 phosphorylated variants of desmin in the electric organs.[93] Phosphorylation of IFs has been linked to their disassembly, in the case of the nuclear lamina for instance.[85] Nevertheless, there are several phosphorus binding sites in desmin, and it is probable that phosphorylation could be involved in other activities such as signal transduction. Desmin is also linked to connexin 43, which is important for electrical coupling among cells.[19]

5. Several (40%) of the functions focus on myofibrils. Since the visualization that desmin is distributed around the Z-lines and dense bodies in cultured cells in 1985,[94] it has been suggested that desmin has a role in the organization of myofibrils, particularly during myogenesis. Yet there are several other places where desmin is concentrated. This progressive change in desmin distribution is well illustrated in the zebrafish embryo myogenesis,[95] where it is possible to follow the initial distribution of desmin around the nuclei, then in striations, then accumulated at the myotendinous junction near the somite's septa (a distribution that does not happen in cultured cells, probably because they do not make strong directional adhesions like actual muscle). Moreover, several muscle organelles, such as endoplasmic reticulum, due to the cytoplasm compression during contraction, not only have a periodical distribution but concentrate at regions that are not compressed, such as the Z line. Furthermore, myofibrillogenesis can happen in desmin KO or in cells transfected with truncated desmin.[67]
6. Some of the alleged functions focus on mechanical forces, sometimes relating the IF network to the microfilaments. Boriek points out the desmin is oriented in all dimensions, while actin has only a single orientation (see Figure 1), and therefore, desmin can dissipate energy in all directions.[17] Besides interacting with myofibrils, desmin has been shown to interact with actin. Actually, actin was a contaminant in the initial desmin purification by Lazarides. More recently, the protein nebullete has been shown to link desmin with the actin cytoskeleton.[96] Another mechanical role is regulation of stiffness. Charrier shows that desmin mutations and the amount of functional desmin alters mechanical properties of the cell,[21] and Diermeier studied stiffness in mutant desmin,[29] besides the aforementioned work of Boriek.[17]
7. Seventeen percent of the functions focus on mitochondria and nucleus. While it is quite clear that alterations in desmin changes the distribution and function of mitochondria,[15,30,52,57,79] it should be noted that other cytoskeletal filaments participate on mitochondria positioning, and other organelles such as endoplasmic reticulum also interact with mitochondria. To further complicate the matter, mitochondria are involved in several cellular processes, including respiration, apoptosis, and calcium control. A few papers point to an involvement of desmin on calcium regulation. Again, calcium is involved in several pathways, and in muscle, the regulation of contraction and regulation of protein degradation (through calpain, for example). Desmin has been implicated in the positioning of other organelles: lysosomes and endoplasmic reticulum[43] and particularly nuclei.[45,60,64,71] Desmin filaments are stably associated with the outer nuclear membrane of muscle cells.[97] Recently, the perinuclear region of muscle cells has been characterized as a membraneless organelle, rich in several cytoskeletal proteins, including desmin.[9] The perinuclear distribution of desmin could indicate a role in mechanotransduction.
8. Some of the listed functions correlate desmin to stress conditions. One could argue that the IF system in muscle is not necessary under normal conditions because muscle has a hypertrophied acto-myosin-based mechanical support, and only when the myofibrils are affected for some reason, like in electric

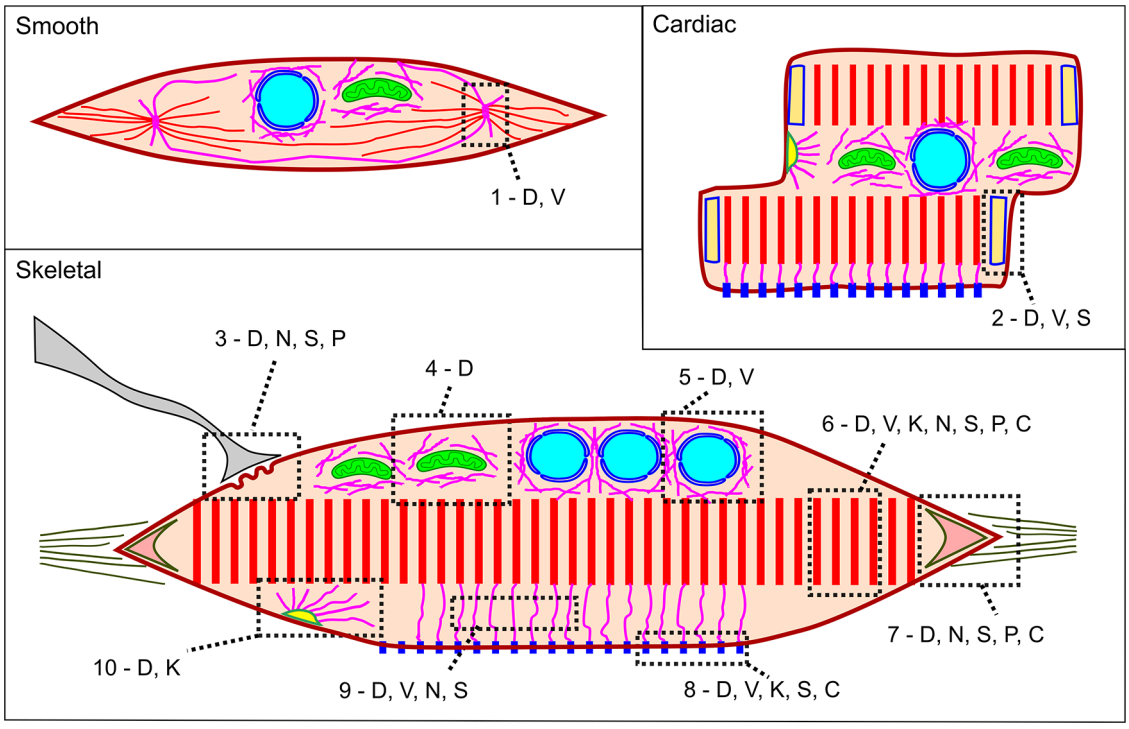

Figure 6. Scheme showing the distribution of intermediate filaments in smooth, cardiac and skeletal muscle: D: desmin, V: vimentin, K: cytokeratin, N: nestin, S: synemin, P: paranemin, C: syncoilin, 1: dense body, 2: intercalated disk, 3: neuromuscular junction, 4: perimitochondrial, 5: perinuclear, 6: sarcomere, 7: myotendinous junction, 8: costamere, 9: cytoplasm, 10: desmosome. We do not depict other regions where IF proteins have been described, such as cytoplasm and sarcolemma because these categories are ambiguous. (A color version of this figure is available in the online journal.)

organ differentiation, or in muscular dystrophies, the function of desmin becomes prominent. Several of the desmin KO features could be explained in this way: only when muscle is stressed, like after repeated contractions, does the difference between KO and wild type appear. Most of the human disease symptoms also appear in older persons, which could be related to the long-term stress of the myofibrillar system. The formation of desmin aggregates has been considered the cause of muscle diseases. However, a recent paper by Singh addressed aggregation as actually an adaptive response to stress.[73] It seems that desmin can involve other cytoskeleton components such as microtubules and gene regulation as stress response.[98] The gene regulatory role of desmin has been confirmed in heart formation through the regulation of the gene Nkx.[99]

It is interesting to compare the alleged functions of desmin to the functions attributed to vimentin, the intermediate filament protein that is highly expressed in the beginning of myogenesis. Besides some functions already mentioned for intermediate filaments in general, vimentin participates in vascular remodeling[100] and epithelial-mesenchymal transition (EMT).[101] Through its linkage to adhesion structures and gene regulation, vimentin is one of the hallmarks of EMT and is related to cancer and cell differentiation.

We show the distribution of intermediate filaments proteins in smooth, cardiac, and skeletal muscle in the scheme in Figure 6. We tried to depict the relative distribution of desmin, vimentin, cytokeratin, nestin, synemin, paranemin, and syncoilin, in previous characterized muscular structures: dense body, intercalated disk, neuromuscular junction, perimitochondrial, perinuclear, sarcomere, myotendinous junction, costamere, cytoplasm, and desmosome. While the only IF protein that has been described in all these structures is desmin, there are a few IF proteins that have been described only in specific cellular regions, such as nestin concentrated in neuromuscular and myotendinous junctions, and cytokeratin concentrated in desmosomes.

Conclusions

It is arguable that the muscular program is quite strong, in the sense that it prevails over other cell differentiation programs in experimental conditions. We showed that the forced expression of the *MyoD* gene in other cell types convert them to muscle.[102] Another sign of the robustness of the muscle gene regulation program is its redundancy, based on the compensatory expression of MyoD and Myf5 in mice knockouts.[103] It is tempting to include in this robustness concept the fact that muscle has an inhibitory differentiation and growth system, based on myostatin, rather than a stimulatory system. Would it be possible that desmin intermediate filaments are part of this "muscle back-up system"? Indeed, experiments such as with the double knockout of desmin and dystrophin[104] are pointing in this direction. They show that desmin can in some ways compensate for the damages of the lack of dystrophin. The function of desmin will probably be understood in the global picture of muscle structure and physiology.

AUTHORS' CONTRIBUTIONS

M.L.C. conceived the work. M.L.C., A.D.J., C.M., G.G., K.A., M.S., and S.A. contributed to the acquisition of data and their analysis. M.L.C. wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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