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A Bioinformatics Search for Potential High-Fidelity Autophagy-Associated Atg8-Interacting Motifs within Arabidopsis Proteins for Better Understanding of their Function in Plants

Qingjun Xie* and Gad Galili
Department of Plant and Environmental Science, Weizmann Institute of Science, Rehovot, 76100 Israel.

Editorial

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***For Correspondence**

Qingjun Xie, Department of Plant and Environmental Science, Weizmann Institute of Science, Rehovot, 76100 Israel, Tel: 972-8-934-211

E-mail: qingjun.xie@weizmann.ac.il

INTRODUCTION

Autophagy is an evolutionary conserved mechanism underlying the degradation of proteins and/or metabolites. Advanced researches have shown that the Autophagy associated gene 8 (Atg8) proteins play key regulatory roles in the operation of the autophagy system. In general, proteins that are associated autophagy tend to bind to Atg8 through the presence of functional Atg8-interacting motifs (AIMs) within their protein sequences. To date, numerous AIMs have been identified from multiple proteins derived from multiple organisms. However, little is known about the evolutionary fate of the AIMs present in these proteins. Here, we show and discuss the correlation between the amount of AIMs and the size of proteins that contain AIMs, which may shed new lights on the correlation between protein size and the potential participation of autophagy in the homeostasis of these proteins.

Macroautophagy (hereafter referred to as autophagy) is a highly conserved biological process in eukaryotes, which mainly functions in the degradation of proteins (or metabolites) in two types of lytic compartments, namely, the lysosome in non-plant organisms and the vacuole in plants [1-3]. As one of the core proteins of the autophagy machinery, Atg8 binds to specific Atg8-interacting motifs (AIMs) present in target proteins that possess AIMs [4]. The core AIM motif is comprised of four F/W/Y-X-X-L/I/V amino acids, in which X represents any amino acid, while AIMs can also defined as comprising of an extended six amino acids X-X-F/W/Y-X-X-L/I/V motifs in which X represents any amino acid [5].

Based on the degenerate consensus amino acid sequences of AIMs, it is quite convenient to screen potential Atg8-interacting proteins by bioinformatics approaches. Recently, such kinds of methods have been developed, such as the “canonical AIM” and “iLIR” systems [6,7]. Both systems are attempted to identify potentially functional AIMs, which could be later proven by a more dedicated research. However, there are still numerous biological noises interrupting such identifications, eventually making it more difficult to identify AIMs at a genome-wide scale. Notably, structural analyses suggested a striking bias towards negatively charged amino acids present within or upstream the core AIM [8-10]. Therefore, it is quite interesting to consider the contributions of the acidic amino acid Asp (D) and Glu (E), and potentially also Ser (S) and Thr (T), whose potential phosphorylation may generate negative charges.

Taking into account the complexity of the prediction of AIMs, we re-defined the prediction of the AIMs by taking into account the specific frequency of acidic amino acids in the experimentally verified functional AIMs (unpublished). Such kinds of regular patterns, hereafter refers as an high fidelity AIM system (hfAIM) , are comprised of seven specific amino acids, which apparently improve the fidelity of the AIM in term of the efficiency of binding of Atg8 to this AIM (unpublished). Moreover, this hfAIM system thus enables the genome-wide screening of AIMs in various organisms, and the identification of the corresponding AIM-containing proteins.

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Subsequently, we were particularly interested in the evolutionary fate of the AIMs. To address this issue, we employed the hfAIM system to identify AIM sequences in the entire Arabidopsis (Arabidopsis thaliana) proteome, and then used bioinformatics to elucidate the potential correlation of the number of given AIMs within proteins and the sizes of proteins. Our results indicated that less than 10% of the total Arabidopsis proteins having sizes of up to 100 amino acids possess 1 AIM (Figure 1), suggesting that the steady state levels of such small proteins are generally not regulated by autophagy, but rather by other mechanisms, such as the ubiquitin proteasome system. In addition, proteins whose sizes progress from 100 amino acids up to >2,000 amino acids possess gradually increasing numbers of AIMs with the most large proteins with sizes up to >2000 amino acids possessing up to four AIMs and a minor part even more than four AIMs (Figure 1).

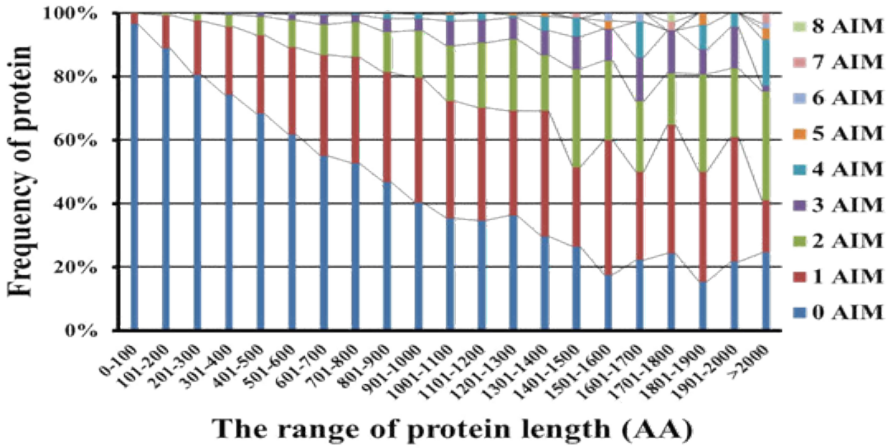

Figure 1: Co-relation between the appearance of AIMs and the protein size. The AIM-Containing Proteins (ACPs) were identified by our hfAIM analysis (unpublished), and the size of ACPs were clustered as indicated in the graph.

These results imply that the small motifs of the AIMs allows their progressing increase in numbers within proteins having progressing increase in sizes, apparently not severely influencing protein structures and functions, but apparently efficiently directing these large proteins for degradation by the powerful autophagy machinery when needed. In general, the largest proteins (>2000 amino acids) are expected to possess more than four AIMs. However, only a small group of these proteins contain more than four AIMs. These findings imply that the presence of AIMs is apparently strictly restrained rather than spontaneously distributed. Therefore, we hypothesized that there might be several possibilities. First, the proteins destined to turned over by autophagy still have to maintain their own functional domains, and hence limit the presence of AIMs in the given size. Second, too much AIMs may accelerate the degradation of the corresponding proteins by enhancing the binding efficiency of Atg8 to these proteins, and then disrupt the regular expression pattern (or function) of the proteins. Third, a part of functional AIMs are missing in the hfAIM analysis. The former two assumptions will be quite interesting concerns for the future research. In respect to the latter one, it is no doubt that much more experimentally verified AIMs benefit the generation of a higher fidelity prediction model.

In plants, autophagy coordinates divergent mechanisms to regulate the homeostasis of proteins, organelles (particularly plastids) as well as metabolism under both favor conditions and in response to stresses [11-14]. To further uncover the role of autophagy in such multiple processes, it will be especially important and interesting to decipher (i) functional AIMs in various proteins derived from various organisms; (ii) the functions of these AIMs

In term of influencing the stability of the protein containing them in response to various cues; and (ii) the types of proteins that contain AIMs and accordingly their functions and the influence of autophagy on their stability. This may aid in answering important biological questions in term of the inter-relationships between protein stability and functions.

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