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SUMMARY The modification of protein by arginine catalyzed by arginyltransferases (ATE1) described by the Kashina group in this issue shows that arginylation of protein occurs widely in biology and is being recognized as a key regulatory reaction like phosphorylation of proteins (Wang et al., 2011).

Everyone in biological sciences knows how important protein phosphorylation is for the biological function. Protein phosphorylation is involved in wide varieties of crucial biological reactions including action of epinephrine (Sutherland, 1972), and various metabolic processes (Krebs, 1997) as well as numerous signaling events that use attachment or hydrolysis of phosphate group as their basic currency. The recent publications from the Kashina group represented by the paper in this issue (Wang et al, 2011) on the protein modification by arginine are reminiscent of the early days of protein phosphorylation when the importance of the phosphorylation was increasingly recognized. The arginylation is catalyzed by arginyl-tRNA-protein transferase (ATE1) (Kaji et al., 1963). Protein modification by aminoacyl tRNA is not limited to the eukaryotes but is also found in the prokaryotes and the crystal structure of the enzyme responsible for the reaction has been determined. There are number of reasons to believe that the protein arginylation is as important as the well-known protein phosphorylation, and below we will outline some of the similarities and parallels between these two different posttranslational modifications.

First, the arginine acceptor proteins are numerous as authors show by exposing *Ate1*-/- cell extracts to ATE1 enzymes and analyzing arginylated protein mixture by SDS-PAGE in combination with autoradiography. These studies show that over 100 proteins are modified by ATE1. In fact, earlier report identified 43 proteins arginylated in vivo (Wong et al., 2007; Xu et al., 2009) and the new study now adds to those findings. Drawing the parallel with

phosphorylation, it is now well established that most of proteins can be phosphorylated though not all the physiological significance of the phosphorylation is known. Second, protein arginylation is an essential reaction for life just like protein phosphorylation is. For example, without ATE1, embryo cannot survive (Kwon et al., 2002). Third, the arginylation of β-actin regulates actin cytoskeleton and consequently the cell motility (Karakozova et al., 2006). This immediately leads to the speculation that arginylation may be involved in the tumor metastasis. In fact, preliminary finding from Kashina's lab suggests this possibility. In protein phosphorylation field, examples of involvement of phosphorylation in tumor development are well documented (for example, phosphorylation of eIF4E (Graff et al., 1995)). Fourth, the translation machinery might be the target for arginylation, as shown in this paper as well as in other paper from the Kashina group (Wong et al., 2007). On the other hand, it is well known that phosphorylation of translational factors plays an important role in the regulation of protein synthesis. Fifth, arginylation is involved in the aging as suggested by the change of the ATE1 expression level depending on how many times normal human cells divided in culture *in vitro* (Kaji et al., 1980). In parallel, protein phosphorylation is closely related to aging and life span (Steffen et al., 2008). Sixth, the similarities between roles of protein phosphorylation and arginylation extend to cognition and brain research as both process were found to play roles in brain physiology (Lamon et al., 1980). Seventh, as shown in Wang et al in this issue, ATE1 may change its specificity depending on the presence of yet unknown cofactors. This reminds the readers of cofactors of protein kinases, which activity might be regulated by different cofactors and binding partners. Eighth, the site of arginylation is not limited to the amino-terminal as originally suggested, but recent results show that the arginylation takes place at various positions in the protein chain. Similarly, the sites of phosphorylation are at various residues such as serine, threonine, tyrosine and histidine. Ninth, intracellular distribution of two processes seems analogous with both arginylation and phosphorylation occurring in the cytoplasm as well as in the nucleus. For arginylation this was suggested in the current paper as well as in a previous publication (Kaji, 1976). Finally, in this paper, the authors showed that ATE1 has isoforms again in striking resemblance to the physiologically important protein kinase isoforms.

Thus, arginylation by ATE1, once thought to play a simple role in protein degradation is now emerging as the major reaction playing crucial role in biology and medicine (Figure 1). Future studies are now needed to extend our understanding of the arginylation process and expand our appreciation of its importance.

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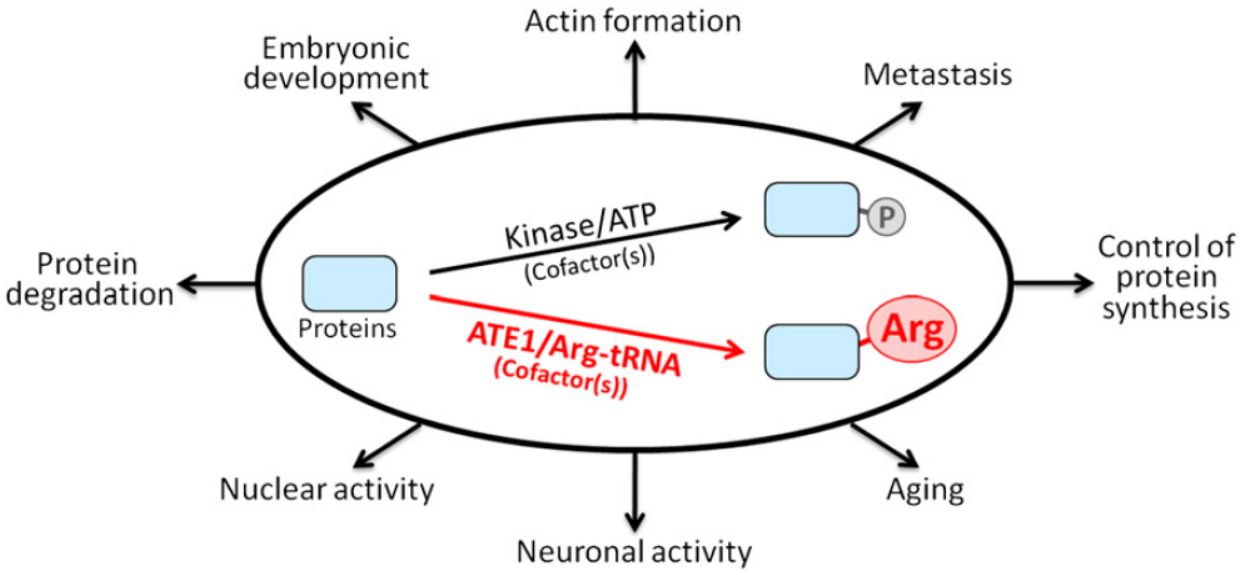

Figure 1. Multiple Regulation by Protein Arginylation or/and Phosphorylation
Arginylation of protein controls multiple biological reactions as much as protein phophorylation does.