Published in final edited form as:

Curr Signal Transduct Ther. 2009 January 1; 4(1): 46–50. doi:10.2174/157436209787048748.

The Role of Methionine Oxidation/Reduction in the Regulation of Immune Response

Abdulkali Agbas and Jakob Moskovitz*

University of Kansas, School of Pharmacy, Department of Pharmacology and Toxicology, Lawrence, KS 66045, USA

Abstract

Methionine oxidation by reactive oxygen species and reduction mediated by the methionine sulfoxide reductase (Msr) system may attenuate protein function in signal transduction pathways. This review will focus on two potential protein targets for methionine oxidation involved in signal transduction of the immune response: Ca^{2+} /calmodulin-regulated phosphatase calcineurin (Cn) and inhibitor of kappa B-alpha ($\text{I}\kappa\text{B}\alpha$). The major known function of Cn is to regulate nuclear localization of the nuclear factor of activated T cells (NFAT), a family of transcription factors during immune stimulus. Like wise, $\text{I}\kappa\text{B}\alpha$ inhibits the activity of nuclear factor kappa B (NF κ B), which is known to regulate the transcription of various genes participating in immunological and oxidative stress response. Modification of Met₄₅ in $\text{I}\kappa\text{B}\alpha$ enhances its resistance to protein-degradation; thereby, preventing NF κ B from activating transcription in cells of the immune system. Similarly, the human Cn molecule contains several methionine residues that are either located next to a cysteine residue or a methionine residue. Accordingly, it is suggested that oxidation of a specific Cn-methionine may interfere with the proper NFAT nuclear-localization and transcriptional activation in T-cell. Thus, the roles of oxidized-methionine residues and their reduction, by the Msr system, are discussed as potential regulators of cellular immune response.

Keywords

Oxidative stress; methionine sulfoxide reductase; posttranslational modification; methionine sulfoxide

THE METHIONINE SULFOXIDE REDUCTASE SYSTEM

Accumulative posttranslational modification to proteins, mediated by the action of reactive oxygen species (ROS), is thought to be one of the major causes of aging and age-related diseases. Thus, mechanisms have evolved to prevent or reverse these protein modifications. While most protein damage by ROS is irreversible, methionine oxidation to proteins can be reversed by the methionine sulfoxide reductase (Msr) system, which consists of MsrA (that reduces *S*-MetO) and MsrB (that reduces *R*-MetO), thioredoxin reductase, thioredoxin, and NADPH [1]. The action of the Msr system may prevent irreversible protein damage (e.g. protein carbonylation), contribute to cellular antioxidant resistance resulting in life span extension of the organism. Evidence for a possible role of Msr system in antioxidant defense is demonstrated by the adverse effects to several organisms that result from *MsrA* ablation [1–4]. Furthermore, overexpression of MsrA in human T cells, plant cell, and fruit fly cells protects them from oxidative stress toxicity and leads to an almost doubling of the life span of flies [5–7]. A major biological role of the Msr system is suggested by the fact that the MsrA

*Address correspondence to this author at the University of Kansas, School of Pharmacy, Department of Pharmacology and Toxicology, Lawrence, KS 66045, USA; Tel: 1-(785)-864-3536; Fax: 1-(785)-864-5219; moskovij@ku.edu.

null mouse (*MsrA*^{-/-}) is more sensitive to oxidative stress, accumulates higher levels of carbonylated protein, and has a shorter life span (by~40%) than WT mice [4]. Additionally, selenium and MsrA are positive expression regulators of the selenoprotein form of MsrB and thioredoxin reductase [8,9]. Furthermore, following a prolonged selenium-deficient (SD) diet (through the F2 generation) the *MsrA*^{-/-} mice exhibited higher protein–MetO and carbonyl levels relative to their WT control in most organs [9]. More specifically, the SD diet caused alteration in the expression and/or activities of certain antioxidants as follows: lowering the specific activity of MsrB in the *MsrA*^{-/-} cerebellum in comparison to WT mice and lowering the activities of glutathione peroxidase and thioredoxin reductase especially in brains of *MsrA*^{-/-} mice [9]. The protein–MetO and carbonyl levels observed in tissues of young mice fed with a SD diet, resembled the levels seen in middle-aged mice fed with selenium adequate diet [8,9]. Therefore, it was suggested that selenium deficiency decreases antioxidant capacity in the cell that in turn increases the levels of faulty proteins to the levels observed with older age. In addition to the antioxidant function of methionine sulfoxide reductases, it has been shown that these enzymes can also regulate protein function, by alternating between active and non-active forms, depending on a reversal of a specific MetO residue to Methionine. So far, methionine-residue oxidation has been shown to affect activities of various proteins *in vitro* [10,11]. For example, in the potassium channel of the brain (as demonstrated in an *ex vivo* system) [12] there is an isoform of the inhibitory protein κ B (IkB) [13,14], and calmodulin [15]. It is suggested that reversal of methionine oxidation may play an important role in regulation of the function of proteins either directly or mediated by signal transduction pathways. Among all cellular organelles, mitochondria are considered to be among the major source of ROS. Thus, the suggested role of the Msr system in maintaining function of proteins under oxidative stress conditions is manifested by the transport of MsrA into mitochondria *via* its N-terminal 23 amino acid region [16].

CA²⁺/CALMODULIN-REGULATED PHOSPHATASE CALCINEURIN

Originally, Calcineurin (Cn) was discovered in brain tissue [17]. Cn is situated in several signaling pathways involved in cellular response to stress-related stimuli. More specifically, hyper-phosphorylation of various proteins and oxidative stress during chronic inflammation are linked to Cn function. Also, except of its role in immune response, Cn participates in several other biological processes including: cAMP pathway, Na⁺/K⁺ ion transportation in nephron, cell cycle progression in lower eukaryotes, cardiac hypertrophy, and memory formation. The role of Cn in signal transduction pathway during T cell activation is extensively studied. According to the crystal structure of Cn, the composite surface of the protein is formed by two subunits CnA and CnB, which function as recognition site for its substrate [18]. This is an important feature when designing new generation of Cn inhibitors, used in cases where attenuation of the immune response is needed (A chronicle discovery of Cn inhibitors is reviewed by Nghiem *et al.* [19]). Cn is the only known protein Ser/Thr phosphatase whose activity is regulated by calmodulin [20,21]. As a heterodimeric protein, calcineurin consists of a 61 kDa catalytic subunit A (CnA) and a 19 kDa regulatory subunit B (CnB). CnA contains four functional domains: a catalytic domain, a CnB binding domain, a calmodulin-binding domain (CnD), and an autoinhibitory domain (AID) [22–25]. The major known function of Cn is to regulate nuclear localization of nuclear factor of activated T cells (NFAT), a family of transcription factors upregulated during immune stimulus. Equally important, Cn-NFAT signaling regulates axon terminal remodeling [26]. The signal transduction signaling starts upon the interaction of the T-helper cell's receptor with an antigen causing the elevation of intra-cellular calcium concentration. Ca²⁺ increase activates Cn, by binding a regulatory subunit and activating calmodulin binding. By its dephosphorylating activity, Cn induces NFATs that are important in the transcription of interleukin 2 (IL-2) genes. IL-2 activates T-helper lymphocytes and induces the production of other cytokines. In this way, it governs the

action of cytotoxic lymphocytes and natural killer cells. The level of IL-2 that is produced by the T-helper cells seems to significantly influence the extent of the immune response.

The high degree of evolutionary conservation of Cn from yeast to mammals suggests that Cn involvement in signal transduction/metabolic pathways are of fundamental physiological importance in prokaryotic and eukaryotic systems. The immunosuppressant binding proteins Cyclophilin A and FKBP12 are also conserved from yeast to mammals, and Cn is potently inhibited in yeast by CsA and FK506. Although the characterization of Cn was performed more than twenty years ago [17,27,28], its identification as a key signaling molecule is relatively new. Recent studies have indicated that involvement of Cn in developmental-related physiological pathways is essential. For example, in osteoclasts genesis [29], renal phosphate (P_i) homeostasis [30], nuclear localization of NFAT [31], skeletal muscle remodeling [32, 33], premitochondrial signaling events, and caspase-3 activation in traumatic spinal cord injury [34]. Lautermilch and Spitzer [35] reported that Cn is required for regulating of neurite outgrowth by spontaneous Ca^{2+} waves in cultured *Xenopus* spinal neuron. Cn and calcium-calmodulin-dependent protein kinase II (CAMKII) provide a switch-like mechanisms to control the direction of Ca^{2+} -dependent growth cone turning [36]. Moreover, studies by Graef *et al.* [37] suggest that Cn/NFAT signaling is required specifically for axon growth stimulated by growth factors like neurotrophins and netrins. All these studies emphasize the importance of Cn in regulating various signal transduction cascades.

I KAPPA B ALPHA (IKBA)

NF κ B (nuclear factor κ B) is a major transcription factor that regulates expression of a large number of genes that code for cytokines, adhesion molecules, and other components of the inflammatory response [38,39]. In unstimulated cells, NF κ B is retained in the cytoplasm as a complex with inhibitory proteins known as I κ B (inhibitor of NF κ B) [40]. Upon stimulation, I κ B α is phosphorylated, ubiquitinated, and degraded by the proteasome [41–43]. The degradation of I κ B α unmasks the nuclear localization sequence of NF κ B, allowing translocation into the nucleus and subsequent initiation of gene expression.

OXIDATIVE STRESS AND OXIDATION OF CN AND IKBA

Signal transduction pathways mediated by proteins that are functionally altered by oxidation-reduction of their methionine residue/s are beginning to be identified. Among them are I κ B α (with experimental evidence) and Cn (with a suggestive hypothesis).

IKBA OXIDATION

There has been considerable interest in the activation of NF κ B by oxidants, but the physiological importance of this mechanism remains controversial [44,45]. Another oxidative process that inhibited NF κ B activation by stimuli such as tumour necrosis factor α (TNF α) was observed in cells treated with taurine chloramine (Tau-Cl) [13]. The inhibitory action of Tau-Cl was consistent with the oxidation of I κ B α at Met₄₅, rendering its resistant to degradation [13,46]. According to the recent observation in the field of I κ B α regulation, it appears that methionine sulfoxide formation on I κ B α prevents its subsequent ubiquitin-mediated degradation. It was shown that oxidized I κ B α was not degraded when the cells were activated with TNF α [14]. The susceptible methionine residue (Met₄₅) is in close proximity to the phosphorylation sites at Ser₃₂ and Ser₃₆. Methionine sulfoxide formation, particularly if it occurs within helices, can cause major conformational rearrangements [47], and it seems most likely that oxidation of Met₄₅ causes structural disruption that makes the protein no longer a target for kinase action [14]. It is suggested that the location of Met₄₅ in the I κ B protein enhances its reactivity towards oxidants, while strengthening its binding activity to NF κ B upon oxidation [14]. Furthermore, it was demonstrated that antioxidants like reduced glutathione

(GSH) could not protect I κ B α from oxidation by chloramines [14]. The sensitivity of I κ B α to oxidants such as chloramines, and its ability to be reduced by the Msr system raise the possibility of I κ B α being a critical cell target for redox regulation. Although involvement of cysteine residues in redox signaling is well documented, selective oxidation of methionine residues as a signaling mechanism has received less attention. Initial views were that methionine residues act as an oxidant sink, with Msr activity enabling regeneration [48]. However, as more proteins are shown to undergo functional changes as a result of methionine oxidation [1,11], a role for methionine in redox regulation is becoming more likely. Regulation of the NF κ B pathway *via* I κ B α oxidation is a potential candidate for this mechanism. In summary, accumulative evidence support the hypothesis that cell-permeable oxidants (e.g. chloramines) could regulate NF κ B activation *via* reversible I κ B α oxidation.

CN OXIDATION

The human Cn molecule contains several methionine residues that are either located next to a cysteine (Cys) residue or a methionine (Met) residue. In subunit CnA there are two Met residues residing next to Cys residues, as follows: Cys₁₇₈Met₁₇₉ and Met₂₂₈Cys₂₂₉. In subunit CnB there are two Met residues that one of them resides next to a Cys residue and one of them resides next to a Met residue, as follows: Met₁₀Cys₁₁ and Met₁₁₇Met₁₁₈. This is not common phenomenon and it is conserved in most of all Cn species. It is suggested the oxidation of either of these Met residues may facilitate the oxidation of the vicinal Cys residues. Oxidation of Cys residues by reactive oxygen species, such as superoxide, generated in normal course of aging compromised the structural integrity of Cn [49]. In this study it was demonstrated that an oxidative modification of the CnA subunit of Cn increased in aged brain. The Cys oxidation may have caused the formation of large aggregates of Cn while reducing its activity. These age-related posttranslational modifications may result in physiological irregularities; such as, the alteration of signal transduction processes at synapses with age and delaying immune response. Taking together, we propose that the Met-Cys and Met-Met sequence pairs in Cn may contribute to the susceptibility of Cn molecule to oxidation. Supporting evidence for the role of methionine oxidation in affecting protein structures is demonstrated in alpha-synuclein. In this protein, methionine oxidation causes a reduction in its fibrillation rather than aggregation in the absence of metal ions [50]. However, having MetO residues in the presence of metal ions may cause irreversible modifications to other amino acids, thereby enhance protein aggregation [50]. It is hypothesized that if the oxidized Met residues in the Met-Cys/Met pairs of Cn are not readily reduced (by the Msr system) similar structural changes may occur to Cn in the presence of metal ions. Taken together, oxidation of sulfur amino acid residues in Cn (namely Cys and Met) may either directly attenuate Cn-related activities/functions or affect Cn solubility and its function especially at older age. Consequently, it will be of great interest to assess the contribution of the Msr system to the maintenance of Cn functions and activities under oxidative stress and inflammation conditions with age. To determine the Msr system and in preventing Cn-oxidation, we plan to investigate the age-dependent oxidation of Cn in the *MsrA* knockout mouse [4]. Generally, chronic inflammation provides oxidizing conditions fostering hyperphosphorylated *tau* accumulation, as seen in Alzheimer's disease [51]. Therefore, efforts are made to down-regulate Cn and its reactions with other molecules by endogenous inhibitors of Cn. Poppek *et al.* [51] concluded that excessive expression of endogenous Cn inhibitor RCAN1 (formerly known as Adapt 78, DSCR1 or calcipressin1) indeed inhibits Cn, but subsequently *tau* remains hyperphosphorylated. Together with chronic inflammation and RCAN1 inhibition of *tau* turnover, phosphorylated-*tau* accumulation and aggregation may enhance cellular toxicity and neurodegeneration [51]. Thus, fine-tuned regulation of Cn is required to ensure that proper physiological response to oxidative stress conditions are not compromised and at the same time not causing other undesired protein damages. In that respect, the Msr system may serve, at least in part, as one of the mechanisms used in controlling Cn function.

CONCLUSION

Methionine oxidations in both I κ B α and Cn may attenuate their functions and consequently affect transcription levels mediated by NFAT and NF κ B (especially in T-lymphocytes of the immune system). It is evident that oxidation of Met₄₅ in I κ B α promotes its role as an NF κ B inhibitor while oxidation of specific methionines in Cn may promote a reduction in NFAT activation (yet to be determined). Indirectly, oxidized Cn may lead to an ineffective activation of I κ B α kinase complex in T lymphocytes within the T-cell receptor/CD3 signal transduction pathway [52]. Thus, reduced level of I κ B α kinase may cause lower level of phosphorylated I κ B α , resulting in a compromised degradation of I κ B α and an enhanced inhibition of NF κ B. In summary, methionine oxidation of I κ B α and possibly Cn may lead to inactivation of NF κ B *in vivo* that may be reversed by MetO reduction (mediated by the Msr system). It is anticipated that with aging or age-associated diseases, there will be an increase in MeO levels in these proteins causing abnormalities in cellular NFAT/NF κ B-related response. The possible role of the Msr system in regulating I κ B α and Cn is illustrated in Fig. 1, using the T-cell immune response as a model. Induction of the pathway(s) responsible for the expression of MsrA and/or MsrB may enhance the immune response that is mediated by NFAT and NF κ B.

References

1. Moskovitz J. Methionine sulfoxide reductases: ubiquitous enzymes involved in antioxidant defense, protein regulation, and prevention of aging-associated diseases. *Biochim Biophys Acta* 2005;1703:213–19. [PubMed: 15680229]
2. Moskovitz J, Rahman MA, Strassman J, et al. Escherichia coli peptide methionine sulfoxide reductase gene: regulation of expression and role in protecting against oxidative damage. *J Bacteriol* 1995;177:502–7. [PubMed: 7836279]
3. Moskovitz J, Berlett BS, Poston JM, Stadtman ER. The yeast peptide-methionine sulfoxide reductase functions as an antioxidant *in vivo*. *Proc Natl Acad Sci USA* 1997;94:9585–89. [PubMed: 9275166]
4. Moskovitz J, Bar-Noy S, Williams WM, Requena J, Berlett BS, Stadtman ER. Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense and lifespan in mammals. *Proc Natl Acad Sci USA* 2001;98:12920–25. [PubMed: 11606777]
5. Moskovitz J, Flescher E, Berlett SB, Azare JA, Poston M, Stadtman ER. Overexpression of peptide-methionine sulfoxide reductase (MsrA) in *Saccharomyces cerevisiae* and human T cells provides them with high resistance to oxidative stress. *Proc Natl Acad Sci USA* 1998;95:4071–75.
6. Romero HM, Berlett BS, Jensen PJ, Pell EJ, Tien M. Investigations into the role of the plastidial peptide methionine sulfoxide reductase in response to oxidative stress in Arabidopsis. *Plant Physiol* 2004;136:3784–94. [PubMed: 15516509]
7. Ruan H, Tang DX, Chen ML, et al. High-quality life extension by the enzyme peptide methionine sulfoxide reductase. *Proc Natl Acad Sci USA* 2002;99:2748–53. [PubMed: 11867705]
8. Moskovitz J, Stadtman ER. Selenium-deficient diet enhances protein oxidation and affects methionine sulfoxide reductase (MsrB) protein level in certain mouse tissues. *Proc Natl Acad Sci USA* 2003;100:7486–90. [PubMed: 12792026]
9. Moskovitz J. Prolonged selenium deficient diet in MsrA knockout mice causes enhanced oxidative modification to proteins and affects the levels of antioxidant enzymes in a tissue-specific manner. *Free Radic Res* 2007;41:162–71. [PubMed: 17364942]
10. Levine RL, Moskovitz J, Stadtman ER. Oxidation of methionine in proteins: roles in antioxidant defense and cellular regulation. *IUBMB Life* 2000;50:301–7. [PubMed: 11327324]
11. Oien DB, Moskovitz J. Substrates of the methionine sulfoxide reductase system and their physiological relevance. *Curr Top Dev Biol*. In-press
12. Ciorba MA, Heinemann SH, Weissbach H, Brot N, Hoshi T. Modulation of potassium channel function by methionine oxidation and reduction. *Proc Natl Acad Sci USA* 1997;94:9932–37. [PubMed: 9275229]

13. Kanayama A, Inoue J, Sugita-Konishi Y, Shimizu M, Miyamoto Y. Oxidation of Ikappa B alpha at methionine 45 is one cause of taurine chloramine-induced inhibition of NF-kappa B activation. *J Biol Chem* 2002;277:24049–56. [PubMed: 11983684]
14. Midwinter RG, Cheah FC, Moskovitz J, Vissers MC, Winterbourn CC. IkappaB is a sensitive target for oxidation by cell-permeable chloramines: inhibition of NF-kappaB activity by glycine chloramine through methionine oxidation. *Biochem J* 2006;396:71–8. [PubMed: 16405428]
15. Sun H, Gao J, Ferrington DA, Biesiada H, Williams TD, Squier TC. Repair of oxidized calmodulin by methionine sulfoxide reductase restores ability to activate the plasma membrane Ca-ATPase. *Biochem J* 1999;23:105–12. [PubMed: 9854031]
16. Hansel A, Kuschel L, Hehl S, et al. Mitochondrial targeting of the human peptide methionine sulfoxide reductase (MSRA), an enzyme involved in the repair of oxidized proteins. *FASEB J* 2002;16:911–13. [PubMed: 12039877]
17. Waisman DM, Tokuda M, Morys SJ, Buckland LT, Clark T. Identification of bovine brain Ca²⁺-binding proteins. *Biochem Biophys Res Commun* 1985;128:1138–44. [PubMed: 2988528]
18. Huai Q, Wang H, Zhang W, Colman RW, Robinson H, Ke H. Crystal structure of calcineurin-cyclophilin-cyclosporin shows common but distinct recognition of immunophilin-drug complexes. *Proc Natl Acad Sci USA* 2002;99:12037–42. [PubMed: 12218175]
19. Nghiem P, Pearson G, Langely RG. Tacrolimus and pime-crolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *Am Acad Dermatol* 2002;46:228–41.
20. Klee CB, Crouch TH, Krinks MH. Calcineurin: a calcium- and calmodulin-binding protein of the nervous system. *Proc Natl Acad Sci USA* 1979;76:6270–73. [PubMed: 293720]
21. Klee CB, Draetta GF, Hubbard MJ. Calcineurin. *Adv Enzymol Relat Areas Mol Biol* 1988;61:149–200. [PubMed: 2833077]
22. Hubbard MJ, Klee CB. Functional domain structure of calcineurin A: mapping by limited proteolysis. *Biochemistry* 1989;28:1868–74. [PubMed: 2541767]
23. Hashimoto Y, Perrino BA, Soderling TR. Identification of an autoinhibitory domain in calcineurin. *J Biol Chem* 1990;265:1924–27. [PubMed: 2153670]
24. Griffith JP, Kim JL, Kim EE, et al. X-ray structure of calcineurin inhibited by the immunophilin-immunosuppressant FKBP12-FK506 complex. *Cell* 1995;82:507–22. [PubMed: 7543369]
25. Kissinger CR, Parge HE, Knighton DR, et al. Crystal structures of human calcineurin and the human FKBP12-FK506-calcineurin complex. *Nature* 1995;378:641–44. [PubMed: 8524402]
26. Yoshida T, Mishina M. Distinct roles of calcineurin-nuclear factor of activated T-cells and protein kinase A-cAMP response element-binding protein signaling in presynaptic differentiation. *J Neurosci* 2005;25:3067–79. [PubMed: 15788763]
27. Manalan AS, Krinks MH, Klee CB. Calcineurin: a member of a family of calmodulin-stimulated protein phosphatases. *Proc Soc Exp Biol Med* 1984;177:12–6. [PubMed: 6089220]
28. Tokuda M, Khanna NC, Waisman DM. Identification of bovine brain calcium binding proteins. *Cell Calcium* 1987;8:229–39. [PubMed: 3607857]
29. Sun L, Peng Y, Zaidi N. Evidence that calcineurin is required for the genesis of bone-resorbing osteoclasts. *Am J Physiol Renal Physiol* 2007;292:F285–91. [PubMed: 16968888]
30. Moz Y, Levi R, Lavi-Moshayoff V, et al. Calcineurin Abeta is central to the expression of the renal type II Na/Pi co-transporter gene and to the regulation of renal phosphate transport. *J Am Soc Nephrol* 2004;15:2972–80. [PubMed: 15579499]
31. Chan B, Greenan G, McKeon F, Ellenberger T. Identification of a peptide fragment of DSCR1 that competitively inhibits calcineurin activity *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 2005;102:3075–80.
32. Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling. *Annu Rev Biochem* 2006;75:19–37. [PubMed: 16756483]
33. Stupka N, Plant DR, Schertzer JD. Activated calcineurin ameliorates contraction-induced injury to skeletal muscles of mdx dystrophic mice. *J Physiol* 2006;575:645–56. [PubMed: 16793906]
34. Springer JE, Azbill RD, Nottingham SA, Kennedy SE. Calcineurin-mediated BAD dephosphorylation activates the caspase-3 apoptotic cascade in traumatic spinal cord injury. *J Neurosci* 2000;20:7246–51. [PubMed: 11007881]

35. Lautermilch NJ, Spitzer NC. Regulation of calcineurin by growth cone calcium waves controls neurite extension. *J Neurosci* 2000;20:315–25. [PubMed: 10627609]
36. Wen Z, Guirland C, Ming GL, Zheng JQ. A CaMKII/calcineurin switch controls the direction of Ca (2+)-dependent growth cone guidance. *Neuron* 2004;43:835–46. [PubMed: 15363394]
37. Graef IA, Wang F, Charron F. Neurotrophins and netrins require calcineurin/NFAT signaling to stimulate outgrowth of embryonic axons. *Cell* 2003;113:657–70. [PubMed: 12787506]
38. Baeuerle PA, Henkel T. Function and activation of NF- κ B in the immune system. *Annu Rev Immunol* 1994;12:141–79. [PubMed: 8011280]
39. Baldwin AS Jr. Series introduction: the transcription factor NF- κ B and human disease. *J Clin Invest* 2001;107:3–6. [PubMed: 11134170]
40. Baeuerle PA, Baltimore D. I κ B α : a specific inhibitor of the NF- κ B transcription factor. *Science* 1988;242:540–46. [PubMed: 3140380]
41. Brown K, Gerstberger S, Carlson L, Franzoso G, Siebenlist U. Control of I κ B α proteolysis by site-specific signal-induced phosphorylation. *Science* 1995;267:1485–88. [PubMed: 7878466]
42. Henkel T, Machleidt T, Alkalay I, Kronke M, Ben-Neriah Y, Baeuerle PA. Rapid proteolysis of I κ B α is necessary for activation of transcription factor NF- κ B. *Nature* 1993;365:182–85. [PubMed: 8371761]
43. Traenckner EB, Pahl HB, Henkel T, Schmidt KN, Wilk S, Baeuerle PA. Phosphorylation of human I κ B α on serines 32 and 36 controls I κ B α proteolysis and NF- κ B activation in response to diverse stimuli. *EMBO J* 1995;14:2876–83. [PubMed: 7796813]
44. Bowie A, O'Neill LA. Oxidative stress and nuclear factor- κ B activation: a reassessment of the evidence in the light of recent discoveries. *Biochem Pharmacol* 2000;59:13–23. [PubMed: 10605930]
45. Hayakawa M, Miyashita H, Sakamoto I, et al. Evidence that reactive oxygen species do not mediate NF- κ B activation. *EMBO J* 2003;22:3356–66. [PubMed: 12839997]
46. Mohri M, Reinach PS, Kanayama A, et al. Suppression of the TNF α -induced increase in IL-1 α expression by hypochlorite in human corneal epithelial cells. *Invest Ophthalmol Vis Sci* 2002;43:3190–95. [PubMed: 12356823]
47. Bigelow DJ, Squier TC. Redox modulation of cellular signaling and metabolism through reversible oxidation of methionine sensors in calcium regulatory proteins. *Biochim Biophys Acta* 2005;1703:121–34. [PubMed: 15680220]
48. Levine RL, Moskovitz J, Stadtman ER. Oxidation of methionine in proteins: roles in antioxidant defense and cellular regulation. *IUBMB Life* 2000;50:301–7. [PubMed: 11327324]
49. Agbas A, Zaidi A, Michaelis EK. Decreased activity and increased aggregation of brain calcineurin during aging. *Brain Res* 2005;1059:59–71. [PubMed: 16150427]
50. Glaser CB, Yamin G, Uversky VN, Fink AL. Methionine oxidation, alpha-synuclein and Parkinson's disease. *Biochim Biophys Acta* 2005;1703:157–69. [PubMed: 15680224]
51. Poppek D, Keck S, Ermak G. Phosphorylation inhibits turnover of the tau protein by the proteasome: influence of RCAN1 and oxidative stress. *Biochem J* 2006;400:511–20. [PubMed: 16939415]
52. Trushin SA, Pennington KN, Algeciras-Schimmich A, Paya CV. Protein kinase C and calcineurin synergize to activate I κ B kinase and NF- κ B in T lymphocytes. *J Biol Chem* 1999;274:22923–31. [PubMed: 10438457]

Fig. 1.

The possible involvement of the methionine sulfoxide reductase (Msr) system in regulating Inhibitory kappa B alpha ($I\kappa B\alpha$) and calcineurin (Cn).

The effect of inflammation on T-cell response with regards to $I\kappa B\alpha$ and Cn is shown.

ROS, reactive oxygen species; NFAT, nuclear factor of activated T cells; NF- κ B, nuclear factor kappa B; IKK, $I\kappa B\alpha$ kinase. MetO, methionine sulfoxide. Dotted frame indicates the proposed mechanism for the indicated protein.