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CK2 as anti-stress factor

Masahiko Watabe and Toshio Nakaki*
Department of Pharmacology; Teikyo University School of Medicine; Tokyo, Japan

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Misfolded proteins are prone to form aggregates, which interfere with normal cellular functions. In general, the ubiquitin-proteasome system degrades such misfolded proteins to avoid aggregation. If this system becomes impaired or overloaded, an inclusion-body-like organelle, aggresome will operate. Misfolded protein aggregates are transported to aggresome with a deacetylase HDAC6 and dynein motors along the microtubule network, and are then removed by autophagic degradation. Although it is well known that the aggresome has evolved to cope with an excess of protein aggregates, the mechanisms underlying its formation remain unclear. It is now established that the protein kinase CK2 is a crucial factor in aggresome assembly and clearance. In particular, this kinase phosphorylates HDAC6 on serine 458 in response to cellular stress which is caused by misfolded proteins. The resultant increase in HDAC6 deacetylase activity is crucial for both the recruitment of misfolded proteins to the aggresome and its clearance. Interestingly, serine 458 is conserved only in higher primates such as the humans and chimpanzee, but not in the mouse, rat, dog, bovine or rhesus macaque. This regulatory mechanism by phosphorylation of the serine residue may have evolutional significance.

Keywords: CK2, histone deacetylase 6 (HDAC6), aggresome, dynein, misfolded protein, higher primate, deacetylation

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*Correspondence to: Toshio Nakaki;
Email: nakaki@med.teikyo-u.ac.jp

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Misfolded proteins are bad news for cells, because they can easily form aggregates that interfere with normal cellular function.[1] Therefore, they are closely monitored, processed and degraded to prevent their accumulation in cells. In particular, such accumulation is carefully avoided by degradation of misfolded proteins via the proteasome.[2] However, when misfolded protein aggregates are not degraded efficiently by proteasome machinery, their efficient disposal is essential for cell survival, because misfolded protein aggregates are toxic.[3]

Protein folding is the process by which a linear polymer of amino acids is converted to a unique three-dimensional structure comprising a functional protein molecule. However, the failure to correctly translocate and integrate such proteins results in the formation of misfolded proteins.

The discovery of the aggresome provides an important clue to elucidating the pathway that is responsible for the clearance of misfolded protein aggregates. Several studies have shown that such proteins are actively transported, via a process involving the deacetylase HDAC6 and the molecular motor dynein, along microtubules to the centrosome, which is a perinuclear microtubule-organizing center.[3-6] The recruitment to the centrosome is performed to facilitate the clearance of these misfolded proteins.[7] When high levels of protein aggregates are recruited to the centrosome, they are organized as electron-dense particles in a central core. A cage of cytoskeletal elements, which made of intermediate filaments such as vimentin, encloses the central core, thereby forming an enlarged centrosomal structure known as an aggresome.[3-5] After formation, the aggresome is later removed by autophagic degradation.[8-10]

Aggresomes have an important clinical aspect, because they are similar to the cytoplasmic inclusion bodies commonly observed in many neurodegenerative diseases. Aggresomes and Lewy bodies, which are the hallmark cytoplasmic inclusion

bodies found in neurons affected by Parkinson disease, share indistinguishably biochemical and morphological characteristics.[11] Therefore, the knowledge of aggresomes is critical to understanding both misfolded protein-induced stress response and the pathogenesis of neurodegenerative disease. Although it is well known that the aggresome has evolved to cope with an excess of protein aggregates, little has been known about the regulatory mechanism underlying aggresome formation.

A few recent papers have drawn the attention to HDAC6 modification by phosphorylation. The phosphorylation at serine 22[12] and threonine 30[13] in HDAC6 has been reported by the large-scale characterization of nuclear phosphoproteins and the global proteomic profiling of phosphopeptides, but the role of phosphorylation in these sites remains unclear. The phosphorylation of tyrosine 570 in deacetylase domain 2 of HDAC6 by EGF receptor results in reduced deacetylase activity.[14] EGF receptor is implicated in the regulation of crucial cellular functions ranging from cell growth, proliferation, and differentiation to cell survival.[15] However, the phosphorylation of HDAC6 by EGF receptor induces the inactivation of deacetylase activity. Since the inactivation of HDAC6 inhibits the recruitment of misfolded proteins to the aggresome,[16] the significance of EGF-mediated phosphorylation remained unclear.

A recent observation indicates the protein kinase CK2 as a crucial factor in aggresome assembly and clearance.[17] This kinase provides a linker that facilitates the interaction between HDAC6 and dynein. Furthermore, in response to cellular stress caused by misfolded proteins, CK2 phosphorylates HDAC6 on serine 458. The resultant increase in HDAC6 deacetylase activity is crucial for both the recruitment of misfolded proteins to the aggresome and its clearance by autophagic degradation. CK2 thus has an important role in maintaining cell viability in times of increased stress from misfolded protein aggregates.

The identified Ser458 as the CK2-mediated phosphorylation site of HDAC6 is conserved only in higher primates such as human and chimpanzee, and not in mouse, rat, dog, bovine or rhesus macaqu.[17] This information is very interesting in terms of the evolutional process. Since the phosphorylation of Ser458 plays an important role in the activation of HDAC6 deacetylase activity,[16,17] this regulatory mechanism by phosphorylation could be one of most important events for cell survival existing only in higher primate.

The tetradecapeptide repeat domain (SE14) of human HDAC6, which is involved in cytoplasmic retention, is not present in C. elegans, Drosophila, mouse or rat.[18] We found in published databases that SE14 is present in both chimpanzee and rhesus macaque but not in dog or bovine. Therefore, SE14 has a specific structure for primate animals. However, the newly identified Ser458-mediated regulatory mechanism of HDAC6 deacetylase activity exists only in higher primates such as human and chimpanzee and not in rhesus macaque. This indicates that the Ser458-mediated regulatory mechanism of HDAC6 is very important and may shed light on the relationship between the evolutional process and the handling of misfolded proteins.

In animal models of Parkinson disease, massive degeneration of dopaminergic neurons occurs in the nigro-striatal dopaminergic pathway, and motor dysfunction is reproduced as in humans. However, the formation of cytoplasmic inclusion body (Lewy body), which is an established hallmark of Parkinson disease, is not observed consistently in animal models.[19] Although intraneural inclusions have been described,[20] classical Lewy bodies, a typical feature of Parkinson disease, have not been demonstrated convincingly.[21] A lack of Ser458 in these animals might be related to these phenomena.

The clearance of misfolded protein aggregates for cell viability is crucial for many normal cellular processes, and the abnormality of this regulation may result in many pathological conditions, including neurodegenerative diseases. CK2 phosphorylates HDAC6, leading to an increase in HDAC6 activity and enhanced disposition of misfolded proteins. Since the newly identified CK2-mediated phosphorylation site Ser458 of HDAC6 is conserved only in higher primates, it is possible for Ser458 to contribute to longevity.

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