Proteome-Wide Analysis of Amino Acid Absence in Composition and Plasticity

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Abstract. Each post-translational modification (PTM) of proteins only modifies one or several limited types of amino acids to ensure regulatory fidelity. Thus proteins without one or several types of amino acids (amino acid absence, AAA) might prohibit some PTMs. We performed a proteome-wide analysis to compute AAA proteins in six eukaryotic organisms. Although most of AAA proteins are generated by random during evolution, there are 1,220 (~10%) AAA proteins conserved in human and mouse, implying the amino acid absence might be important for a small proportion of proteins as an evolutionary mechanism. In addition, five of 25 K-deficient proteins are static keratin-associated proteins, which interact with keratins and play important roles in animal hair organization.

Keywords: post-translational modification, amino acid absence, Keratin-associated proteins, ubiquitination.

1 Introduction

Each protein has a unique and ordered sequence genetically defined by the coding sequence of the DNA, with different numbers and types of twenty amino acids. And the distinct order of a protein primary sequence determines its specific 3D structure and biological function in vivo.

Besides to build 3D structures of proteins as structural elements, most of the twenty amino acids also afford distinctly post-translational modifications (PTMs). Proteins modified by specific PTMs play important roles in regulating the functions and dynamics of proteins, and are involved in numerous cellular processes [1]. One protein could be modified on a single site or multi-sites by one or several competitive PTMs [2]. And even for the same protein sequence, isoforms contain different PTMs will carry out distinct functions. Thus, PTMs of proteins enhance the complexity and molecular diversity of a proteome [3, 4]. To date, there are more than 350 types of

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PTMs discovered (http://abrf.org/index.cfm/dm.home). And totally fifteen amino acids could be modified except five hydrophobic residues (L, I, V, A, and F) [3].

Identification of PTMs sites in proteins is fundamental for understanding regulatory mechanisms of protein dynamics at molecular level. However, only several types of PTMs were well characterized by experimental or computational approaches, e.g., phosphorylation [5-7], glycosylation [8], sumoylation [9], S-palmitoylation [10], acetylation [11], methylation [12], and ubiquitination [13], etc. Most of PTMs are carried out by specific enzymes or spontaneously in vivo. Each PTM only modifies one or several kinds of residues specifically. For example, phosphorylation performed by serine/threonine (S/T) Kinases or Tyrosine (Y) Kinases could modify specific S/T or Y residues of a protein in eukaryotes [5-7]. And O-glycosylation usually occurs on S/T residues [8], while palmitoylation recognizes cysteine (C) residues [10]. Sumoylation, acetylation and ubiquitination could take place on lysines (K) [9, 11, 13]. And methylation commonly modifies arginines and lysines [12].

Since each PTM recognize distinct types of amino acids, in theory, proteins without a specific kind of amino acids may prohibit some PTMs. For example, proteins without K will not be modified by sumoylation and ubiquitination, etc. And proteins lack Y residue will prevent tyrosine phosphorylation. Also, proteins without C might not be modified by S-palmitoylation. Then an interesting question is emerging: How many proteins with at least one type of amino acid absence (AAA) exist in eukaryotes?

To address the problem, we took a proteome-wide analysis of amino acid absence in protein sequences of six eukaryotic organisms, including *S. cerevisiae* (Budding yeast), *S. pombe* (Fission Yeast), *C. elegans* (Nematode), *D. melanogaster* (Fruit Fly), *M. musculus* (Mouse) and *H. sapiens* (human). The phenomena of amino acid absence are much ubiquitous in eukaryotes. There are about 18.5% ~ 25.5% of proteins with at least one type of amino acid absence. In addition, we noticed that many protein sequences still remain fragment status. To avoid the bias, we removed all fragment sequences from six eukaryotic proteomes and re-calculated AAA proteins. Again, there is still about 14.1% ~ 23.4% of six proteomes composed of AAA proteins. The AAA Proteins tend to be shorter sequences with average lengths from 129.2 aa ~ 197.6 aa, while average lengths of total proteins in six organism fluctuate from 401.1 aa to 503.5 aa. Also, amino acid abundances and distributions were calculated and proposed to be negatively correlated with amino acid absences. Furthermore, we detected 1220 AAA proteins conserved in mouse and human. Specifically, there are 25 conserved AAA proteins without Lysine (K) residues. These proteins with diverse functions might not be ubiquitinated and degraded in vivo. Interestingly, five of 25 K-absence proteins are Keratin-associated proteins (KRA24, KRA42, KRA131, KRA71 and KRA81), which interact with keratins to organize the animal hair.

2 Materials and Methods

2.1 Data Preparation of Protein Sequences for Six Organisms

In this work, we focused on analyzing AAA proteins in eukaryotes. Six eukaryotic proteomes were chosen, including *S. cerevisiae* (Budding yeast), *S. pombe* (Fission

Yeast), *C. elegans* (Nematode), *D. melanogaster* (Fruit Fly), *M. musculus* (Mouse) and *H. sapiens* (human).

Protein sequences were retrieved from Sequence Retrieval System (SRS5) at ExPASy website (http://www.expasy.ch/srs5/). The taxonomic code (TaxID) of each organism, e.g., 4932 of *S. cerevisiae* and 9606 of *H. sapiens*, was employed to query protein sequences from Swiss-Prot & TrEMBL database. Totally, there were 68,504, 63,966, 29,117, 23,263, 5,243 and 7,400 proteins obtained from *S. cerevisiae, S. pombe*, *C. elegans*, *D. melanogaster*, *M. musculus* and *H. sapiens*, respectively.

Previously, we found that many proteins remained to be fragment status, and more than 30% of all human proteins were fragment with short sequence [14]. Intuitively, these short, fragment sequences might frequently lack of one or several types amino acids. To avoid the bias, we used the keyword of "fragment" with each TaxID to query fragment proteins in six organisms, respectively. Then fragment sequences were removed, and we re-calculated AAA proteins again. The information of data preparation is shown in Table 1.

Table 1. Fragment protein sequences of several organisms in Swiss-Prot & TrEMBL database. The TaxID of each organism was used to retrieve all protein sequences of these organisms, while the keyword of "fragment" plus the TaxID to retrieve all fragment sequences separately. And the proteome of R.norvegicus (rat) is unintegrated to be removed in our study.

Swiss-Prot & TrEMBL	TaxID	Fragment	Total	Percentile
H.sapiens	9606	23028	68504	33.62%
M.musculus	10090	15662	63966	24.48%
R.norvegicus	10116	3043	14705	20.69%
D.melanogaster	7227	3327	29117	11.43%
C.elegans	6239	508	23263	2.18%
S.pombe	4896	275	5243	5.25%
S.cerevisiae	4932	326	7400	4.41%

2.2 Computational Detection of AAA Proteins

We considered a protein as an AAA protein if at least one type of twenty amino acids was absent from its sequence. By this way, twenty types of AAA proteins in six organisms were computed by PERL language, separately (Table 2).

To avoid the bias, we retained full length proteins to remove all fragment sequences. Again, AAA proteins in fragment and full-length protein sequences were also calculated, respectively. For comparison, percentiles of AAA proteins in all protein sequences and full-length proteins are shown in Fig. 1A. Also, percentiles of AAA proteins in fragment protein sequences are diagramed in Fig.1B.

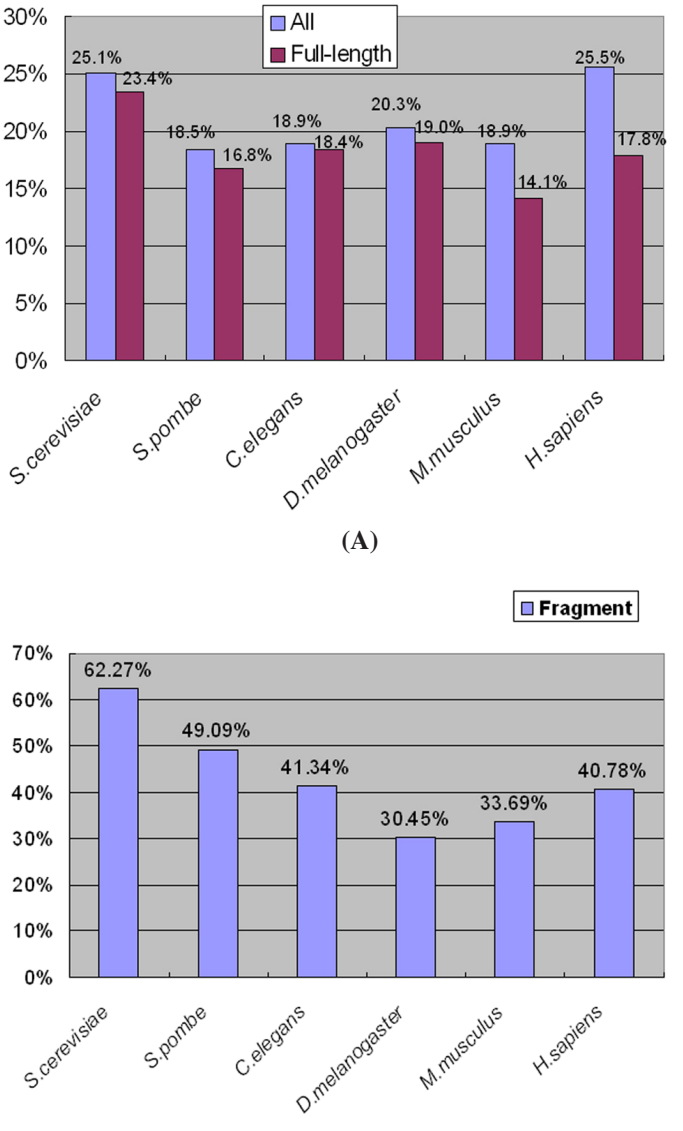


Fig. 1. Percentiles of AAA proteins in six organisms. (A) AAA proteins in all protein sequences vs. full-length proteins; (B) AAA proteins in fragment sequences.

2.3 Identification of the AAA Proteins Conserved between Human and Mouse

To investigate whether and how many AAA proteins are conserved, we chose human and mouse to survey orthologue pairs between two organisms. We downloaded the

Table 2. Twenty types of AAA proteins of all proteins from six organisms. Due to the page limitation, only the numbers of AAA proteins in six organims are shown. SC, S. cerevisiae; SP, S. pombe; CE, C. elegans; DM, D. melanogaster; MM, M. musculus; HS, H. sapiens.

Absent aa	SC	SP	CE	DM	MM	HS
A	98	15	63	90	419	913
C	761	461	1413	1669	3248	5490
D	184	32	193	433	1101	2403
E	145	26	163	353	673	1514
F	70	43	158	450	1262	2821
G	115	31	99	150	437	1003
H	363	130	928	876	2261	4012
I	62	14	100	210	1317	3056
K	55	12	125	265	926	2100
L	14	5	28	56	269	497
M	36	28	83	218	1368	3285
N	76	14	121	334	1515	3274
P	93	37	151	245	624	1268
Q	215	42	182	321	885	1829
R	107	21	153	182	587	1296
S	24	3	37	50	244	679
T	47	8	115	168	503	1314
V	48	10	43	160	561	1080
W	1014	574	2769	3393	6587	8122
Y	176	55	504	977	2629	4788
All AAA proteins	1859	968	4407	5920	12093	17497
Total proteins	7400	5243	23263	29117	63966	68504

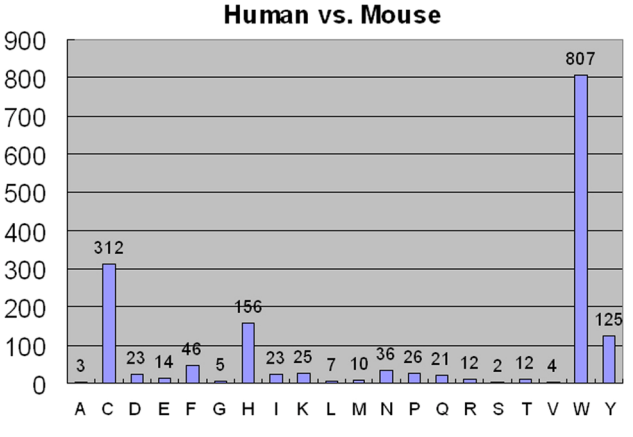


Fig. 2. Totally, there are 1,220 AAA proteins discovered to be conserved in human and mouse

Stand-alone InParanoid Program (ver. 1.0) (http://inparanoid.sbc.su.se/) [15] and computed orthologue pairs between *H. sapiens* and *M. musculus*, with default parameters. Totally, there were 17,733 pairs of orthologs calculated. Then 1,220 AAA proteins were found to be conserved between human and mouse. The information of twenty kinds of 1,220 conserved AAA proteins is shown in Fig. 2.

3 Results and Discussion

3.1 The AAA Proteins Are Ubiquitous in Eukaryotes and Tend to Be Shorter Sequences

In this work, we concerned a series of intriguing problems: Are there any proteins lack of at least one specific type of amino acids (amino acid absence, AAA)? And how many AAA proteins exist in eukaryotes? Are these AAA proteins conserved? And what about their functions are?

To address these questions, we performed a proteome-wide analysis of amino acid absence in protein sequences of six eukaryotic organisms, including *S. cerevisiae* (budding yeast), *S. pombe* (fission Yeast), *C. elegans* (nematode), *D. melanogaster* (fruit Fly), *M. musculus* (mouse) and *H. sapiens* (human). A protein was computed as an AAA protein, if at least one type of twenty amino acids was absent from its sequence. By this simple rule, we calculated twenty types of AAA proteins in six organisms, separately (Table 2).

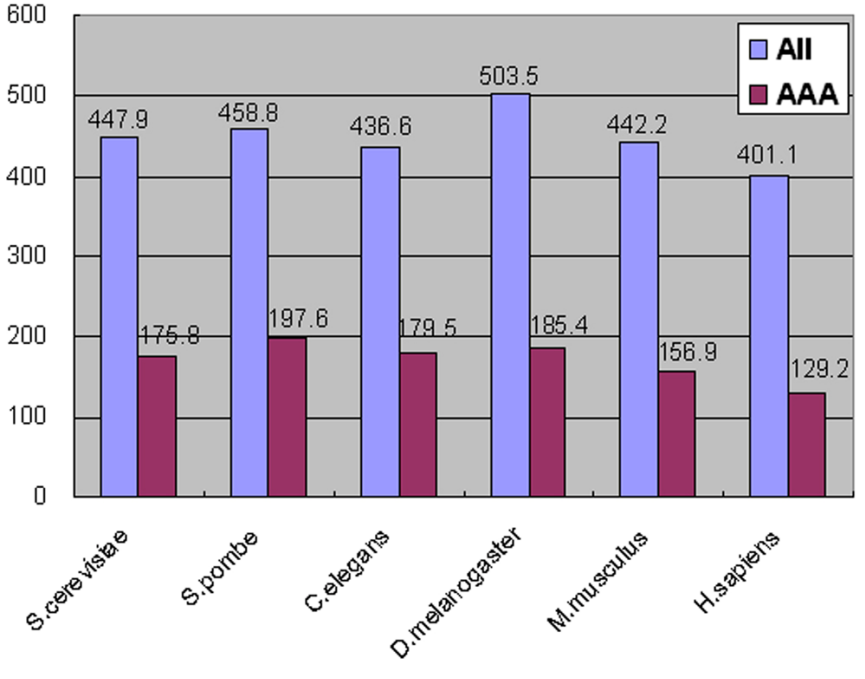


Fig. 3. The average length of AAA proteins is much shorter than the average length of all proteins. All, all proteins in an organism; AAA, AAA proteins in an organism.

Unexpectedly, AAA proteins in eukaryotes are much abundant. There are about 25.12%, 18.46%, 18.94%, 20.33%, 18.91% and 25.54% of proteomes to be AAA proteins in *S. cerevisiae*, *S. pombe*, *C. elegans*, *D. melanogaster*, *M. musculus* and *H. sapien*s. In table 2, W-type AAA proteins are the most abundant, while L- and S-type AAA proteins are much less than other types. We noticed that many proteins were fragment to be short sequence (Table 1), and removed these fragment sequences to obtain the full-length data sets. The AAA proteins in fragment and full-length proteins were also calculated. Obviously, percentiles of AAA proteins in fragment sequences are very high, from 30.45% to 62.27% (Fig. 1B). However, AAA proteins are still much ubiquitous in full length data sets, from 14.1% to 23.4% (Fig. 1A).

Theoretically, shorter proteins will be more frequent to be AAA proteins than longer proteins. Shorter proteins contain fewer amino acids, so one or several types of amino acids may be absent. Indeed, average lengths of AAA proteins in six organisms are much shorter than average length of all proteins (Fig. 3). Average lengths of all proteins in six species fluctuate from 401.1 aa to 503.5 aa, while average lengths of AAA proteins are from 129.2 aa ~ 197.6 aa.

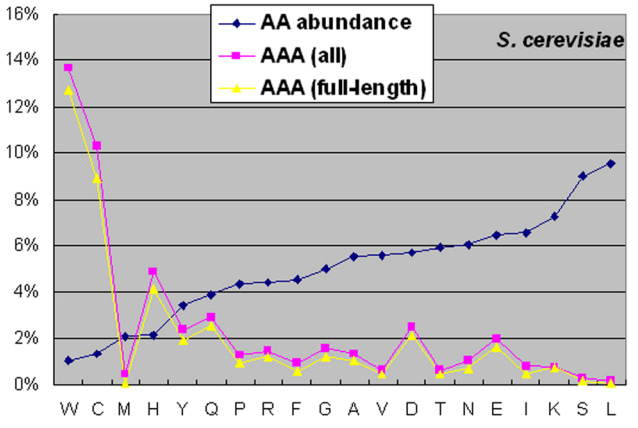
3.2 Amino Acid Absence Is Negatively Correlated with Amino Acid Abundance

To dissect the underlying mechanisms of Amino acids absence, we also calculated amino acid abundances and distributions of twenty types of residues in six organisms. In Fig. 4A and 4B, only results of *S. cerevisiae* and *H. sapiens* are shown.

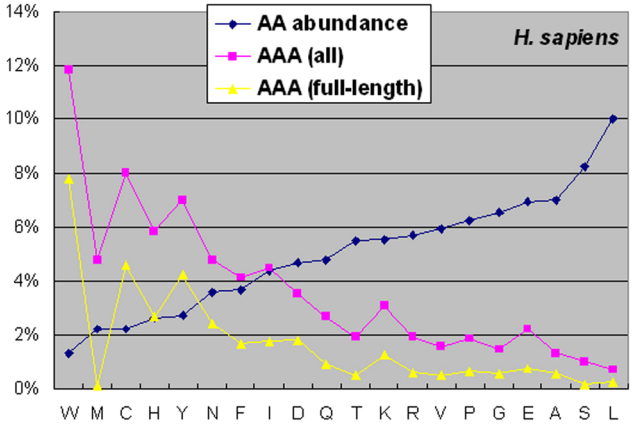
The amino acid absence is negatively correlated with amino acid abundance. And the only exceptional case is methionine (M). The M residue is usually located at the first position for transcription of proteins and coded from the standard genetic code of ATG. So at least, all of eukaryotic proteins should contain one residue at the first position. However, N-terminal M residues are often removed from mature proteins after translation. And many proteins are fragments without N-terminus. Thus, first positions of several proteins in Swiss-Prot & TrEMBL (UniProt) are not annotated as M.

In both *S. cerevisiae* and *H. sapiens*, the most abundant AAA protein is W-type AAA proteins, while its abundance and distribution is much less than other residues. The top two most abundant amino acids are S and L, while S- and L-types AAA proteins are much less than other types. The negative correlations were also found in other organisms (data not shown).

Taken together, we identified two general characteristics of AAA proteins. Eukaryotic AAA proteins tend to be very short sequences and amino acid absence is negatively correlated with amino acid abundance and distribution. Thus, we propose that most of AAA proteins are generated randomly during evolution. If a residue is not much important for a protein, it could be lost from the sequence or replaced by other similar residues, e.g., I to L and R to K, etc. Such mutations of a protein occur on its coded DNA under neutral evolution, and don't alter the function of the protein. And many short proteins lack of one or several types of amino acids might still keep their natural functions. Again, the ubiquity of AAA proteins implies that not all of twenty amino acids are indispensable to form a protein sequence.



(A)



(B)

Fig. 4. The amino acid absence is negatively correlated with the amino acid abundance and distribution. For AAA proteins, both AAA proteins in all proteins and in full-length proteins are counted. (A) *in S. cerevisiae*; (B) in *H. Sapiens*.

3.3 The Conserved AAA Proteins with Important Functions

Based on above analyses, most of AAA proteins are generated by random. However, proteins without one or several types of amino acids may also be important for their normal functions. We recalled that fifteen of the amino acids could be modified by various PTMs. And each PTM recognizes one or several kinds of specific amino acids to ensure the regulatory fidelity. Thus, a protein lack of a specific type of amino acids might prohibit some PTMs, and such mechanisms might be conserved during evolution. For example, sumoylation and ubiquitination usually modify lysine (K) residues in proteins. Thus, proteins without K residues may not be modified by sumoylation and ubiquitination. In addition, if a lysine might be less useful or even potentially

harmful for a protein's function, absence of K-amino acid will be conserved during evolution.

In this study, we considered two organisms of human and mouse to identify conserved AAA proteins. Two mammalian organisms are separated with proper evolutionary distances. So, if one or several types of amino acid absence are potentially important for proteins function, such absent events will be conserved between two organisms. With a popular software of InParanoid (ver 1.0), we identified 17,733 pairs of orthologs conserved in human and mouse. And there were 1,220 conserved AAA proteins identified (Fig. 2). Totally, there were 12,093 and 17,497 AAA proteins identified in mouse and human, respectively. Although fragment sequences were not removed in the process of orthologs detection, we can roughly estimate that ~10% of AAA proteins are conserved in human or mouse.

Table 3. There are 25 K-type AAA proteins conserved between human and mouse

Human	Mouse	Function (UniProt)
R4RL2_HUMAN	R4RL2_MOUSE	Axon regeneration
GDF1_HUMAN	GDF1_MOUSE	Cell differentiation
Q3B7T3_HUMAN	Q9EQG5_MOUSE	Unknown
BBC3_HUMAN	BBC3_MOUSE	Essential mediator of p53- dependent and p53-independent apoptosis
GP1BB_HUMAN	GP1BB_MOUSE	Formation of platelet plugs
KRA24_HUMAN	Q9D3H4_MOUSE	Interacts with hair keratins
Q5JY54_HUMAN	Q9DA47_MOUSE	Unknown
Q6UWH7_HUMAN	Q8BN06_MOUSE	Unknown
KRA42_HUMAN	Q3V4B7_MOUSE	Interacts with hair keratins
NKG7_HUMAN	NKG7_MOUSE	Integral to Membrane
KR131_HUMAN	Q8K198_MOUSE	Interacts with hair keratins
Q86SM2_HUMAN	Q8BUT3_MOUSE	Unknown
CJ035_HUMAN	CJ035_MOUSE	Unknown
Q7Z750_HUMAN	Q6PGA6_MOUSE	Unknown
MYLE_HUMAN	MYLE_MOUSE	Unknown
Q96GZ3_HUMAN	Q8BZE0_MOUSE	Mitotic cell cycle, nervous system development
KRA71_HUMAN	KRA71_MOUSE	Interacts with hair keratins
Q6IQ42_HUMAN	Q8CF51_MOUSE	Unknown
Q96B49_HUMAN	Q9CQN3_MOUSE	Unknown
KRA81_HUMAN	KRA81_MOUSE	Interacts with hair keratins
Q96AN0_HUMAN	Q8VD25_MOUSE	Unknown
Q4ZG53_HUMAN	Q6P220_MOUSE	Unknown
Q8NFP0_HUMAN	Q8K459_MOUSE	Unknown
SARCO_HUMAN	SARCO_MOUSE	Regulation of calcium ion transport
Q8IUH7_HUMAN	Q8CFD2_MOUSE	Unknown

To dissect functions of these conserved AAA proteins, we analyzed functions of twenty types of conserved AAA proteins and presented 25 conserved K-type AAA proteins in Table 3. Analyses for other types of AAA proteins are not shown due to page limitation. For 25 K-types AAA proteins, we obtained their functions from functional annotations of UniProt database, Gene Ontology annotation and literature, etc. These proteins might not be either sumoylated or ubiquinated for degradation. Totally, eleven of them are functional annotated. These AAA proteins play important roles in diverse cellular processes. For example, mouse GDF-1 (growth/differentiation factor 1) regulates left-right patterning in embryonic stem cells at early stages of development [16]. And Bcl-2-binding component 3 (BBC3), also called PUMA, is a pro-apoptotic protein and plays important roles in apoptosis of colon cancer cells [17, 18]. Its gene expression is activated by p53, then replaces p53 from Bcl-xL and leads to p53-dependent apoptosis [19], or dissociates Bax and Bax-xL to cause p53-independent apoptosis [18]. Interestingly, five Keratin-associated proteins (KRA24, KRA42, KRA131, KRA71 and KRA81) are conserved K-type AAA proteins. Keratin-associated proteins (KAPs) comprise a large superfamily, with at least 85 distinct members reported [20]. These KAPs interact with keratins to be the "glue" to hold the hair fiber together. Since the hair is hard to be degraded, it's not strange that many components of hair are hard to be degraded. In this circumstance, the K residue might be less useful for five KAPs. And conservations of five KAPs between human and mouse imply the amino absent mechanism might be also conserved.

4 Conclusions

Intuitively, proteins lack of one or several types (AAA proteins) might be much scarce, since each type of amino acid is important for a protein's function. However, our results propose that AAA proteins ubiquitously exist in eukaryotes. There are about 18.5% ~ 25.5% of proteomes in six organisms to be AAA proteins. After fragment removed, proportions of AAA protein in full-length proteins are still much high, from 14.1% ~ 23.4%. Given evidences that AAA proteins tend to be shorter sequences and amino acid absence is negatively correlated with amino acid abundance and distribution, we propose that most of AAA proteins are generated by random during evolution. However, if one type of amino acid is less useful or even harmful for a protein's function, then the amino acid absent mechanism will be conserved. Indeed, we identified 1,220 AAA proteins (~10%) to be conserved in human and mouse. These proteins play important roles in diverse functions and processes. Among 25 K-types AAA proteins, there are five Keratin-associated proteins (KRA24, KRA42, KRA131, KRA71 and KRA81) to interact with hair keratins and hold hair fibers together. The ubiquitination and degradation of these proteins are potentially not useful or even harmful for these proteins. And the K-residue absent mechanism might be conserved in these proteins.

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