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LETTER TO THE EDITOR, NEWS AND VIEWS

Commentary to Gorelenkova Miller and Mieyal (2015): sulfhydryl-mediated redox signaling in inflammation: role in neurodegenerative diseases

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Abstract Gorelenkova Miller and Mieyal (Arch Toxicol 89(9): 1439–1467, 2015) recently published a review paper suggesting that reversible cysteine plays a key role in redox-linked signal transduction via alteration of protein function, resulting in an association with many diseases including neurodegenerative disorders. Following their suggestions, we considered the correlation between sulfhydryl-mediated redox signaling and neurodegenerative diseases by focusing on RET proteins, a protein tyrosine kinases (PTKs) potentially sited upstream of the signal transduction cascade. c-RET is the receptor for glial cell line-derived neurotrophic factor family ligands. c-RET has been reported to be involved in not only Hirschsprung disease via development of the enteric nervous system but also neurodegenerative diseases including Parkinson's disease and amyotrophic lateral sclerosis. We also showed that c-RET might be associated with hearing loss via neurodegeneration of spiral ganglion neurons in the inner ear after birth in mice and humans. Moreover, we have reported that three kinds of oxidative stress, ultraviolet light-induced stress, osmotic stress and arsenic-induced stress, modulate kinase activity of RET-PTC1 without an extracellular domain as well as c-RET by conformational change of RET protein (dimerization) via disulfide bond formation. The oxidative stresses also modulate kinase activity of RET-PTC1 with cysteine 365 (C365) replaced by alanine with promotion of dimer formation, but not with cysteine 376 (C376) replaced by alanine. Since C376 of Ret-PTC-1 or its equivalent is most highly conserved and crucial for activity in PTKs, the cysteine could be one of major targets for oxidative stresses.

Keywords RET · Cysteine · Redox · Neurodegeneration

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Dear Editor,

Recently, Gorelenkova Miller and Mieyal (2015) have reported that posttranslational modifications of cysteine sulfhydryl (–SH) moieties control cellular responses to various oxidative stresses. They suggested that reversible cysteine modifications play an important role in modulation of redox-linked signal transduction via alteration of protein function, resulting in contribution to many diseases including neurodegenerative disorders. However, mechanistic and functional relationships of protein-modified cysteine sulfhydryl moieties remain largely unknown. The biological significance of reversible cysteine in various diseases including neurodegenerative disorders also remains unclear. Following suggestions by Gorelenkova Miller and Mieyal, we considered the correlation between sulfhydryl-mediated redox signaling and neurodegenerative diseases by focusing on protein tyrosine kinases (PTKs) potentially sited upstream of the signal transduction cascade.

The c-*RET* gene encodes a receptor-type tyrosine kinase (Kato et al. 2000b). c-RET protein is a receptor for glial cell line-derived neurotrophic factor (GDNF) family ligands (Kato et al. 2002). Activity of c-RET is controlled by receptor cross-linkage (dimerization) with natural ligands (Kato et al. 2000a). c-RET-mediated signaling regulates the development and survival of various neural cells

(Kato et al. 2002; Ohgami et al. 2010). c-RET is known as a major causal molecule for Hirschsprung disease, a developmental disorder characterized by colon aganglionosis in mice and humans (Kato et al. 2002; Ohgami et al. 2010). Recently, we further showed that c-RET is correlated with age-related hearing loss (Ohgami et al. 2012) as well as congenital deafness (Ohgami et al. 2010) in mice and humans via neurodegeneration of spiral ganglion neurons (SGNs) in the inner ear after birth. Previous studies also showed that c-RET is involved in neurodegenerative diseases including Parkinson's disease (Marco et al. 2002) and amyotrophic lateral sclerosis (ALS) (Ryu et al. 2011). Thus, c-RET has been recognized as one of key molecules for neurodegenerative diseases.

We previously showed redox-linked effects of oxidative stresses on c-RET protein in vitro. Our in vitro kinase assay with immunoprecipitation of RET protein and immunoblot analysis for RET protein showed that ultraviolet light (UV) irradiation (Kato et al. 2000b), osmotic stress (Takeda et al. 2001) and arsenic (Kato et al. 2010) modulated c-RET kinase activity though modulated level of dimerized c-Ret protein with an extracellular domain. The kinase activity of c-RET stimulated by UV irradiation was decreased by treating the c-RET protein with a reducing reagent such as 2-mercaptoethanol (2ME) and dithiothreitol (DTT) before the in vitro kinase assay, which suppressed the dimerization of c-RET protein (Kato et al. 2000b). L-Cysteine decreased arsenic-mediated increased levels of c-RET kinase activity and dimerized c-RET protein in vitro (Kato et al. 2011). These results suggest that dimerization of c-RET protein involves the formation of disulfide bonds. The same results were obtained for the RET-PTC1 protein without an extracellular domain after the oxidative stresses, suggesting that cysteine sulfhydryl moieties in the intracellular domains of RET protein are associated with the oxidative stress-mediated dimer formation. We then focused on cysteine 365 (C365) and cysteine 376 (C376), which are highly conserved in various PTKs. All of the oxidative stresses modulated the activity of RET-PTC1 with C365 replaced by alanine with promotion of dimer formation, but not with C376 replaced by alanine. Furthermore, cysteine 475 of Lck and cysteine 498 of v-Src, equivalent cysteines for C376 of Ret-PTC-1, crucially regulate either catalytic activity or transforming activity of the kinase (Veillette et al. 1993; Senga et al. 2000). Taken together, these results suggest that the cysteine may act as one of major targets for various oxidative stresses.

At present, the correlation between oxidative stress-mediated temporal activation of RET kinase and neurodegeneration is still unclear. However, undesirably activated RET kinase by oxidative stresses may suppress survival of neural cells through secondarily activating downstream molecules crucially regulating cell death such as JNK and caspases (Hossain et al. 2000; Yajima et al. 2012), resulting in the development of neurodegenerative diseases. Thus, sulfhydryl-mediated redox control for neurotrophic controllers sited upstream of the signal transduction cascade may be one of key factors for neurodegenerative diseases.

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