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Minireview

AAA+ proteins and substrate recognition, it all depends on their partner in crime

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Abstract Members of the AAA+ superfamily have been identified in all organisms studied to date. They are involved in a wide range of cellular events. In bacteria, representatives of this superfamily are involved in functions as diverse as transcription and protein degradation and play an important role in the protein quality control network. Often they employ a common mechanism to mediate an ATP-dependent unfolding/disassembly of protein–protein or DNA–protein complexes. In an increasing number of examples it appears that the activities of these AAA+ proteins may be modulated by a group of otherwise unrelated proteins, called adaptor proteins. These usually small proteins specifically modify the substrate recognition of their AAA+ partner protein. The occurrence of such adaptor proteins are widespread; representatives have been identified not only in *Escherichia coli* but also in *Bacillus subtilis*, not to mention yeast and other eukaryotic organisms. Interestingly, from the currently known examples, it appears that the N domain of AAA+ proteins (the most divergent region of the protein within the family) provides a common platform for the recognition of these diverse adaptor proteins. Finally, the use of adaptor proteins to modulate AAA+ activity is, in some cases, an elegant way to redirect the activity of an AAA+ protein towards a particular substrate without necessarily affecting other activities of that AAA+ protein while, in other cases, the adaptor protein triggers a complete switch in AAA+ activity. © 2002 Published by Elsevier Science B.V. on behalf of the Federation of European Biochemical Societies.

Key words: AAA+ superfamily; Adaptor protein; Chaperone; Protease

1. Introduction

In a bacterial cell, several vital cellular processes including cell division [1], cell differentiation [2], and regulation of the heat-shock response [3] are controlled by members of the AAA+ superfamily [4]. Members of this superfamily also include chaperones and regulatory components of proteolytic machines. Consequently, AAA+ proteins play a prominent role in the proper functioning and maintenance of the cell, not only under normal growth conditions but also following stress (for review, see [5]), as they are involved in the removal of misfolded and damaged proteins. In order to maintain a high degree of substrate specificity for a wide range of substrates, AAA+ proteins utilise specific adaptor proteins to extend and regulate their binding repertoire. Following recognition of the substrate, the AAA+ protein, through ATP hydrolysis, drives substrate unfolding, resulting in either the release of an activated/unfolded protein or the translocation of the substrate into the catalytic chamber of the associated peptidase. In this review we shall focus primarily on substrate recognition by bacterial AAA+ proteins involved in the protein quality control network in the cytosol, with a particular emphasis on the role played by adaptor proteins in this process.

2. The AAA+ superfamily: domain structure

The AAA+ superfamily, as strictly defined, encompasses both the Clp/Hsp100 family [6] and the more extensive AAA (ATPases associated with a variety of cellular activities) family [7]. It is, as the name suggests, a diverse protein family in which family members participate in a wide range of important cellular events, ranging from thermotolerance [8,9] to regulation of transcription [3,4,10]. They nevertheless employ a common mechanism to achieve their biological function (i.e. the disassembly of protein–protein or DNA–protein complexes), usually with a high degree of specificity [11]. This superfamily is characterised by a conserved segment of about 220 amino acids, commonly referred to as an AAA domain (or nucleotide binding domain (NBD)), which contains several conserved motifs including those necessary for ATP binding and hydrolysis, the Walker A and Walker B motifs, respectively. In a number of cases, AAA+ proteins also contain specialised domains within a single polypeptide (e.g. FtsH and Lon also contain a peptidase domain, see Fig. 1). The superfamily can be divided into two distinct classes, based solely on the number of AAA domains (or NBDs) present in the protein [6]. Class I proteins (e.g. ClpA, ClpB, ClpC and ClpE) contain two highly conserved NBDs, referred to as AAA-1 (or D1) and AAA-2 (or D2), separated by a linker sequence (or middle region) of variable length. In contrast, class II proteins (e.g. ClpX and HslU(ClpY)) contain only a single NBD (homologous to D2). In most cases AAA+ proteins, regardless of class, also contain an extra domain, usually at the N-terminus, often of undefined function. In contrast to the NDBs, these N domains vary considerably between different AAA+ proteins, although, in some cases,

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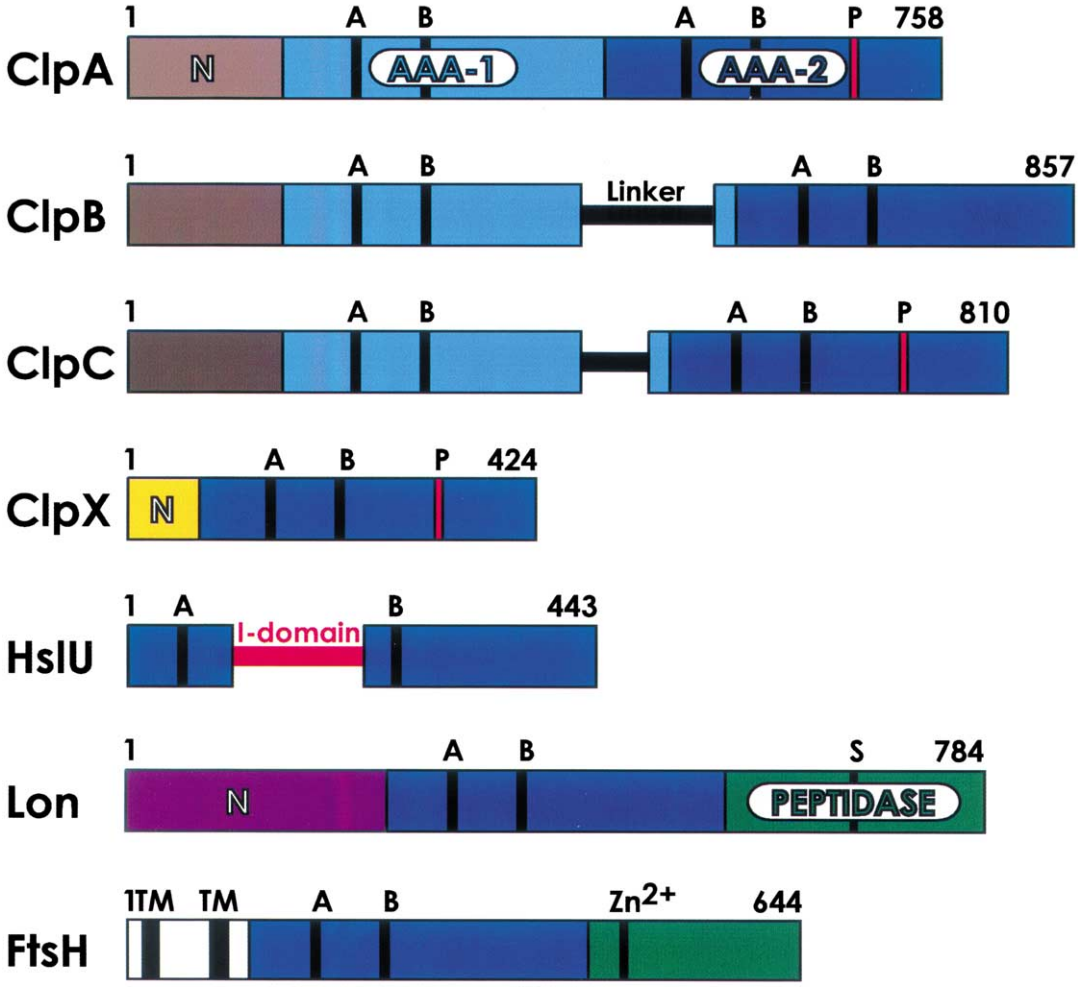

Fig. 1. Structural features of AAA+ proteins. The ATPase domains (AAA-1 and AAA-2), although highly conserved, contain significant differences and hence can be classed accordingly. Both domains contain the Walker A (GX_4GKT) acid and Walker B (HyDE) nucleotide binding motifs, where X = any amino acid and Hy = hydrophobic amino acids. Association of ClpA, ClpC and ClpX with the peptidase ClpP is dependent on the presence of a ClpP recognition motif P ([LIV]-G-[FL]) in AAA-2. In HslU, the AAA domain is interrupted by a specialised domain referred to as the I domain. This domain is proposed to mediate substrate interaction. Similarly, the first AAA domain of ClpB and ClpC is interrupted by a linker of varying length. The function of this region is currently unknown, although as a coiled-coil it is likely to be involved in protein–protein interactions. Interestingly, it is also predicted that the N-terminal domain of Lon contains a coiled-coil structure and mutations in this region affect substrate binding. The N-terminal domains of AAA+ proteins are variable and are in most cases are involved in substrate recognition, whether it be directly or indirectly through the use of adaptor proteins. Lon and the membrane-bound FtsH (TM: transmembrane regions) also contain an additional proteolytic domain. Lon is a serine protease (S: the catalytic residue Ser679), whereas FtsH is a metallo protease (Zn^{2+}: Zn^{2+}-binding motif 417HEAGH421).

this region shares limited sequence homology. For instance, the N domains of ClpA, ClpB and ClpC consist of two weakly homologous repeats each of approximately 75 amino acids [12]. In contrast, ClpX and ClpE contain a Zn-binding site at the N-terminus and HslU, instead of an N-terminal domain, contains an alternative domain, inserted between the Walker A and Walker B motifs of the AAA domain, called an I domain (Fig. 1). The I domain, located at the distal end of HslU in the HslUV complex [13,14] was shown to play an important role in substrate binding [15]. Similarly the N domain is located at the distal end of the AAA+ chaperone, also in an ideal position to interact with and prepare the substrate for refolding or degradation. Currently, however, it is unclear if the N domains of AAA+ proteins are directly or indirectly involved in substrate recognition. For example, the N-terminal Zn-binding region of ClpX was proposed to play a role in chaperone oligomerisation and hence formation of the proteolytic machine, ClpXP [16]. Nevertheless, a mounting body of evidence suggests that the N domain of AAA+ proteins may serve to modulate substrate binding [17,18] not only through direct interaction with the substrate but also through interaction with specific adaptor proteins [19–21].

2.1. *AAA+ and proteolysis: substrate recognition, unfolding and translocation*

Although in some cases the AAA+ protein and the peptidase are located on a single polypeptide (e.g. Lon and FtsH), most bacterial proteolytic machines are composed of two separate components, a regulatory component (e.g. ClpA) and a peptidase (e.g. ClpP). Structural investigations of peptidase components (ClpP [22] and HslV [13,14]) have shown that the access to the catalytic residues located within the peptidase chamber is limited. Therefore, in order to successfully degrade

a protein substrate, the protein must first be unfolded by the AAA+ chaperone in order to pass through the 10 Å pore of the peptidase and enter the catalytic chamber. ClpA has proven to be a useful model system to study mechanistic aspects of AAA+ (Clp/Hsp100) proteins, not only as an ATP-dependent unfoldase but also as the regulatory component of the ClpAP proteolytic machine (reviewed in [23,24]). Likewise, the SsrA-tag, an 11- amino acid peptide (AANDENYALAA) has also proved a valuable tool in studying the mechanisms of several bacterial proteases. In vivo, the SsrA-tag is attached to incomplete proteins synthesised by the ribosome and the resulting tagged proteins can be degraded, in vitro, by several different ATP-dependent proteases, including ClpAP [37]. Together these systems have been used successfully to demonstrate three fundamental steps (substrate recognition, unfolding and translocation into the peptidase) in protein degradation. A series of elegant experiments recently demonstrated that ClpA mediates the global unfolding of protein substrates [25]. By monitoring the fluorescence of GFP, Horwich and colleagues [25] were able to show that ClpA is able to unfold GFP–SsrA. Furthermore, by comparing the hydrogen–deuterium exchange of GFP–SsrA in the presence and absence of ClpA they were able to elucidate that ClpA was responsible for the complete unfolding of the substrate. Subsequently, similar experiments were also used to demonstrate the unfolding activity of ClpX [26].

Using a combination of cryo- and negatively stained electron microscopy, Stevens and colleagues were able to show that translocation of specific substrates through both ClpXP [27] and ClpAP [28] occurs in a stepwise fashion. The directionality of substrate translocation, through ClpA, into the ClpP chamber was elucidated using a combination of time-dependent fluorescent anisotropy and fluorescence resonance energy transfer. By labelling ClpP with a donor fluorophore and different substrates with an acceptor fluorophore it was shown that for SsrA-tagged substrates the C-terminus (where the tag is located) was translocated into the ClpP-chamber before the N-terminus [29]. These data suggested that, at least for some substrates, after unfolding a protein substrate is threaded through ClpA into the catalytic chamber of ClpP in a linear fashion.

3. Adaptor proteins

Adaptor proteins form a novel class of proteins, which, through a variety of means, specifically modulate the binding specificity or chaperone activity of AAA+ proteins. They are unrelated not only in sequence but also in structure [30] (K.Z., B.B. and D.A.D., unpublished results) and vary considerably in size although they are generally small. Adaptor proteins can in many cases assert their effects on their AAA+ partner protein through directly binding to particular substrates, while in some cases substrate binding is only altered after the AAA+/adaptor protein complex is formed. The number of adaptor proteins characterised in bacteria and higher organisms is increasing (Table 1). They are a simple yet effective way to modulate the activity of a chaperone. In this respect, regulation of the adaptor protein itself can be an efficient method to quickly and specifically respond to changing environmental conditions and thereby redirect the activity of the AAA+ protein. In this review we shall concentrate primarily on adaptor proteins involved in protein quality control in the bacterial cytosol while briefly mentioning some well-characterised examples from higher organisms.

3.1. *E. coli* adaptor proteins

Currently only a handful of adaptor proteins have been characterised in *E. coli*. Generally they fall into two categories: those which modulate the kinetics of substrate binding and those which are absolutely required for the recognition and hence the subsequent degradation of specific substrates. ClpX is known to utilise two such adaptor proteins to modulate its activity. The first protein, RssB (also known as SprE or MviA [31,32]) is an example of the latter class of adaptor protein, and is an essential factor for the degradation of the starvation sigma factor (σ^S) by ClpXP [33]. Binding to and,

Table 1
Adaptor proteins and their adaptation of AAA+ function

Organism	Adaptor protein	AAA+	Role	Reference
E. coli				
	ClpS	ClpA	Switches ClpAP-mediated degradation of SsrA-tagged proteins to aggregated proteins in vitro	[19]
	RssB	ClpX	Required for the ClpXP-mediated degradation of σ^S	[31–33]
	SspB	ClpX	Binds to the SsrA-tag enhancing ClpXP-mediated degradation and inhibiting ClpAP-mediated degradation	[34,36]
B. subtilus				
	MecA	ClpC	MecA binds to and mediates ClpCP degradation of Spx and the competence proteins (ComK, ComS)	[2,54]
	YpbH	ClpC	YpbH is necessary for the ClpCP-mediated degradation of Spx	[54]
Higher eukaryotes				
	p47	p97	Essential for the p97-mediated fusion of Golgi and transitional endoplasmic reticulum membranes and the growth of the nuclear envelope	[50,52]
	Ufd1/ Npl4	p97	Required for growth of a closed nuclear envelope, but inhibits Golgi membrane fusion	[21,51]
	UFD2	CDC48	UFD2 is an E4-type ubiquitin ligase and is proposed to link the disassembly of ubiquitinated proteins to their degradation by the proteasome	[55]
	CED-4	MAC-1	Proposed role in regulation of growth or development in young larvae	[52]
	Rnd2	Vsp4-A	The specific target of the complex is unknown; however, it is proposed to play a role in regulation of endocytosis	[53]

consequently, degradation of σ^S by ClpXP only occurs via RssB. RssB, a two-component response regulator, is activated for σ^S degradation by phosphorylation of its receiver domain. The histidine kinase responsible for this phosphorylation has yet to be identified. The second ClpX adaptor protein, the stringent starvation protein B (SspB), recognises a specific sequence in the SsrA-tag [34] added to 'stalled' and unfinished translation products (reviewed in [35]). In contrast to RssB, SspB does not radically change ClpX substrate specificity; rather, it merely alters the kinetics of SsrA-tagged protein degradation [36]. Interestingly, ClpA also utilises an adaptor protein, ClpS, which can modulate the ClpAP-mediated degradation of SsrA-tagged proteins [19]. ClpS was identified as the upstream gene in a putative operon with ClpA. ClpS forms a stable complex with ClpA (also in the presence of the peptidase, ClpP) in an ATP-dependent manner. The binding of ClpS to the N domain of ClpA not only prevents further degradation of SsrA-tagged proteins but also triggers the release of prebound SsrA-tagged substrates. In contrast to other known adaptors, ClpS exhibits dual activity when complexed with ClpA, as it also enhances the recognition of aggregated model substrates [19]. With respect to SsrA-tagged proteins, two adaptor proteins – ClpS together with ClpA and SspB together with ClpX – are able to alter the fate of these substrates. Together these findings resolve long-standing inconsistencies between the in vitro and in vivo effectiveness of both proteolytic machines, ClpAP and ClpXP, towards SsrA-tagged proteins. ClpS blocks the binding of SsrA-tagged proteins to ClpA while SspB, located at the ribosome, efficiently redirects SsrA-tagged proteins to the ClpXP system. Therefore, in vivo, ClpXP is the major protease responsible for the degradation of SsrA-tagged proteins [37].

In *E. coli* adaptor proteins are not only limited to the protein quality control network, they are also involved in other processes such as transcription and DNA replication. Moreover the N domain is not the only site responsible for adaptor protein binding and in the absence of such a domain other sites may be used. For instance, the AAA+ σ^{54} activator, PspF, lacks an N domain, yet it still appears to be regulated by an adaptor protein (PspA) which specifically binds to the AAA domain of the transcription activator, PspF [38,39]. Similarly, the AAA+ protein RuvB, which also lacks an N domain, is regulated by an adaptor protein RuvA through an interaction with a specialised β-hairpin within the AAA domain [40,41].

3.2. *Bacillus subtilis adaptor proteins*

Adaptor proteins are not unique to *E. coli*. In fact, the first characterised adaptor protein, MecA, comes from the gram-positive soil bacterium *B. subtilis*. MecA was identified in a genetic screen for repressors of competence development (natural uptake of DNA) [42,43]. MecA specifically recognises the transcription factor ComK (the master regulator of competence development). In growing cells ComK is an unstable protein that is degraded by the ClpCP machine in a MecA-dependent manner [2]. MecA contains two domains, an N-terminal domain responsible for recognition of the substrate ComK, and a C-terminal domain which binds specifically to the AAA+ protein ClpC [44]. In stationary phase competence develops through a quorum-sensing system, which results in the synthesis of a small protein ComS, which like ComK interacts with MecA [2]. Under these conditions, in the presence of high ComS levels, ComK binding to MecA is inhibited and as a consequence the transcription factor ComK is stabilised. After the quorum-sensing signal is removed, MecA once again binds to ComK, resulting in its specific degradation by the ClpCP/MecA system. This proteolytic control of ComK activity ensures that a previously competent cell can return to its normal physiological state [45,46]. These data suggest that MecA is a specific adaptor protein for competence regulation. However, as homologues of MecA and ClpC are also widespread in other bacterial species which lack ComK homologues, it is tempting to speculate that the role of MecA is not only limited to that of competence development. Nevertheless, it remains to be seen if MecA is responsible for general ClpCP-mediated activities in *B. subtilis*. Interestingly, a homologue of MecA known as YpbH also interacts with ClpC [47]. YpbH, however, is not involved in the control of ComK activity, but is responsible for the recognition of other ClpC substrates (T. Schlothauer and K.T., in preparation). Furthermore, in the forespore compartment of a sporulating *B. subtilis* cell the specific ClpCP-mediated degradation of the sigmaF anti-sigma factor, SpoIIAB, also appears to require an additional factor [48,49].

3.3. *Eukaryotic adaptor proteins*

Adaptor proteins have also been characterised in yeast and other higher organisms (see Table 1). p97 (also known as Cdc48 in yeast and VAT in Archean) is directed towards different cellular tasks through its interaction with various adaptor proteins. The first protein, p47, specifically regulates the ATPase of p97 and is required for p97-mediated membrane fusion [50]. The second adaptor, a binary complex of two proteins (Ufd1 and Npl4), inhibits Golgi membrane fusion [21] and redirects the activity of p97 towards the growth of a closed nuclear envelope [51]. Interestingly, p47 and the Ufd1/Npl4 complex compete for binding to the N-terminal domain of p97 [20,21]. In *Caenorhabditis elegans*, CED-4, a protein involved in the regulation of programmed cell death, was recently shown to bind to the AAA+ protein MAC-1 [52]. MAC-1 also interacts with Apaf-1, the mammalian homologue of CED-4 [52]. Interestingly, although the N-terminal domain alone is sufficient for CED-4 binding, the C-terminal domain of MAC-1 also contributes to CED-4 binding. Furthermore, it was recently shown that Rnd2, a new member of the Rho family with unknown function, specifically interacted with the N-terminal region of the mouse AAA+ protein, Vsp4-A [53]. These proteins are co-localised to the early endosomes and hence a role for Rnd2 in the regulation of endosomal trafficking has been suggested.

4. Concluding remarks

The currently emerging picture suggests that the functional diversity of AAA+ proteins is, in part, due to a diverse protein family collectively known as adaptor proteins. These proteins control the substrate specificity of an increasing number of AAA+ proteins, and only now are we beginning to recognise their importance. Their ability to modify AAA+ substrate affinity or specificity enables the control of specific AAA+ activities by regulation of the adaptor proteins themselves. In this way the cell can elegantly control one activity of a particular AAA+ protein without compromising another activity of that same AAA+ protein. For instance, the modula-

tion of ClpXP activity by two different adaptor proteins, RssB and SspB, is a classic example of such an orchestrated system. These systems are, nevertheless, not only limited to bacteria, as adaptor proteins also play important roles in modulating the activity of a number of AAA+ proteins from higher organisms. Furthermore, it would appear from the limited data available that these adaptor proteins, although divergent in sequence, utilise a common platform (the N domain) for binding to and regulating AAA+ activity. Consistently, structural analysis of several proteolytic machines has revealed that the N-terminal domain is distal to the peptidase binding site and hence in a suitable position to regulate substrate recognition. Nevertheless, it remains to be seen if this role for the N domain of AAA+ proteins, as a platform for adaptor proteins, is generally applicable.

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