Amino Acids (2012) 43:505–517
DOI 10.1007/s00726-011-1175-9

REVIEW ARTICLE

Modulating protein activity and cellular function by methionine residue oxidation

Zong Jie Cui · Zong Qiang Han · Zhi Ying Li

Received: 30 June 2011 / Accepted: 21 November 2011 / Published online: 7 December 2011

Abstract The sulfur-containing amino acid residue methionine (Met) in a peptide/protein is readily oxidized to methionine sulfoxide [Met(O)] by reactive oxygen species both in vitro and in vivo. Methionine residue oxidation by oxidants is found in an accumulating number of important proteins. Met sulfoxidation activates calcium/calmodulin-dependent protein kinase II and the large conductance calcium-activated potassium channels, delays inactivation of the *Shaker* potassium channel ShC/B and L-type voltage-dependent calcium channels. Sulfoxidation at critical Met residues inhibits fibrillation of atherosclerosis-related apolipoproteins and multiple neurodegenerative disease-related proteins, such as amyloid beta, α-synuclein, prion, and others. Methionine residue oxidation is also correlated with marked changes in cellular activities. Controlled key methionine residue oxidation may be used as an oxi-genetics tool to dissect specific protein function in situ.

Keywords Protein methionine oxidation · Methionine sulfoxide · Calcium/calmodulin-dependent protein kinase II · BK potassium channel · Protein fibrillation · Neurodegenerative diseases · Singlet oxygen

Introduction

Protein post-translational modifications are important for proper protein function. Among the many types of post-translational modifications, protein side chain oxidation has been found in an increasing number of proteins both in vitro and in vivo. Reactive oxygen species (ROS), such as hydrogen peroxide, superoxide anion, hydroxyl radical, singlet oxygen, and hypochloric acid oxidize protein side chains, especially on sulfur-containing amino acid residues (Nohl et al. 2005; Schöneich 2005; Han and Cui 2010). Of the sulfur-containing amino acids of methionine, cysteine, homocysteine, and taurine, only methionine and cysteine are incorporated into protein peptide chains (Brosnan et al. 2007). Methionine (Met) residue is readily oxidized to methionine sulfoxide [Met(O)] (Ciorba et al. 1997; Liu et al. 2008a). Methionine residue is rather hydrophobic and most Met residues are embedded deep inside protein structures in the hydrophobic cores; surface-exposed methionine residues are the major targets for oxidation (Giglione et al. 2003).

Methionine sulfoxide could be oxidized further to methionine sulfone [Met(O_2)], but only rarely under physiological conditions (Han and Cui 2010; Vogt 1995; Nakao et al. 2003; Maiti et al. 2011). Methionine sulfoxide can be reduced back to the native methionine by a class of physiological enzymes, the methionine sulfoxide reductases (Msr), but methionine sulfoxide oxidation to methionine sulfone is irreversible (Schöneich 2005; Han and Cui 2010; Vogt 1995; Nakao et al. 2003; Sharov and Schöneich 2000; Butterfield and Boyd-Kimball 2005; Wolschner et al. 2009). Indeed, invariably methionine residues in most of the naturally oxidized proteins examined have been found to be oxidized to methionine sulfoxide only. The oxidation-induced changes in the structure and activity of protein molecules and the corresponding alterations in cellular activities could all be reversed by methionine sulfoxide reductases (Msr).

One rare exception has been found with the protein DJ-1. DJ-1 from the frontal cortex tissues of Parkinson's disease patients (aged ≧66 years) has been found to be

Z. J. Cui (✉) · Z. Q. Han · Z. Y. Li
Institute of Cell Biology, Beijing Normal University, Beijing 100875, China
e-mail: zjcui@bnu.edu.cn

oxidized to methionine sulfone at Met-17 and Met-133, although only to Met sulfoxide at Met-134 (Choi et al. 2006). This additional oxidation from methionine sulfoxide to methionine sulfone at Met-17 and Met-133 in vivo would not be expected to be reversible; therefore, progressive neurodegeneration was seen in these Parkinson's disease patients. But the detailed mechanism for sulfoxidation in vivo from sulfoxide to sulfone at Met-17 and Met-133 are not known.

The introduction of one oxygen atom to the sulfur atom in methionine results in two optical isomers: methionine-(*R*)-sulfoxide and methionine-(*S*)-sulfoxide. Methionine-(*S*)-sulfoxide is reduced by MsrA, whereas methionine-(*R*)-sulfoxide is reduced by MsrB1-3; therefore, in mammalian cells there are at least four separate genes (*msrA*, *msrB1-3*) encoding Msr (Han and Cui 2010; Sharov and Schöneich 2000; Moskovitz et al. 1996). This arsenal of Msr enzymes indicates that methionine oxidation to methionine sulfoxide and its reversal is likely to play a physiological role in the functional modulation of multiple classes of proteins. This mini-review outlines the cases of both positive and negative regulations of protein activity and cellular function changes after Met residue oxidation.

Positive regulations on cell signaling

Activation of calcium/calmodulin-dependent protein kinase II

The multifunctional calcium/calmodulin-dependent protein kinase II (CaMKII) is a key enzyme in the calcium signaling pathway. The hallmark of CaMKII is its autophosphorylation at T286/287, which renders the enzyme autoactive independent of calcium/calmodulin, with enhanced affinities for protein substrates (Cui 1997; Abiria and Colbran 2010). Autophosphorylation at T305/306, in the CaM-free state, inhibited its subsequent association with calmodulin (Robison et al. 2007). Interestingly, two Met residues close to T286/287, M281 and M282, once oxidized, activated the kinase in a manner similar to T286/287 autophosphorylation (Erickson et al. 2008) (Fig. 1). Analogous to T305/306 autophosphorylation, CaMKII oxidation at M308 rendered it unable to bind CaM (Erickson et al. 2008).

Such M281/M282 oxidation has obvious physiological significance, since angiotensin II stimulation of cardiomyocytes led to oxidative activation of CaMKII and subsequent cardiomyocytes apoptosis; such actions were reversed by MsrA, forming a complete regulatory cycle (Erickson et al. 2008). In addition, $MsrA^{-/-}$ mice show exaggerated CaMKII oxidation and myocardial apoptosis, leading to impaired cardiac function, and increased mortality after myocardial infarction (Erickson et al. 2008). Such in vivo studies confirm a physiologically regulatory role for methionine oxidation of CaMKII in the cardiomyocytes.

CaMKII M281/M282 oxidation has distinctive effects on downstream target proteins, as exemplified by the L-type voltage-dependent calcium channels. Ca^{2+}-dependent facilitation of L-type Ca^{2+} channels ($I_{Ca,L}$) has been known to be mediated by CaMKII. Recently, it was found that in the freshly isolated rat ventricular cardiomyocytes, H_2O_2 not only induced an increase in $I_{Ca,L}$ amplitude, but also slowed $I_{Ca,L}$ inactivation (Robison et al. 2007). This facilitation of $I_{Ca,L}$ by H_2O_2 was abolished by the specific CaMKII inhibitor KN-93, but not by an autophosphorylation inhibitor AIP. It is therefore concluded that oxidation-dependent facilitation of L-type Ca^{2+} channels was mediated by oxidation-dependent CaMKII activation (Song et al. 2010). Oxidation-dependent CaMKII activation is likely to be involved in other CaMKII-dependent processes, such as exocytosis, both at presynaptic membrane and in secretory cells. Other than CaMKII, calmodulin itself is also known to be readily oxidized at Met residues. H_2O_2-oxidized calmodulin (CaM^{ox}) was not able to bind to and activate CaMKII, did not support Thr286 autophosphorylation, and did not block Thr305 and Thr306 autophosphorylation (Robison et al. 2007).

Calmodulin in its peptide chain has nine Met residues. All nine Met residues could be oxidized by H_2O_2 (Vougier et al. 2004), or by singlet oxygen generated by photosensitizer 4′,5′-bis(1,3,2-dithioarsolan-2-yl)fluorescein (FlAsH) attached to N-terminal mutant Cys residues replacing Glu6, Glu7, Ala10, and Glu11 (Yan et al. 2006). Met oxidation led to decreased binding affinity for adenylate cyclase (AC). CaM-AC complex oxidation by tBHP at Met144, Met109, Met124, and Met145 has also been found to be correlated with decreased binding affinity (Vougier et al. 2004).

H_2O_2-oxidized CaM shows decreased α-helix content and changed tertiary structure. CaM-L7 with all Met residues substituted by Leu, except for M144 and M145, however, remained capable of activating the plasma membrane Ca^{2+}-ATPase (PMCA). Oxidation of M144 and M145 in CaM-L7 had nominal effect on secondary structure but resulted in global changes in tertiary structure. In PMCA, the CaM-binding sequence PMCA (C28W) specifically interacted with CaM or CaM-L7. Oxidation of M144 and M145 in CaM and CaM-L7, which caused conformational changes in C-terminal domain and central linker region but not N-terminal domain, decreased their binding affinity to PMCA C28W (Anbanandam et al. 2005). CaM oxidation at Met144 and Met145 residues resulted in a 50% decrease in maximal CaM-dependent activation of PMCA. Met144 oxidation was largely responsible for decreased enzyme activation; Met145 oxidation altered the apparent affinity of CaM for PMCA (Bartlett et al. 2003).

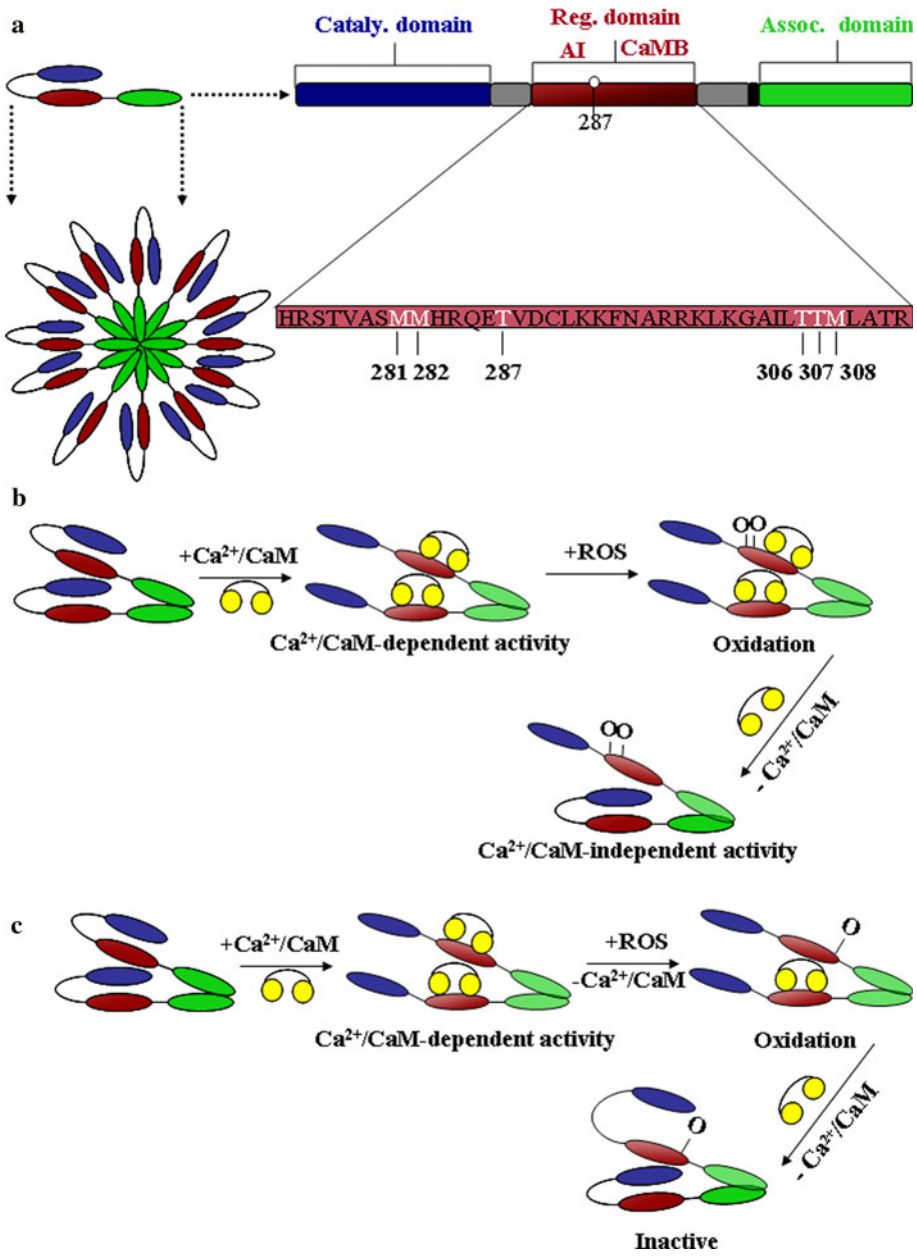

Fig. 1 Met residue oxidation activates the multifunctional calcium/calmodulin-dependent protein kinase II (CaMKII). **a** CaMKII structure: N-terminal catalytic domain, central regulatory domain (composed of autoinhibitory AI and calmodulin-binding Cam-B portions), and C-terminal association domain. Sequence of the regulatory domain highlight locations of Met281, Met282, Met308 and Thr287, Thr306, Thr307. **b** Methionine oxidative activation of CaMKII. Ca^{2+}/CaM-bound CaMKII is activated, Met281 and Met282 are oxidized by ROS blocking regulatory domain inhibition, Met-oxidized CaMKII remains activated independent of Ca^{2+}/CaM. **c** CaMKII inactivation by Met308 oxidation. Ca^{2+}/CaM-bound CaMKII is activated, Met308 is oxidized by ROS after Ca^{2+}/CaM removal, inhibiting further Ca^{2+}/CaM binding, CaMKII remains inactive. Modified from Erickson et al. (2008); Meyer et al. (1992); Colbran (1993) (color figure online)

Decreased binding strength of the CaM^{ox}-AC assembly due to CaM oxidation as mentioned above could be reversed after reduction of CaM^{ox} by MsrA and MsrB (Vougier et al. 2004). Although multiple Met-oxidized CaM failed to activate PMCA, yet CaM-Met^{ox} activity could be partially restored after MsrA-catalyzed reduction of Met(O) to Met (Sun et al. 1999). Although Met-oxidized CaM also failed to bind RS20, the CaM-binding sequence of smooth muscle myosin light chain kinase, this loss of CaM activity could also be restored by MsrA and MsrB (Tsvetkov et al. 2005). These data would present another typical case of Met oxidation and reduction cycle in action, in a regulatory process.

Sulfoxidation of M144/M145 could destabilize CaM, because oxidation of M144 and M145 promoted CaM degradation by 20S proteasome. CaM-$M145^{ox}$ was more prone to degradation than CaM-$M144^{ox}$, because the tertiary structure of M145-oxidized CaM was more readily recognized by proteasome and more likely destined for degradation (Sacksteder et al. 2006).

Methionine residue oxidation in CaM, therefore, not only undermines its role as a transducing agent to transmit calcium signal to CaM-binding proteins directly, but also does so by simply reducing the total amount of CaM available to execute such a transductionary role. These data clearly highlight the importance of methionine residue oxidation in regulating CaM-mediated calcium signaling.

Other than CaM and CaMKII, additional protein members of the calcium signaling pathway (too numerous to list

here, but could include SERCA, RyaR, IP_3R, and NCX) could also be subject to Met oxidative regulation. A well-studied case is the large conductance calcium-activated potassium channels, which are activated by Met residue oxidation.

Potassium channel activation and delayed inactivation

Membrane-impermeable small molecular oxidants have proven to be very useful and handy tools to dissect Met oxidative modulation of plasma membrane protein function in the cellular environment. There are at least four such oxidants that have been commonly used in such investigation. Chloramine T (Ch-T) will oxidize Met and Cys residues, whereas 5,5′-dithio-bis(2-nitrobenzoic acid) (DNTB), methanethiosulfonate ethylammonium (MTSEA), *p*-chloromecuribenzoic acid (PCMB) will oxidize only Cys residues. These specific oxidants, which when used in combination with dithiothreitol (DTT), the reducing agent for oxidized Cys residue, would identify whether the exposed Met residue is involved in oxidant-induced changes in protein function.

Chloramine T (Ch-T) oxidation of large conductance calcium-activated potassium channels BK_{ca}/Slo at Met residues enhanced channel current progressively, with subsequent addition of dithiothreitol having no effect on oxidation enhancement (indicating that only Met oxidation was involved), but MsrA partially reversed the activation (indicating a complete Met oxidation–reduction cycle) (Tang et al. 2001). BK_{ca}/Slo channel oxidation at Cys residues by 5,5′-dithio-bis(2-nitrobenzoic acid) (DTNB), methanethiosulfonate ethylammonium (MTSEA), *p*-chloromecuribenzoic acid (PCMB), on the other hand, rather decreased the channel current (Tang et al. 2001). Slo under blockade condition was not modified by Ch-T (Tang et al. 2001), indicated that the responsible Met residues were shielded in the blocked channel conformation. These data clearly demonstrated that the calcium-activated potassium channel BK was activated by Met residue oxidation. The Ch-T oxidant enhancement of BK current became larger in the presence of the beta subunit, suggesting a marked role for auxillary subunit during BK oxidative activation (Santarelli et al. 2004).

More specifically, Ch-T oxidation shifted the BK channel IV curve significantly to the left, with a $V_{0.5}$ change of about 30 mV, and slowed down channel deactivation, with a change of deactivation time constant of τ 0.05 ms (Santarelli et al. 2006). Individual single Met → Leu mutants (29 Met residues in total) in the hSlo1 alpha subunit had no effect on such oxidant activation. But a triple mutant (Met536L/Met712L/Met739L) rendered the channel completely insensitive to Ch-T treatment, indicating that concerted oxidation of all three Met residues were needed for oxidative BK activation (Fig. 2). A triple beta1 subunit mutant (Met7, Met23, Met177), however, had no such effect. Single glutamate mutants Met712E and Met739E, each surrogating Met(O) with a glutamate, mimicked Ch-T oxidant effect (Santarelli et al. 2006).

Met residue oxidation enhanced not only Slo potassium channel current, but also P/Q type voltage-dependent calcium current. Hydrogen peroxide oxidation of P/Q type calcium channels (alpha1A:alpha2/delta:beta3) enhanced the channel current significantly (Li et al. 1998). The Cys residue oxidant 2,2′-dithio-bis(5-nitropyridine) (DTNBP), however, decreased such P/Q calcium channel currents (Li et al. 1998).

Other than directly activating BK_{ca}/Slo channels, Met oxidation also slowed down Shaker potassium channel inactivation. Voltage-dependent Shaker potassium channels ShC/B and ShB showed varied inactivation. Met/Cys oxidant chloramine T (Ch-T) slowed down ShC/B inactivation significantly, but had no effect on ShB channel inactivation. MsrA co-expression specifically reduced ShC/B slow inactivation. ShC/B had at position 3 a Met residue, but ShB had no Met in the first 20 deduced amino acids in the sequence (Ciorba et al. 1997). ShC/B mutant ShC/B-M3L also showed reduced slow inactivation in comparison with wild-type ShC/B. In ShBD6-46:T449V expressing cells, microinjection of native synthetic peptide resulted in fast inactivation, but microinjection of Met-oxidized synthetic peptides resulted in slowed inactivation, being reversible by co-injecting MsrA. It is concluded that M3 oxidation in ShaC/B is essential for the slow N-type inactivation (Ciorba et al. 1997). In ShB channel, both hydrogen peroxide and oxygenation (with 100% O_2) accelerated P/C type ShBΔ6-46:T449S channel inactivation, but did not alter the inactivation time course of ShBΔ6-46:M440L:T449S, indicating a critical role for Met oxidation in hydrogen peroxide acceleration of P/C type inactivation (Chen et al. 2000).

Voltage-dependent sodium channels once activated by depolarization, inactivate rather fast (complete inactivation within 3 ms). But after channel protein oxidation by Ch-T, a dose-dependent slowing down of the inactivation process has been observed for $Na_v1.4$. Similar oxidant effects were also observed in $Na_v1.2$, $Na_v1.5$_C373Y, and $Na_v1.7$ (Kassmann et al. 2008). Such oxidant effect on $Na_v1.4$ was progressive with time and irreversible even after DTT treatment, indicating non-involvement of Cys residues. Simultaneous mutation of Met1305L, Met1469L, and Met1470L in $Na_v1.4$ relieved the oxidant effect. Lucifer yellow-mediated photodynamic action had a similar effect in $Na_v1.4$ as Ch-T (Kassmann et al. 2008).

Although sodium and potassium channel inactivations are partially relieved by Met oxidation, Met oxidation inhibited hERG activation and tail currents (Su et al. 2007).

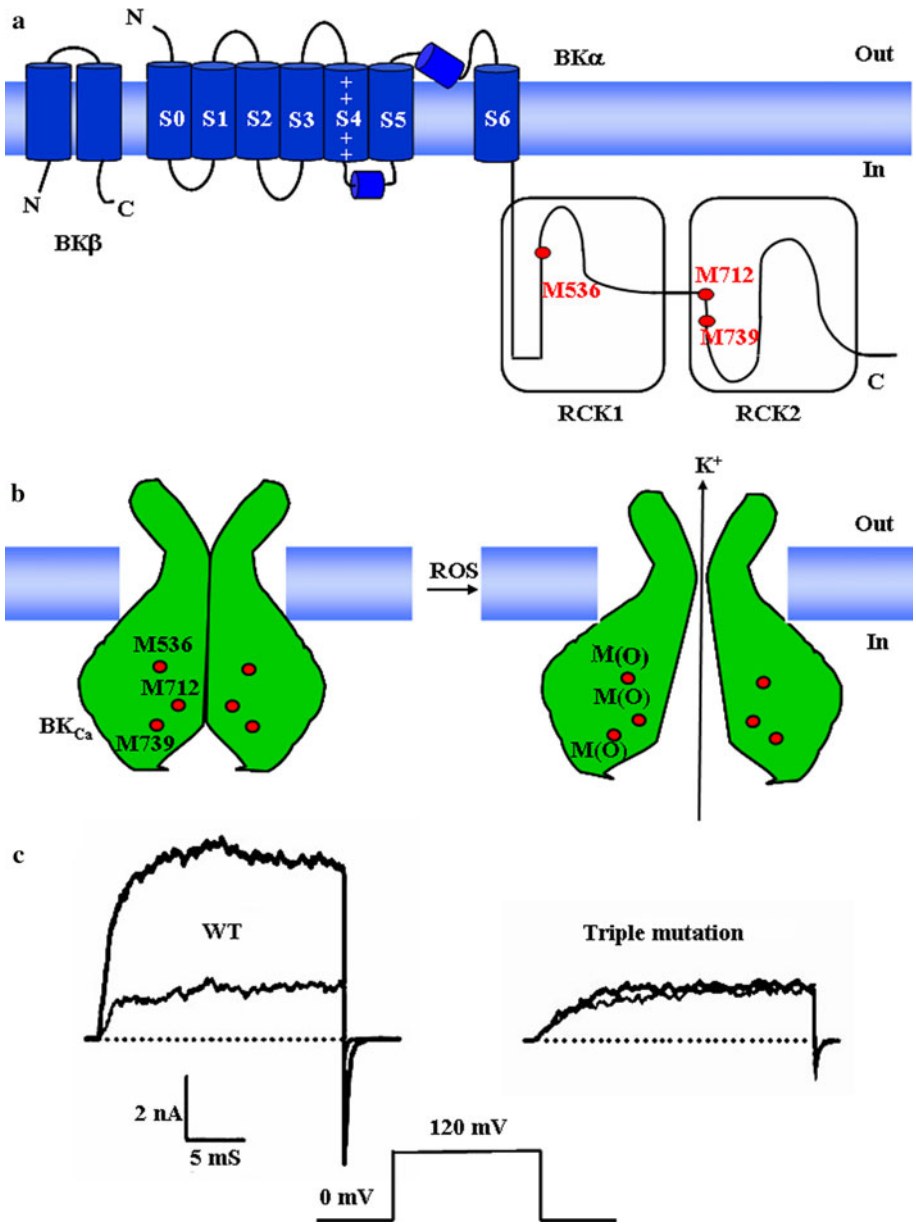

Fig. 2 Met residue oxidation activates BK_{Ca} potassium channel. **a** Topographical representation of a BK_{Ca} channel monomer. BK_{Ca} channel is composed of the pore-forming α subunit and accessory β subunit. BK_{Ca} β subunit is composed of two transmembrane segments. BK_{Ca} α subunit is composed of seven transmembrane segments S0–S6 and two cytosolic conductance regulator domains (RCK1, RCK2). Note location of M536 in RCK1, and M712/M739 in RCK2 (*solid red balls*). **b** BK_{Ca} channel activation by Met residue oxidation. The tetrameric BK_{Ca} channel (only two monomeric units are shown here) under oxidative stress is oxidized on three Met residues (M536, M712, M739), leading directly to channel opening. **c** Enhanced potassium currents after chloramines T oxidation in wild-type BK_{Ca} (*left*), and lack of such enhancement in triple Met mutant (*right*). Currents were elicited by a voltage pulse from 0 to 120 mV. Modified from Santarelli et al. (2006); Cui et al. (2009); Hou et al. (2009) (color figure online)

Other than modulating the calcium signaling enzyme CaMKII and BK/Slo potassium channels, Met oxidation plays an important role in modulating protein fibrillation both of neurodegenerative diseases-associated proteins and the high density lipoprotein (HDL) apolipoproteins, as described below.

Negative regulations on protein fibrillation

Apolipoproteins

Apolipoproteins bind lipids to form lipoprotein particles. Some apolipoproteins are exchangeable between lipoprotein particles, such as apoA-I, apoA-II, apoA-IV, apoC-I, apoC-II, apoC-III, and apoE3 (Bolanos-Garcia and Miguel 2003). These exchangeable lipid-free apolipoproteins could self-associate to form twisted ribbon-like amyloid fibrils similar to those found in neurodegenerative brain neurons (Bolanos-Garcia and Miguel 2003; Hatters and Howlett 2002).

Hydrogen peroxide oxidation of the full-length apoA-I (apoA-I) at Met86, Met112, and Met148 resulted in a partially unfolded protein with lowered thermal stability (Wong et al. 2010). Comparison of serum components from patients with hepatocellular carcinoma (HCC) with those from normal subjects found that oxidized apoA-I was especially high in HCC patients; apoA-I sequence analysis showed that Met85 and Met216 were oxidized (Fernández-Irigoyen et al. 2005). Met112 and Met148 oxidation by

H_2O_2 in lipid-bound HDL apoA-I reduced its structural stability, making the oxidized central region of apoA-I more prone to proteolysis (Sigalov and Stern 2001). Met148 is located near the center of lecithin/cholesterol acyltransferase (LCAT) activation domain in apoA-I. LCAT activity was impaired after Met148 oxidation by myeloperoxidase (MPO)-hypochloric acid (HOCl); mutant Met148Leu had improved LCAT activity (Shao et al. 2008). HDL apoA-I facilitates cellular cholesterol efflux, which has been found to be impaired by myeloperoxidase due to Met oxidation in the apoA-I motif of MxxY (Shao et al. 2006).

Exposure of isolated HDL to aqueous peroxide radicals led to selective early oxidation of surface apoA-I and apoA-II, at one or two Met residues, respectively (Garner et al. 1998b). Native apoA-I and apoA-II reduced cholesteryl ester hydroperoxides (CE-OOH) to cholesteryl ester hydroxides (CE-OH), with concurrent selective oxidation of apoA-I and apoA-II (Garner et al. 1998a). Canine HDL apoA-I and apoA-II lacking Met112 and Met148 exhibited little such reducing activity; it is therefore concluded that Met112 and Met148 of apoA-I, and Met26 of apoA-II were oxidized by peroxide radicals via reduction of hydroperoxides of cholesteryl esters and phosphatidylcholine (Garner et al. 1998a).

ApoC-II Met residues were oxidized by hydrogen peroxide; the oxidized apoC-II could be reduced by Msr (MsrA or MsrB2). The monomeric apoC-II^{ox} was reduced more readily than fibrillar apoC-II^{ox}. Mass spectrum studies with mutants Met9Val and Met60Val showed that a single oxygen atom was added to the Met residues each (Binger et al. 2010). All-atom molecular dynamics simulations of peptide apoC-II (56–76), of the oxidized form apoC-II (56–76)Met60^{ox}, and of apoC-II (56–76)Met60Gln mutant revealed a consistent beta-turn structure in the N-terminal region forming a hydrophobic core in the native peptide, a structure element essential for monomer self-assembly and amyloid formation. In contrast, the oxidized apoC-II (56–76)Met60^{ox} showed less flexibility and tended to form helical conformation in the N-terminus region containing Met60ox, leading to inhibition of fibril formation. The mutant apoC-II (56–76)Met60Gln showed a structure similar to the native reduced peptide (Legge et al. 2009). Thioflavin T fluorescence measurements showed that native apoC-II (56–76) readily assembled into fibril, but oxidized apoC-II (56–76)Met60^{ox} did not, even over extended time period (Legge et al. 2009). These data together suggest that Met oxidation strongly modulate apolipoprotein fibrillation.

β-Amyloid peptide

β-Amyloid peptide (Aβ1–42) forms aggregates in brain neurons in Parkinson's and Alzheimer's patients. Aβ aggregates trigger a complex pathological cascade leading to neurodegeneration. It has been found that Met35 oxidation to Met35(ox) in Aβ(1–40) and Aβ(1–42) inhibited β-stand formation, β-stand aggregation, and fibril formation (Bitan et al. 2003; Hou et al. 2002, 2004). It may be noted here that Met35 residue by itself probably does not confer on it the oxidation potential, since comparative gamma and pulse radiolysis studies in N_2O-flushed solutions indicated that Abeta1–40 was readily oxidized at Met35, but the reverse order Abeta40–1 was not oxidized at Met35 (Kadlcik et al. 2004). Aβ(1–42) and Aβ1–40Arctic(E22G) oxidation at Met35 to Met(O) led to decreased Aβ aggregation and neurotoxicity (Johansson et al. 2007a, b). Whereas Aβ(1–42) induced significant apoptosis in human neuroblastoma cell IMR-32, Aβ(1–42)Met35^{ox} was much less effective (Clementi et al. 2006). When IMR-32 cells were treated with AβMet35^{ox}, MsrA expression was increased but ROS generation was decreased in comparison with Aβ(1–42) or AβM35N treatment (Piacentini et al. 2008). ROS scavenger TEMPO inhibited cell viability decrease by both Aβ(1–42) and AβMet35^{ox}; TEMPO reduced AβMet35 but not AβMet35^{ox}-induced increases in cytosolic calcium in neuroblastoma cells (Piacentini et al. 2008). AβP(31–35)ox addition to isolated rat brain mitochondria resulted in cytochrome *c* release, mitochondrial respiration inhibition, and mitochondrial membrane potential decrease; the native reduced AβP(31–35) had no such effects (Misiti et al. 2004). Therefore, Aβ oxidation at Met35 to Met35 sulfoxide reduced Aβ(1–42) neuronal toxicity (Misiti et al. 2010). But if Met35 sulfoxide was further oxidized to Met35 sulfone, the suppressed neuronal toxicity seemed to return (Maiti et al. 2011). Such experiments were done with synthesized Aβ(1–42) with Met(O_2) incorporated at position 35, whether Aβ(1–42) could be oxidized to Met(O_2) at Met35 in vivo remains to be determined.

Those in vitro data have been corroborated by work in a MsrA$^{-/-}$ knockout mouse model, which showed enhanced neurodegeneration in the hippocampus, including a loss of astrocyte integrity, elevated levels of beta-amyloid deposition and tau phosphorylation, together with increased sensitivity to H_2O_2 (Pal et al. 2007). The in vivo activity of AβM35 oxidation, however, may be rather complex. In another mouse model of Alzheimer's disease (the PDAPP mouse model), it was found that mutant APPM631L (corresponding to AβM35) led to increased protein oxidation and lipid peroxidation in the mouse brain. Aβ plaque formation decreased in mutant APPM631L mouse brain, but mutant APPM631L did not improve mouse memory (Butterfield et al. 2010). In this latter mouse model, oxidative stress was neither required nor sufficient for memory dysfunction (Butterfield et al. 2010).

α-Synuclein

The major component of intracellular Lewy body inclusions in dopaminergic neurons in Parkinson's disease (PD) brain is α-synuclein. Native α-synuclein could form fibrils; dopamine inhibited fibrillation but promoted α-synuclein aggregation into soluble oligomers (Leong et al. 2009). α-Synuclein aggregation has been found by NMR studies to be triggered by Met residue oxidation to Met(O), preventing end-to-end molecular association, but promoting oligomer formation (Rekas et al. 2010). Long-range hydrophobic interactions between hydrophobic clusters in C-terminus and hydrophobic central part, and electrostatic attraction between negatively charged residues at the C-terminus and positively charged residues at the central region were important for α-synuclein to remain in the unfolded form. Oxidation by H_2O_2 occurred at N-terminal Met1, Met5, and C-terminal Met116, Met127. Met116 and Met127 being located in the C-terminal hydrophobic cluster, their oxidation altered the long-range interactions, resulting in inhibition of fibril formation, but promoted soluble oligomer formation (Zhou et al. 2010). Oxidation of Met1, Met5, Met116, and Met127 to Met(O) inhibited α-synuclein fibrillation (Uversky et al. 2002). Met → Leu mutations revealed that inhibition by Met(O) was proportional to the number of Met residues oxidized; with increasing numbers of Met(O) residues, the kinetics of fibrillation became progressively slower (Hokenson et al. 2004). Met → Leu substitution mutations promoted soluble oligomer aggregation but slowed down fibril formation (Hokenson et al. 2004). Mutating Met5, Met116, or Met127 inhibited dopamine-promoted α-synuclein aggregation (Leong et al. 2009). All these evidence indicate that Met residue oxidation inhibits fibril formation but promotes soluble oligomer formation. Importantly, oligomers of Met-oxidized α-synuclein were not toxic to dopaminergic or GABAergic neurons (Zhou et al. 2010). Inhibition of α-synuclein fibrillation by Met oxidation could be overcome by certain environmental pollutant metals such as Ti^{3+}, Zn^{2+}, Al^{3+}, and Pb^{2+} (Yamin et al. 2003).

Met residue oxidation in recombinant α-synuclein was efficiently reversed (reduced) by MsrA; MsrA expression in primary midbrain cultures from day 17 rat embryos suppressed α-synuclein self-assembly and cell death (Liu et al. 2008a). In vivo relevance of α-synuclein-Met(O) was also confirmed by impaired α-synuclein clearance in MsrA-null yeast cells (Oien et al. 2009). These data together suggest that enhanced MsrA enzymatic activities may be a potential therapeutic option against Parkinson's disease (Liu et al. 2008a).

Prion

Transformation, from the normal cellular protein prion (Prp^c) to infectant "scrapie" agent Prp^{sc}, is believed to be the cause for fatal transmissible neurodegenerative prion diseases of sheep scrapie, bovine spongiform encephalopathy, and human Creutzfeldt-Jakob disease (Canello et al. 2010; Silva et al. 2010; Grabenauer et al. 2010). The Prp^c → Prp^{sc} transition involved an α-helix to β-sheet shift in protein secondary structures, and Met residue oxidation played an important role in such a transition process (Canello et al. 2010; Silva et al. 2010; Grabenauer et al. 2010; Requena et al. 2004; Breydo et al. 2005; Bergström et al. 2007) (Fig. 3).

Each cellular prion molecule contains nine Met residues: M109, Met112, Met129, Met134, Met138, Met139, Met154, Met206, and Met213 (Wolschner et al. 2009; Requena et al. 2004; Wong et al. 1999). Met109, Met112, Met129, Met134, Met154, Met206, and Met213 could be oxidized by H_2O_2, for example, resulting in an α-helix → β-sheet structural shift, but no change in tertiary structure (Requena et al. 2004). Met109, Met112, Met129, and Met134 have been found to be located in a region critical for transformation from PrP^c to PrP^{sc} (Requena et al. 2004). Such α-helix → β-sheet shift was corroborated by a recent Met mutation experiment. Met replacements in human recombinant PrP(23–231) by hydrophobic Nle or hydrophilic methoxinine (Mox) resulted in predominantly alpha-helix Nle-hrPrP^c or beta-sheet Mox-hrPrP^c, respectively (Wolschner et al. 2009).

Such α-helix to β-sheet structural shift after M213 oxidation could be distinguished actually by a monoclonal antibody. Antibody IPC2 recognized the α-helix-rich/non-infectious PrP^c, but not the infectious PrP^{sc} (Canello et al. 2008). PAb, antibody against the PrP helix-3 epitope (including Met206 and Met213, conserved in all species), recognized PrP but not PrP^{sc} (Canello et al. 2010). Prior treatment of PrP^{sc} with Met(O) reducing agent (*N*-methylmercaptoacetamide), rendered PrP^{sc} recognizable by pAb again (Canello et al. 2010). It is now suggested that sulfoxidation of the C-terminal helix 3 Met residues of Met206, Met213 is a specific covalent signature and essential for Prp^c → Prp^{sc} conversion (Canello et al. 2008, 2010; Colombo et al. 2009). But a recent in vivo study to detect quantitatively by nanoflow chromatography/tandem mass spectroscopy the amount of PrP^cMet(O)213 in infected hamsters indicated that more works need to be done to correlate in vitro and in vivo studies (Silva et al. 2010). In the future, it would be interesting to see the influence of Msr genes and enzymes on Prp^c → Prp^{sc} transition both in vitro and in vivo, and on the progression

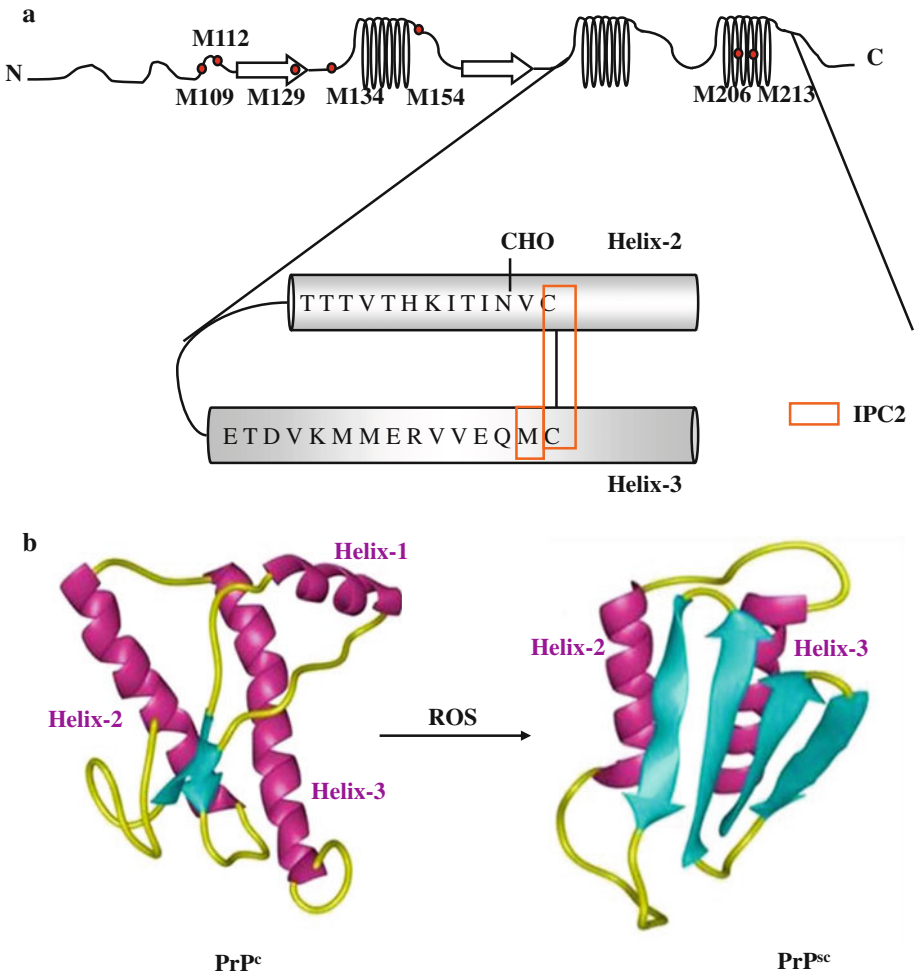

Fig. 3 Prion structural changes induced by Met oxidation. **a** Graphical representation of prion secondary structure, note the two strand and three helix domains. The approximate positions of Met109, Met112, Met129, Met134, Met154, Met206, and Met213 (*solid red balls*) are indicated. An intact disulfide bond between helix 2 and helix 3, and reduced Met are required for antibody IPC2 recognition [an anti-PrP mAb against a-rMoPrP(23–230)]. **b** Met oxidative conversion from PrP^{c} to PrP^{sc}. Under oxidative stress, PrP^{c} α-helix content decreases, but β-strand content increases. Modified from Canello et al. (2008, 2010); Colombo et al. (2009); Huang et al. (1996); Prusiner (2001); Redecke (2009); Wong et al. (1999) (color figure online)

of transmissible encephalopathies in disease models of different animals.

Other proteins of note

In addition to proteins highlighted above, there are other examples of Met residue sulfoxidation resulting in changed protein activities.

It has been found that human IgG1 oxidization at Met33 and Met209 residues by H_2O_2 increased IgG1 aggregation (Liu et al. 2008b), oxidation by H_2O_2 at M252 and M358 residues decreased binding to the Fc receptor (FcRn) (Bertolotti-Ciarlet et al. 2009), oxidation at Met256 and Met432 residues by tert-butyl hydroperoxide (tBHP) decreased its binding affinity toward proteins A and G (Gaza-Bulseco et al. 2008). IgG2 oxidation by tert-butyl hydroperoxide (tBHP) at Met252, Met428, Met358, and Met397 residues led to decreased binding toward protein A and Fc receptor (FcRn) (Pan et al. 2009).

Oxidation of α1-antitrypsin (a neutrophil elastase inhibitor) by H_2O_2 at Met351 and Met358 resulted in its inactivation, thereby providing a way by which neutrophil elastase inhibition is overcome by ROS at sites of inflammation (Taggart et al. 2000). Met 63/Met83-oxidized S100A9 (a neutrophil cytosolic calcium-binding protein) no longer regulated leukocyte migration (Sroussi et al. 2007). Neutrophil respiratory burst products HOCl, taurine chloramines, and glycine chloramine readily oxidized IκBα at Met45, leading to inhibition of NF-κB activation (Kanayama et al. 2002). IκB-$Met45^{ox}$ due to its prolonged intracellular life time (6 h), was no longer degraded or dissociated from NF-κB; NF-κB therefore failed to enter cell nucleus (Midwinter et al. 2006).

Endothelial thrombomodulin oxidation by chloramine T and H_2O_2 at Met338 resulted in thrombomodulin inactivation (Glaser et al. 1992). Coagulation factor VII (FVIIa) oxidation by hydrogen peroxide and tBHP at Met298 and Met306 diminished soluble tissue factor-binding, leading to reduced rate of factor X activation (Kornfelt et al. 1999). Actin sulfoxidation, at Met176, Met190, and Met269 residues, blocked actin polymerization, but rather promoted actin filament depolymerization (Dalle-Donne et al. 2002). Oxidation by chloramine T of a β1-bungarotoxin subunit,

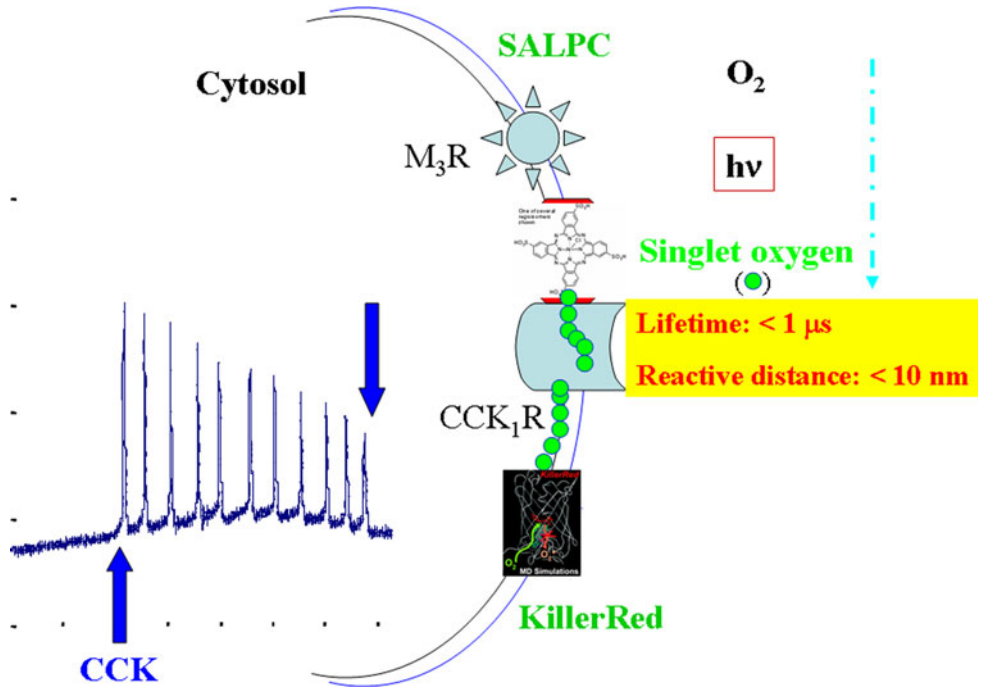

Fig. 4 Oxidative activation of cell surface receptor by plasma membrane-localized singlet oxygen or photodynamic action. Photosensitizer sulfonated aluminum phthalocyanine (SALPC) mainly localizes at the plasma membrane after brief incubation. Photon (hν)-driven SALPC photodynamic action generates singlet oxygen which due to limited life time (1 μs) has limited diffusion distance (10 nm). Singlet oxygen selectively activates the CCK1 receptors triggering regular cytosolic calcium oscillations, but has no effect on M3 muscarinic receptor. A protein photosensitizer, KillerRed, could potentially be targeted to the plasma membrane to trigger similar calcium oscillations. *Drawn* based on data from Cui and Kanno (1997); An et al. (2003); Cui (2005); Carpentier et al. (2009) (color figure online)

phospholipase A2, at Met6 and Met8 rendered it non-lethal (LD_{50} increased by more than 200-fold) in mice and incapable to block neuromuscular junction in chick biventer cervicis muscle (Chu et al. 1993). P53 oxidation by H_2O_2 at Met340 blocked tetramerization of the tumor suppression protein and transcriptional activation (Nomura et al. 2009). These additional examples of Met oxidation resulting in changed protein activities provide ample support for a pivotal role of Met oxidation in regulation of protein function.

The above data notwithstanding, it must not be neglected that Met oxidation by ROS and Met(O) reduction by Msr may actually serve as a redox buffering system in some proteins to regulate micro-environmental redox status. This may become more critical under increased or prolonged oxidative stress conditions, such as during ischemia-reperfusion, and in aging. Ready sulfoxidation of Met residues which is nonessential for protein activity would also suggest that such Met residues may serve as reducing agents, in order to protect from oxidation of amino acid residues, which are more important in maintaining vital protein functions, such as Cys which may be located at or near the reaction center in enzymes, at the pore or selectivity filter region in ionic channel proteins, or close to the hinge region of complex proteins.

In this context, it must also be pointed out that data obtained from in vitro studies may not always correlate with data from in vivo works. This is adequately illustrated by the examples of Aβ(1–42) oxidation at Met-35, DJ-1 oxidation at Met-17/Met-133, PrP^c oxidation at Met213, as described above. But in some other cases, in vitro data correlated well with in vivo data, such as the case of α-synuclein oxidation of Met residue in yeast. In cases of discrepancy, future attention may be directed to the need to closely mimic in vivo conditions when designing in vitro studies. Due caution must be exercised when interpreting data from in vitro studies when in vivo mechanistic proof is not readily available, although the great potential for artificial methionine oxidation studies is apparent to all.

Conclusion and perspectives

Recent works on an increasing number of proteins have revealed that protein methionine residues are easily oxidized to methionine sulfoxide, resulting in enhanced or suppressed protein activities. Methionine residue oxidation is reversed by methionine sulfoxide reductases. Such reversible Met oxidation entails significant changes in the life activities in live cells or organisms. When protein Met

residues are oxidized irreversibly, either due to oxidation to methionine sulfone, or due to a lack of local methionine sulfoxide reductase activity, the function of the involved protein in intact cell or organism would be *highlighted*. This in practice may, in gene regulation studies, avoid the tedious process of genetic manipulation or potential genetic compensation by functionally related genes.

Confined generation of ROS at selected sub-cellular compartments or on particular target proteins, in the future, may be used for the functional elucidation of sub-cellular organelles or proteins in physiological processes. The recent appearance of high-quantum yield protein-photosensitizer, KillerRed (Bulina et al. 2006; Roy et al. 2010; Teh et al. 2010), to generate selectively singlet oxygen at defined location close to vital proteins, makes this a fascinating field for future research, because singlet oxygen-modulated major changes in cellular functions have long been recognized in the field of photodynamic action. Both excitable cells such as neurons (Breitenbach et al. 2010; Pooler 1972), cardiomyocytes (Yonuschot et al. 1992), and non-excitable cells such as secretory epithelial cells (Cui and Kanno, 1997; Cui et al. 1997; An et al. 2003) are subject to photodynamic/singlet oxygen modulation (Fig. 4). In this context, the regulation of methionine sulfoxide reductase expression or enzyme activity would also be a potential new target for pharmacology and therapeutics.

Acknowledgments Work supported by The MOST China "973" Program (2011CB809101), by NSFC (No. 30728020, 30870580; 30970675), and by NSFBJ (No. 5102020).

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