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MINIREVIEW

Calpain involvement in the remodeling of cytoskeletal anchorage complexes

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Keywords

adhesion; calpain; cytoskeleton; focal complexes; ischemia; muscle

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Cells offer different types of cytoskeletal anchorages: transitory structures such as focal contacts and perennial ones such as the sarcomeric cytoskeleton of muscle cells. The turnover of these structures is controlled with different timing by a family of cysteine proteases activated by calcium, the calpains. The large number of potential substrates present in each of these structures imposes fine tuning of the activity of the proteases to avoid excessive action. This phenomenon is thus guaranteed by various types of regulation, ranging from a relatively high calcium concentration necessary for activation, phosphorylation of substrates or the proteases themselves with either a favorable or inhibitory effect, possible intervention of phospholipids, and the presence of a specific inhibitor and its possible degradation before activation. Finally, formation of multiprotein complexes containing calpains offers a new method of regulation.

Introduction

The importance of cytoskeletal anchorages and their renewal is evident in both physiological and pathological situations. During fast processes, such as cell shape modification, adhesion to extracellular matrix, cell migration, and growth factor-induced signaling pathways, the turnover of anchorage complexes is involved in the rapidity of the response to cell polarization and directional movements. On the other hand, adhesive contacts of muscle cells need stabilization of the cytoskeleton to resist long-term forces induced by acto-myosin interactions. Coupling between actin microfilaments and organized integrin complexes must also include a regulatory mechanism able to disassemble these structures with minimal inertia, thus with a limited number of participants, to ensure convenient timing during motile progression. Calcium-dependent proteolysis is this ubiquitous mechanism, based on

calpain 1 and calpain 2, designed to modulate key aspects of adhesion and migration phenomena, including spreading, membrane protrusion, integrin clustering, and cytoskeleton detachment.

Transitory adhesion complexes

Motile cells (for review see [1]) assemble transient adhesions at the leading edge, called focal complexes [2]. In fibroblasts, focal complexes are highly transient structures and some of them mature into more stable adhesions called focal adhesions (FAs) [3]. FAs are clustered integrins that mediate cell adhesion and signaling in association with numerous proteins (≈ 50) [4], some of which participate in anchorage of actin stress fibers. These structures are the sites of multiple interactions (Fig. 1) of low affinity [5], which may facilitate protein exchange dynamics. FAs have been shown to be motile in stationary cells, whereas the vast majority

Abbreviations

FA, focal adhesion; FAK, focal adhesion kinase; MARCKS, myristoylated alanine-rich C-kinase substrate; MAP, microtubule-associated protein; PKC, protein kinase C.

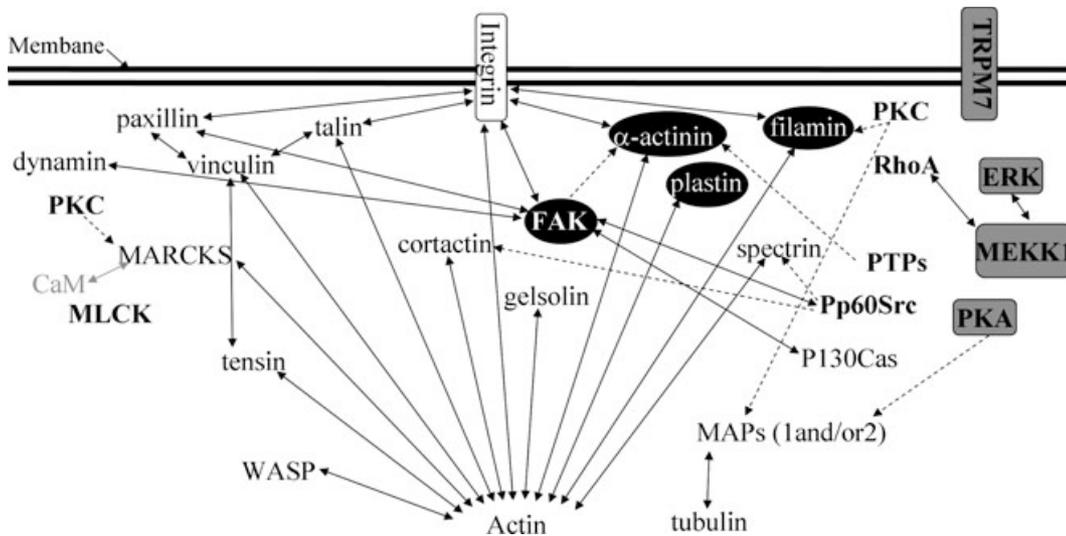


Fig. 1. Schematic representation of the various contacts established by calpain substrates in adhesion structures. Contacts are indicated by double arrows. Proteins with kinase or phosphatase activity are noted in bold; those that have been demonstrated to interact with calpain are circled in black; calpain regulators appear in grey boxes. Phosphorylation (and dephosphorylation) events are indicated by dashed arrows.

of FAs in migrating cells do not move [6], consistent with a role for these sites as traction points (associated with the presence of myosin in stress fibers). As the cell moves forward, FAs are located inside the cell and disappear from the rear.

The formation of FAs obeys a consensus model according to which integrin engagement with extracellular matrix initiates the activation of focal adhesion kinase (FAK), recruited from the cytosol, followed by one of the actin and cytoskeletal proteins. In the past two years, there have been a large number of studies of the regulation of FA dynamics. In particular, from live cell imaging of fluorescently labeled FA components, it appeared that the cytoskeletal protein, talin [7], in addition to kinases and adaptor molecules, including FAK [8], Src, p130CAS, paxillin, extracellular signal-regulated kinase and myosin light-chain kinase (MLCK), are critical for adhesion turnover [9]. Moreover, FAs have been shown to be sensitive (disassembly) to calcium increase [10,11].

Calpain involvement in FA originates with a study showing that inhibitors of calpain are responsible for a decrease in the number of FAs with stabilization of the peripheral contacts [12,13]. These studies were confirmed with calpain null cells (regulatory subunit), which also showed a decreased number of FAs [14]. The calcium-activated protease was in fact first identified in FAs by Beckerle *et al.* [15], with colocalization of talin with the catalytic subunit of calpain. More recently, the mechanism necessary to recruit calpain 2 to peripheral adhesion sites was shown to involve FAK [16].

It now seems clear that calpains not only act on the destabilization of adhesion to the extracellular matrix which is necessary at the rear of the cell to allow migration, but also play an important function in the formation and turnover of adhesion complexes. The importance of these proteases at this particular place is highlighted by the impressive list of potential substrates of calpains found in adhesive structures (Table 1).

Assembly/disassembly of FAs

The importance of FAs in assembly was highlighted by integrin-containing clusters, which are present at the very early stages of cell spreading [17]. These structures, which have been proposed to precede the focal complexes that mature into FAs, were shown to form in a calpain-dependent mechanism and are characterized by the presence of $\beta 3$ integrin subunit and spectrin, both cleaved by calpain [17,18]. The authors suggest that such cleavages could have active roles, such as regulation of the recruitment of other proteins in these clusters and decreasing the tension associated with microfilament contacts to allow better clustering of the integrins [18]. Furthermore, it has been suggested that talin cleavage by calpain may contribute to the effects of the protease on the clustering and activation of integrins [19,20]. The importance of calpain in FA assembly during myoblast fusion has also been proposed [21]. As inhibition of calpains following calpastatin overexpression is responsible for a decrease in

Table 1. Calpain substrates found in adhesion structures (focal adhesion, focal complexes, podosomes or integrin containing clusters).

	Comments	References
Structural proteins of cytoskeleton		
α -Actinin	Difference site of cleavage depending on the isoforms generating cleavage in the COOH terminal	[39,86]
Filamins	For the γ isoform (specific for muscle), cleavage in the hinge 2 region phosphorylation of the filamin C-terminus domain by PKC α protects the ABP against proteolysis	[32]
L-Plastin	The cleavage separates the N-terminal domain from the core of the molecule	Lebart <i>et al.</i> (unpublished)
Vinculin	In platelets, the major fragment is 95 kDa, corresponding to the head of the molecule	[87]
Talin	The cleavage separates the talin N-terminal from the C-terminal domains and unmasks the integrin-binding site	[20]
Paxillin	<i>In vivo</i> proteolysis inhibited by ALLN; Proteolysis inhibited by siRNA of calpain 2	[7,88]
MARCKS	Phosphorylated MARCKS is a good substrate for calpains, The cleavage reveals an actin-binding site	[30,89]
Cortactin	Cleavage by calpain 2 regulates cell migration Phosphorylation increases its sensitivity to calpain	[29,90]
Spectrin	Phosphorylation decreases spectrin sensitivity to calpain <i>in vitro</i> Exclusive presence of the cleaved form in integrin-containing clusters	[18,31]
P130Cas	Cleavage appears <i>in vitro</i>	[91]
Tensin	Cleavage <i>in vitro</i> and inhibition of protein cleavage <i>in vivo</i> by calpain inhibitor	[92]
Gelsolin	Cleavage between the G1-3 and the G4-6; localization in podosomes	C. Roustan (personal communication)
WASP family proteins	WASP (essential component of podosomes) and WAVE are substrates	[93–95]
Signal transduction proteins		
Pp60Src	Possible cleavage by calpain as demonstrated <i>in vivo</i> using calcium ionophore and inhibition of proteolysis using calpeptin as inhibitor	[96]
FAK	<i>In vivo</i> and <i>in vitro</i> cleavage, responsible for the loss of association of FAK with paxillin, vinculin, and p130cas	[88]
PKC	<i>In vitro</i> proteolysis of three isoforms, α , β , γ ; Phosphorylated PKC μ translocates to the membrane where there is a distinction between PKC α and δ and the calpain isoforms (μ versus m) involved in the cleavage	[97–99]
RhoA	Cleavage (<i>in vivo</i> and <i>in vitro</i>) responsible for the creation of a dominant negative form of RhoA; identification of the cleavage site	[100]
PTPs	The phosphorylated form of SHP-1 is protected against proteolysis by calpain PTP-1B is cleaved by calpain in spreading platelets	[101] [102,103]
MLCK	Proposed cleavage by calcium-activated protease depending on the presence of CaM	[104]
Tubulin	Possible cleavage of α tubulin Better action of the protease before microtubule formation	[105] [106]
MAPs	MAP1 and 2 are substrates Phosphorylation of MAP2 protects from calpain 2 cleavage	[106] [107]
Dynamamin	Isoform 1 (synaptic vesicles) would be cleaved	[108]

adhesiveness, the authors propose that, in such situation, the formation of new FAs could be altered. They also observed, as a consequence of calpain inhibition, a marked decrease in myristoylated alanine-rich C-kinase substrate (MARCKS) proteolysis, adding a new substrate to the list of potential calpain substrates (Table 1).

The proposition of calpain participation in the disassembly of FAs is more straightforward and originates with the studies of Huttenlocher *et al.* [12] showing that inhibiting calpain stabilizes peripheral

adhesive complexes. Then, using live cell imaging, Huttenlocher's group further demonstrated that calpain action on the disassembly of adhesive complex sites could be the result of influencing α -actinin–zyxin colocalization [22], as inhibition of calpain disrupts α -actinin localization to zyxin-containing focal contacts. Finally, considering that microtubules promote the disassembly of adhesive contact sites [23], the group analyzed the effect of the protease in the context of nocodazole treatment. They observed that recovery of focal complex turnover after nocodazole wash-out

was inhibited in the presence of calpain inhibitors, suggesting that calpain is required for this mechanism. More recently, another study, also based on live cell imaging, proposed a role for calpain in disassembly of adhesive structures. The very elegant work using a mutant of talin in the calpain cleavage site shows that direct talin proteolysis is the key mechanism by which calpain influences the disassembly of talin from adhesion and by doing so regulates the dynamics of other adhesion components, such as paxillin, vinculin and zyxin [24]. The authors discuss the eventual role of the proteolytic fragment in intracellular signaling. The idea of a calpain fragment having specific functions is very interesting. It underlies the fact that the protease has a very small number of sites in the target molecule with a particular way to generate complete structural domains. In favor of this hypothesis are the results that we have obtained with an actin crosslinking protein, L-plastin, found in FAs and podosomes [25]. We have found that this actin-binding protein is a new substrate of calpain 1 separating the core domain, able to bind actin and the N-terminal domain which supports the protein regulation (calcium and phosphorylation) (unpublished work). As synthetic peptide containing the N-terminal sequence of L-plastin (fused with a penetrating sequence) has been shown to activate integrins [26,27], it is tempting to speculate that the N-terminal domain, being free from the rest of the molecule, has a specific role.

Regulation of cleavage activity

Because the calcium concentration necessary to activate these proteases does not exist normally in the cell, except under pathological conditions, researchers have focused on the idea that other regulatory mechanisms may lower this requirement. They identified phosphorylation and phospholipids as possibly having an important role in adhesion. The latter were proposed after *in vitro* demonstration that certain combinations of phospholipids considerably lower the calcium concentration required for calpain activation [28], but this field of investigation is poorly supported by *in vivo* experiments.

Phosphorylation of the substrates has been shown to regulate both positively and negatively the proteolytic activity of calpain. The first example found in the literature concerns cortactin for which the phosphorylation of several unidentified Tyr residues by pp60Src would accelerate the cleavage by calpain 1 [29]. Similarly, it was recently shown that MARCKS proteolysis by calpain is positively influenced by its phosphorylation [30]. On the other hand, another French group

identified a Tyr residue located in the calpain cleavage site of α II-spectrin as an *in vitro* substrate for Src kinase and further demonstrated that phosphorylation of this residue decreases spectrin sensitivity to calpain *in vitro* [31]. Finally, in our laboratory, Raynaud *et al.* [32] showed that phosphorylation of the filamin C-terminus domain by protein kinase C (PKC) α protected γ -filamin against proteolysis by calpain 1 in COS cells. They further illustrated their idea using myotubes, showing that the stimulation of PKC activity prevents γ -filamin proteolysis by calpain, resulting in an increase in myotube adhesion.

An alternative mode of regulation of protease activity in the adhesive context may involve phosphorylation of calpain itself. Again, both activating and inhibiting roles of calpain phosphorylation have been reported with an isoform-specific action. In particular, this was discovered using different effectors, namely epidermal growth factor and a chemokine (IP-9), both inducing loss of FA plaques [33]. The significant result comes from the fact that when these effectors are used on the same cells, they induce different activation of calpain 1 and 2 [33,34]. In this context, epidermal growth factor was shown to utilize the microtubule-associated protein (MAP) kinase signaling pathway with phosphorylation of calpain 2 by extracellular signal-regulated kinase and activation of the protease in the absence of calcium [34,35]. On the other hand, calpain inactivation can be achieved when calpain 2 is phosphorylated by protein kinase A [36].

Activation of the protease activity, as followed by FAK cleavage and FA disruption, can also be associated with the degradation of the specific inhibitor of calpain, calpastatin. Indeed, Carragher *et al.* [37] have identified a positive feedback loop whereby activation of v-Src promotes calpain 2 synthesis, which in turn promotes calpastatin degradation, further enhancing calpain activity. Moreover, a new way of activating calpain was proposed with the discovery of the presence of an ion channel (TRPM7) in adhesion complexes. This channel may be able to activate calpain 2, although independently of an increase in the global calcium concentration [38].

Finally, one should keep in mind that calpain may interact with a potential target without proteolysis. This introduces the notion of recognition without proteolysis. This concept emerged in our laboratory in 2003, with the discovery that α -actinin could interact *in vitro* with calpain 1 in the absence of any proteolysis [39]. We have observed the same phenomenon with L-plastin (our unpublished data). Moreover, it is now clear that multimeric complexes containing calpain can exist, which is particularly true in the adhesion context

[16,40,41]. These complexes may be an alternative way of recruiting calpain to FAs, thereby positioning the protease at the very place needed for action.

In conclusion, calpains have much to do (and do much) in adhesive structures. Control of their activities is guaranteed by a high calcium concentration associated with a multitude of factors varying from phospholipids to phosphorylation, including phosphorylation of potential substrates (with either a favorable or inhibitory effect) or even phosphorylation of the protease itself. Association with a specific inhibitor, possible control of degradation of the inhibitor, and association with a potential substrate are security measures to avoid anarchic action of the proteases.

Perennial structures

Role of calpain in myofibril disassembly

Muscle cell renewal involves elimination of useless myofibrils before replacement during growth or after tissue damage [42–44]. The role of ubiquitous calpains has been highlighted in the disassembly of sarcomeres upstream of proteasomal degradation [45,46]. Investigations on muscle wasting [47] induced by hindlimb unloading [48], food deprivation [49], or during various pathologies [50] showed cleavage and dissociation of proteins to be essential preliminary steps in sarcomeric cytoskeleton stability. The involvement of calpains 1 and 2 in this muscle damage was clearly demonstrated by overexpressing calpastatin in transgenic mice, which reduced muscle atrophy by 30% during the unloading period [48,51]. On the other hand, calpain 3 (p94), the muscle-specific isoform which is insensitive to calpastatin inhibition and is affected in atrophy processes, should also be considered [52].

Myofibril organization appears as a dense bundle of three classes of filaments (thin, thick and elastic) in the long axis associated with desmin filaments and connecting proteins in the transverse direction [53]. The early dissociation events in which calpains participate [54] pointed to the I–Z–I complex of sarcomeres and the costameric region (Fig. 2A). Sarcolemmal invaginations (transverse tubules) and sarcoplasmic reticulum (terminal cisternae) are closely associated with the I–Z–I structure [53,55] to trigger muscle contractions in a Ca^{2+} -dependent fashion [56]. The first signs of degradation are nebulin disappearance and emergence of a large titin fragment of 1200 kDa, which covers the region I-band to the A–I junction, followed by continuous release of α -actinin (Z-filament) and degradation products from cleavages of desmin, filamin and dystrophin [57,58]. During this early stage, no

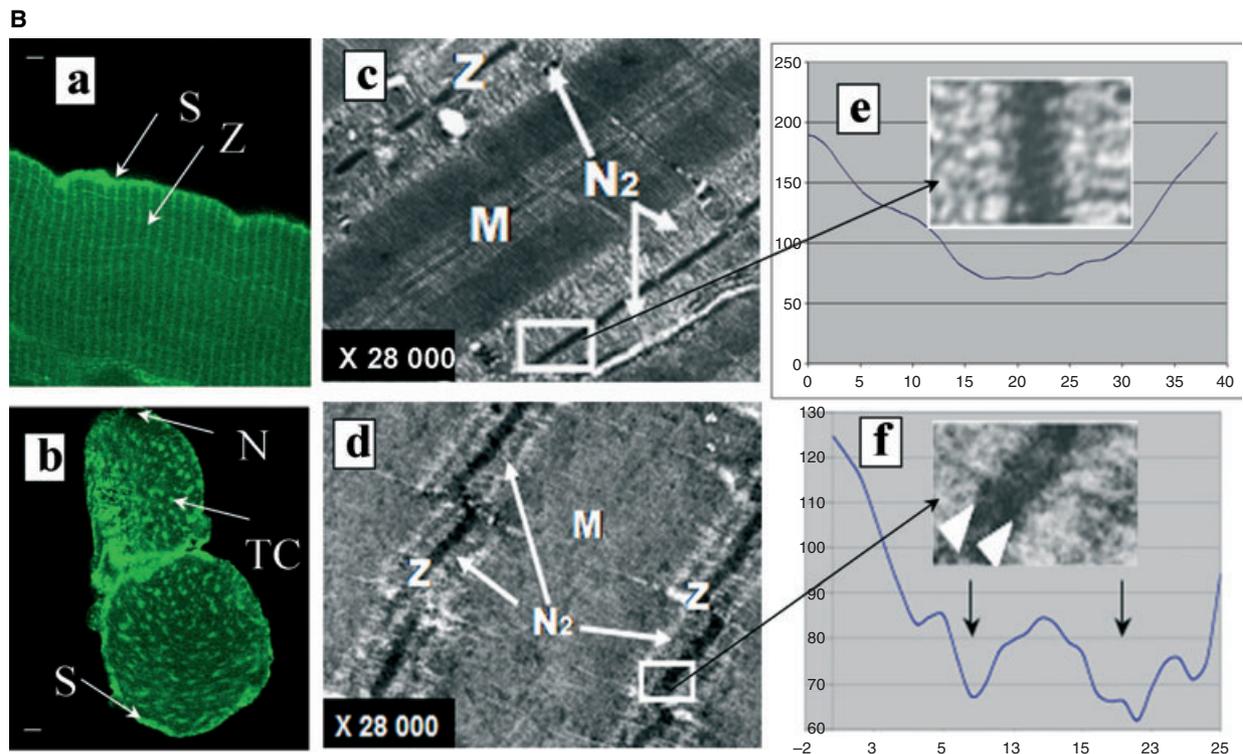
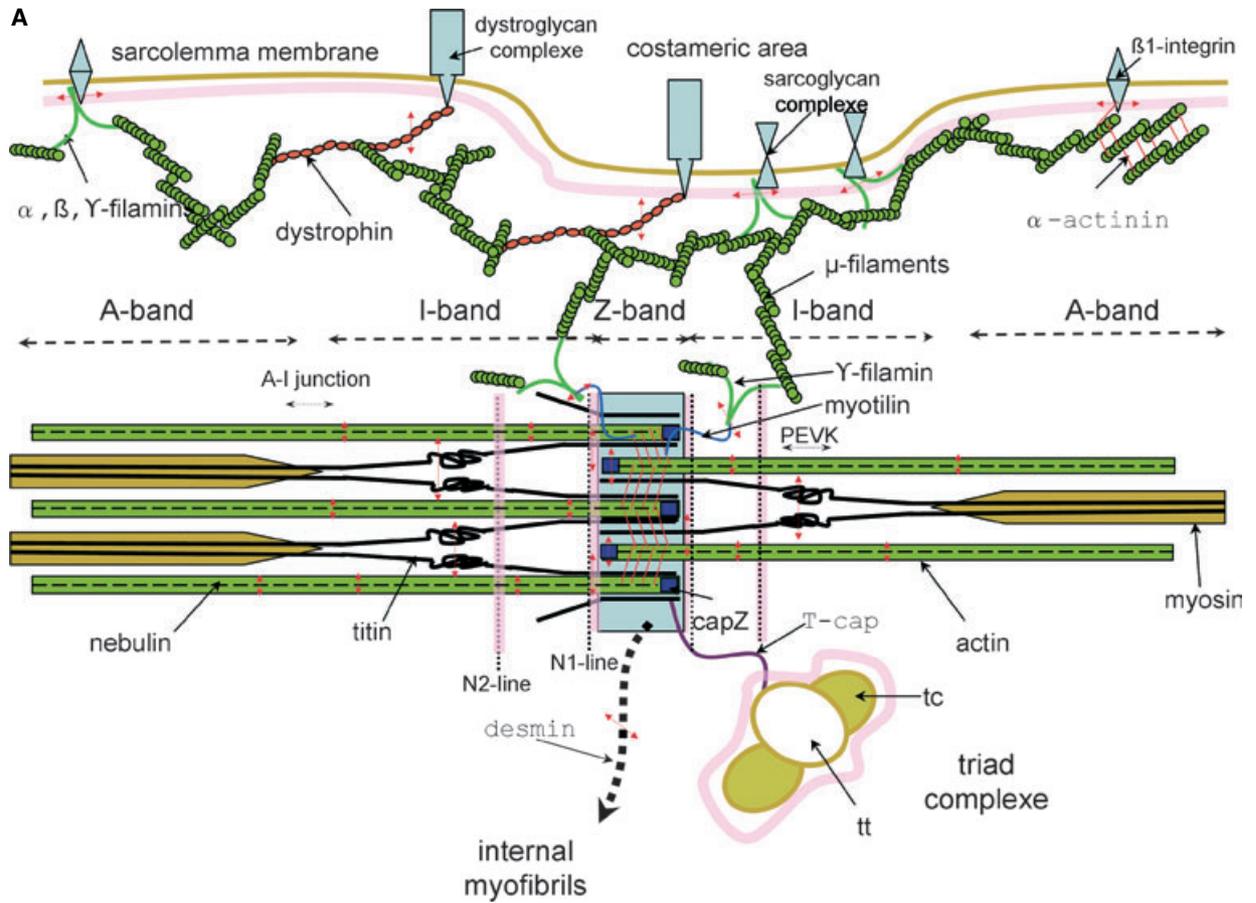
solubilized myosin or its related degradation products are observed. Electron microscopic observations show a decreased density of the I–Z–I region associated with detachment of sarcolemma from the myofibril core [59,60]. The kinetics of these degradations are closely related to muscle type: red versus white muscle [61,62].

Calpain location in the I–Z–I structure

Similar amounts of calpains 1 and 2 were generally found in mammal skeletal muscle, mainly associated with subcellular elements [54,63]. Previous immunolocalizations have shown that the two proteases are essentially concentrated in the myofibrils near the Z-disk and, to a lesser extent, in the I-band [64–66]. Their presence has also been reported under the sarcolemma membrane [43] closer to the cytoskeletal anchorage sites [59], which roughly corresponds to the calpastatin position [66]. Furthermore, calpain 3 was detected in the I-band at the N2-line, in the M-band, and also at the Z-line [67,68]; for more details, see Duguez *et al.* [68a] in this minireview series. Recently [32], calpain 1 was located between the Z-line and N1-line on each side of the Z-disk and in the N2-line vicinity (Fig. 2B). At least three proteins in this region, titin, α -actinin and γ -filamin, are able to bind calpain 1 with increasing affinity in the presence of calcium [32,39,69]. Specific binding sites have been identified in the C-terminal EF-hand part of α -actinin [39], the Z8–15 N-terminal titin region [69], in the titin I-band section near the PEVK region [69], and in the C-terminal region (hinge 2) of γ -filamin [32].

Sequence of I–Z–I disorganization

The role of calpain has been mainly explored during the postmortem stage of progression or on isolated myofibrils [43,58–60]. Analysis of protein cleavage, tissue imaging and the involvement of calpain isoforms have been explored simultaneously [57,59,70]. Muscle ischemia leads, in a few hours in fish white muscle [71] and in 1–2 days in red muscle models, to ATP depletion and Ca^{2+} ion release into the cytosol, followed by a decrease in pH to 5.5, which induces intense myofibril contraction (rigor mortis). Early calcium-dependent proteolysis affects the cytoskeletal anchorages at the costameric junctions, where filamin isoforms and dystrophin are quickly cleaved [57,61,62], as well as desmin filaments [58], leading to dissociation of the myofibril network with loss of register and delamination of the sarcolemmal membrane [59,61]. In contrast with mammalian red muscle [59], Z-disks are quickly dissociated in fish white



muscle with a concomitant release of α -actinin [61,72]. The fact that white muscle represents a simpler organization, with a single sheet of Z-filaments (α -actinin) which connects elastic and thin filaments [73], probably explains the different observations. During rigor mortis in red muscles, myofibril fractures are often observed in the I-band at the N1-line and N2-line close to calpain positions [69]. This was attributed to the intense muscle contraction associated with calpain cleavage. At the end of this calcium-dependent proteolysis process [59,61], myofibrils appear dissociated and fragmented into pieces mainly composed of A-bands with large blank spaces (I-Z-I structures).

Regulation of calpains during I-Z-I disorganization

As in the case of adhesion complexes, Ca^{2+} concentrations above $10\ \mu\text{M}$ are nonphysiological but can be reached during severe ischemia, calcium channel deregulation, or cell membrane injury [56,74]. The intracellular pH, which falls to acidic values in post-mortem conditions, only partially (40%) decreases calpain 1 activity [57]. It has also been shown using p94 knock-out mice that, in these extreme conditions, calpain 3 would not play an active role, in contrast with calpain 1 [75]. On the other hand, lower Ca^{2+} concentrations ($1\text{--}5\ \mu\text{M}$), reached during excessive exercise [42,76] or experimentally applied to skinned fibers [77], induce a loss of the excitation-contraction coupling associated with a decrease in the passive force production related to titin proteolysis [77]. This response can be inhibited by leupeptin, a powerful cysteine protease inhibitor, but not by calpastatin, which neutralizes ubiquitous calpains and not p94 [77]. Thus, damage observed during a Ca^{2+} -rigor period would be a deleterious effect of calpain 3.

The presence of phospholipids in the sarcolemma and reticulum membranes [63,78] or in Z-disks [79] could decrease the Ca^{2+} concentration requirements

for autolysis of calpain 1 to levels found in the rigor state [80]. Such regulation implies release of calpain 1 from its potential inhibitor molecule, calpastatin [81], or cytoskeletal proteins such as titin [69] and γ -filamin [32] which can bind calpains as stable complexes. A recent study [82] has highlighted a possible regulation of the ubiquitous calpain system by p94, which is able to cleave calpastatin and also titin and γ -filamin [68,83] in regions close to calpain 1-binding sites [32,69]. Thus, activation of p94 may lead to the release of calpain 1 from its regulators and phospholipid activation [84]. Validation of such a model would involve identification of p94 in the activation process [47].

Conclusion

A growing body of evidence indicates that the two calpain isoforms perform vital operations in cell motility and tissue renewal. However, this potential is sometimes deviated from the normal physiological benefits to pathological behaviors such as invasive properties of cells [85] or ischemia and genetic diseases which affect calcium homeostasis [50]. Control of calpain activity by treatment with inhibitory drugs may limit the invasive properties of metastasis and tissue injury. Such investigations involve searching for efficient competitive inhibitors of cellular substrates as well as modeling of the domain II active conformation in calpain 1 and calpain 2 to optimize specificities. The concept of a cell-diffusive molecule able to tie up calpains in their inactive conformation, as calpastatin does, would be another option. The numerous possible targets in cells (Table 1), the broad spectrum of the cleaved sequences, and the fact that the two ubiquitous isoforms can substitute for each other in differentiated cells are serious problems. A way of perturbing communication between domains IV and III or maintaining domain I anchorage within domain VI, thus locking the open conformation regardless of the calcium concentration, would be an

Fig. 2. Location of calpain 1 and its targets in the myofibril. (A) Schematic representation of a peripheral myofibril [53] in skeletal muscle (I-Z-I part), representing calpain 1 location (pink area) as well as several of its main targets (red double arrow) assumed to be essential for cell adhesion and membrane stability (β -integrin, dystrophin), thin filament cohesion (nebulin, capZ), myofibril-cytoskeleton linkage (γ -filamin, desmin) and the passive tension in sarcomeres (titin). Connections between myofibrils and the sarcolemma were drawn by using peripheral actin cytoskeleton anchored in a costameric structure. The triad complex including transverse tubule (tt) and terminal cisterna (tc) was located near the Z-line in the interaction with T-cap [55]. Intermediary filaments (desmin) that maintain sarcomere alignment are suggested by a dashed line towards the myofibril core. (B) Immunofluorescent (a,b) and immunoperoxidase (c,d) patterns of calpain 1 in longitudinal (a,c,d) and transverse (b) sections of mouse (a,b) and bovine (c,d) muscle fibers. The Z-line was expanded and scanned for density (e,f) to compare the control muscle strip treated with the secondary peroxidase-labeled antibody alone (c,e) with the one treated with calpain 1 antibody (d,f). Note the increased intensity of the N2-line (d) and the doublet (arrowhead) at the Z-line edges (f). S, sarcolemmal membrane; Z, Z-line; N, nucleus; TC, triad complex; M, M-line; N2, N2-line. Experimental conditions for calpain 1 location were previously described [32,69].

exciting breakthrough in pharmacological investigations.

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