Nitric Oxide Special Issue: PREFACE

“Frontiers in Nitric Oxide and Redox Signaling”

Takaaki Akaike

Department of Microbiology

Graduate School of Medical Sciences, Kumamoto University

1-1-1 Honjo, Kumamoto 860-8556, Japan

Tel: 81-96-373-5100

E-mail: takakaik@gpo.kumamoto-u.ac.jp

Albert van der Vliet

College of Medicine, Department of Pathology, University of Vermont

89 Beaumont Avenue, Burlington, VT 05405, U.S.A.

Tel: 1-802-656-8638

E-mail: albert.van-der-vliet@uvm.edu

Philip Eaton

Cardiovascular Division, King's College London

The Rayne Institute, St Thomas' Hospital, London SE1 7EH, U.K.

E-mail: philip.eaton@kcl.ac.uk

This special issue commemorates the 6th International Conference on the Biology, Chemistry, and Therapeutic Applications of Nitric Oxide, which was held in Kyoto, June 14-18, 2010. The Conference was co-sponsored by the Nitric Oxide Society of Japan (NOSJ) and was held jointly with the 10th Annual Scientific Meeting of the NOSJ and the 2nd International Meeting on NO and Cancer.

NO is now widely recognized as a master signaling molecule that regulates almost all cellular events in organisms. After the 1998 Nobel Prize in Physiology or Medicine was awarded to three leading scientists for their work on NO as a signaling molecule in the cardiovascular system, the field of NO research grew rapidly, and it continued to make steady progress during the past decade [1, 2]. The Kyoto meeting therefore addressed, as one central theme, new aspects of NO chemistry and biology, including diverse signal transductions, which depend not only on the chemistry of NO as a pure gas but also on rather complicated pathways mediated by different reactions of NO, i.e., oxidation, nitrosation, and nitration of various biological molecules [3-6]. This special issue, therefore, will cover not only a classical NO-cGMP signal pathway and NO synthase regulation but also NO interactions with molecular oxygen and reactive oxygen species (ROS), which regulate hypoxia and oxidative stress responses in cells.

Research on the cell signaling mechanism of NO has achieved several breakthroughs, such that many researchers in this field are now advancing the frontiers of basic research and clinical medicine in such topics as infection, cancer biology, metabolic syndromes, and even stem cell research. The rapid expansion of research on NO has included the current focus on oxidative stress and redox signaling mediated by ROS [7-10]. ROS are thought to be toxic substances that cause oxidative stress by inducing nonspecific destructive alterations in biological molecules [11]. Indeed, involvement of ROS in the pathogenesis of various diseases has been suggested [12]. These disorders include infections; inflammations; cancers; lifestyle-related and metabolic diseases such as arteriosclerosis and diabetes mellitus; and neurological diseases such as Alzheimer’s disease. Clinical application of antioxidant agents for

treatment and prevention of these diseases has not yet achieved the anticipated results, however.

Nevertheless, investigations of ROS toxicology have led to the belief that ROS may play important roles in regulating physiological cell signal transductions [7-10]. This new concept of ROS signaling, which derives from NO biology, was discussed at the Kyoto meeting sessions and is another central theme of this special issue. This specific area of ROS research is now widely known as “redox signaling” [7-10]. In fact, NO and ROS, which are rather unstable primary signaling molecules, mediate redox signaling and are then transformed into more stable secondary signals. Aiding this process is expression of chemical sensors of NO/ROS by cells with a wide range of repertoires [7-10, 13-17]. For example, interaction of NO/ROS with various sensors, such as nucleic acids, lipids, and protein sulfhydryls, results in production of stable secondary signaling molecules (e.g., 8-nitro-cGMP and nitro-fatty acids) [18, 19]. Also, sensor proteins such as Keap1 and protein kinase G, which possess cysteine sulfhydryls, directly or indirectly mediate the receptor function for redox signaling, because of high redox activity [20-25].

Identification and analysis of these sensor molecules are critical for understanding of the sensing specificity and structural basis of the NO/ROS signaling system. Thus, several articles in this special issue describe these NO/ROS sensor molecules, with a focus on their chemical sensing mechanisms. Articles also explain the structures and functions of sensor and effector proteins modified by the NO/ROS signaling system and its secondary electrophilic signaling molecules (e.g., 8-nitro-cGMP) [18, 20, 26]. More important, identification of new ROS or electrophile sensors will clarify the various mechanisms of NO/ROS signal transmission [27-30].

The biological functions of effectors, being directly affected by NO and ROS or indirectly mediated by secondary electrophilic compounds, can be induced by NO/ROS signal-caused structural changes in sensor proteins, which in some cases act simultaneously as effectors. For example, phosphorylation and transcriptional

signaling pathways are regulated via structural changes occurring in sensor-effector proteins (e.g., specific redox-sensitive protein kinases and phosphatases) and transcription factors [31-33]. These structural changes result from chemical modification—such as oxidation, nitrosylation, alkylation, and guanylation of cysteine sulfhydryls—by NO and ROS, or most effectively by their secondary electrophilic molecules [10, 20, 30]. Clarifying the molecular mechanisms of various sensor-effector relationships with NO and ROS is an important area of investigation. Therefore, some authors in this issue discuss the cell response mechanisms (cell proliferation and cell death) mediated by NO and ROS signaling, with a concentration on particular sensor-effector proteins involved in intracellular signal transduction involving phosphorylation; transcriptional regulation; endoplasmic reticulum stress; and neuronal and vascular signal transduction [34-36].

The evidence provided in this special issue illustrates that the belief that ROS-induced toxicity causes nonspecific injuries of biomolecules has changed drastically in recent years. Researchers in a wide variety of life science fields have come to recognize the physiological, rather than just the pathological, cell signaling functions of ROS. Comprehensive understanding of the molecular mechanisms that conduct NO and ROS cellular signals through receptors to effector molecules at molecular, cellular, and organismal levels will contribute to the remarkable innovative progress occurring in cell signaling research. More important, this NO and ROS signaling research has the potential to promote progress in various life science fields including plant biology and medical sciences [37-40].

In summary, this special issue describes new developments in the area of signal transductions mediated not only by NO but also by ROS and will advance understanding of the implications of these signal transductions in diverse physiological and pathophysiological phenomena in terms of chemical biology, the scientific discipline that integrates the fields of chemistry and biology. In addition to discussing research on new aspects of NO chemistry and biology, describing molecular

mechanisms of sensor-effector relationships with NO and ROS, and NO/ROS signaling mechanism with an emphasis on redox-dependent regulation mechanisms, this issue also covers newly developing concepts with respect to the regulation of NO production (through NOS regulation or nitrite reduction), and interactions between NO and O_2 distribution or ROS signaling. These various advances have led to several significant discoveries in basic biology research and in clinical medicine, including disease pathogenesis, inflammation and infection, and cancer biology.

Acknowledgements

The cited work from the authors' groups (TA, AV, PE) was supported in part by Grants-in-Aid for Scientific Research and Grants-in-Aid for Scientific Research on Innovative Areas (Research in a Proposed Research Area) from the Ministry of Education, Sciences, Sports and Technology (MEXT), Japan (TA); National Institutes of Health Grants (AV); and the Leducq Foundation and the Department of Health via the NIHR cBRC award to Guy's & St Thomas'NHS Foundation Trust (PE). We thank Judith B. Gandy for editing of the manuscript.

References

[1] L.J. Ignarro, Introduction and overview, in: L.J. Ignarro (Ed.), Nitric Oxide in Biology and Pathobiology , Academic, San Diego, 2000, pp. 3-19.

[2] F. Murad, Cyclic guanosine monophosphate as a mediator of vasodilation, J. Clin. Invest. 78 (1986) 1-5.

[3] T. Sawa, T. Akaike, H. Maeda, Tyrosine nitration by peroxynitrite formed from nitric oxide and superoxide generated by xanthine oxidase, J. Biol. Chem. 275 (2000) 32467-32474.

[4] T. Akaike, Y. Noguchi, S. Ijiri, K. Setoguchi, M. Suga, Y.M. Zheng, B. Dietzschold, H. Maeda, Pathogenesis of influenza virus-induced pneumonia: involvement of both nitric oxide and oxygen radicals, Proc. Natl. Acad. Sci. USA 93 (1996) 2448-2453.

[5] T. Akaike, S. Okamoto, T. Sawa, J. Yoshitake, F. Tamura, K. Ichimori, K. Miyazaki, K. Sasamoto, H. Maeda, 8-Nitroguanosine formation in viral pneumonia and its implication for pathogenesis, Proc. Natl. Acad. Sci. USA 100 (2003) 685-690.

[6] J.S. Stamler, S. Lamas, F.C. Fang, Nitrosylation. The prototypic redox-based signaling mechanism, Cell 106 (2001) 675-683.

[7] H.J. Forman, M. Maiorino, F. Ursini, Signaling functions of reactive oxygen species, Biochemistry 49 (2010) 835-842.

[8] S.G. Rhee, H_2O_2, a necessary evil for cell signaling, Science 312 (2006) 1882-1883.

[9] B. D'Autreaux, M.B. Toledano, ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis, Nat. Rev. Mol. Cell Biol. 8 (2007) 813-824.

[10] T. Sawa, H. Arimoto, T. Akaike, Regulation of redox signaling involving chemical conjugation of protein thiols by nitric oxide and electrophiles, Bioconjug. Chem.

21 (2010) 1121-1129.

[11] A. van der Vliet, NADPH oxidases in lung biology and pathology: host defense enzymes, and more, Free Radic. Biol. Med. 44 (2008) 938-955.

[12] B. Halliwell, Oxidative stress and neurodegeneration: where are we now? J. Neurochem. 97 (2006) 1634-1658.

[13] K. Uchida, Lipid peroxidation and redox-sensitive signaling pathways, Curr. Atheroscler. Rep. 9 (2007) 216-221.

[14] T. Tsujita, L. Li, H. Nakajima, N. Iwamoto, Y. Nakajima-Takagi, K. Ohashi, K. Kawakami, Y. Kumagai, B.A. Freeman, M. Yamamoto, M. Kobayashi, Nitro-fatty acids and cyclopentenone prostaglandins share strategies to activate the Keap1-Nrf2 system: a study using green fluorescent protein transgenic zebrafish, Genes Cells 16 (2011) 46-57.

[15] B.A. Freeman, P.R. Baker, F.J. Schopfer, S.R. Woodcock, A. Napolitano, M. d'Ischia, Nitro-fatty acid formation and signaling, J. Biol. Chem. 283 (2008) 15515-15519.

[16] T.K. Rudolph, B.A. Freeman, Transduction of redox signaling by electrophile-protein reactions, Sci. Signal. 2 (2009) re7.

[17] H. Ihara, T. Sawa, Y. Nakabeppu, T. Akaike, Nucleotides function as endogenous chemical sensors for oxidative stress signaling, J. Clin. Biochem. Nutr. 48 (2011) 33-39.

[18] T. Sawa, M.H. Zaki, T. Okamoto, T. Akuta, Y. Tokutomi, S. Kim-Mitsuyama, H. Ihara, A. Kobayashi, M. Yamamoto, S. Fujii, H. Arimoto, T. Akaike, Protein *S*-guanylation by the biological signal 8-nitroguanosine 3',5'-cyclic monophosphate, Nat. Chem. Biol. 3 (2007) 727-735.

[19] D.G. Lim, S. Sweeney, A. Bloodsworth, C.R. White, P.H. Chumley, N.R. Krishna, F. Schopfer, V.B. O'Donnell, J.P. Eiserich, B.A. Freeman, Nitrolinoleate, a nitric

oxide-derived mediator of cell function: synthesis, characterization, and vasomotor activity, Proc. Natl. Acad. Sci. USA 99 (2002) 15941-15946.

[20] T. Akaike, S. Fujii, T. Sawa, H. Ihara, Cell signaling mediated by nitrated cyclic guanine nucleotide, Nitric Oxide 23 (2010) 166-174.

[21] H. Motohashi, M. Yamamoto, Nrf2-Keap1 defines a physiologically important stress response mechanism, Trends Mol. Med. 10 (2004) 549-557.

[22] K. Taguchi, H. Motohashi, M. Yamamoto, Molecular mechanisms of the Keap1-Nrf2 pathway in stress response and cancer evolution, Genes Cells 16 (2011) 123-140.

[23] K. Itoh, K.I. Tong, M. Yamamoto, Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles, Free Radic. Biol. Med. 36 (2004) 1208-1213.

[24] M. Kobayashi, L. Li, N. Iwamoto, Y. Nakajima-Takagi, H. Kaneko, Y. Nakayama, M. Eguchi, Y. Wada, Y. Kumagai, M. Yamamoto, The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds, Mol. Cell. Biol. 29 (2009) 493-502.

[25] J.R. Burgoyne, M. Madhani, F. Cuello, R.L. Charles, J.P. Brennan, E. Schroder, D.D. Browning, P. Eaton, Cysteine redox sensor in PKGIa enables oxidant-induced activation, Science 317 (2007) 1393-1397.

[26] S. Fujii, T. Sawa, H. Ihara, K.I. Tong, T. Ida, T. Okamoto, A.K. Ahtesham, Y. Ishima, H. Motohashi, M. Yamamoto, T. Akaike, The critical role of nitric oxide signaling, via protein *S*-guanylation and nitrated cyclic GMP, in the antioxidant adaptive response, J. Biol. Chem. 285 (2010) 23970-23984.

[27] T. Yoshida, R. Inoue, T. Morii, N. Takahashi, S. Yamamoto, Y. Hara, M. Tominaga, S. Shimizu, Y. Sato, Y. Mori, Nitric oxide activates TRP channels by cysteine *S*-nitrosylation, Nat. Chem. Biol. 2 (2006) 596-607.

[28] T. Uehara, T. Nakamura, D. Yao, Z.Q. Shi, Z. Gu, Y. Ma, E. Masliah, Y. Nomura, S.A. Lipton, *S*-Nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration, Nature 441 (2006) 513-517.

[29] M. Nishida, Y. Maruyama, R. Tanaka, K. Kontani, T. Nagao, H. Kurose, Ga_i and Ga_o are target proteins of reactive oxygen species, Nature 408 (2000) 492-495.

[30] D.T. Hess, A. Matsumoto, S.O. Kim, H.E. Marshall, J.S. Stamler, Protein *S*-nitrosylation: purview and parameters, Nat. Rev. Mol. Cell Biol. 6 (2005) 150-166.

[31] H. Kamata, S. Honda, S. Maeda, L. Chang, H. Hirata, M. Karin, Reactive oxygen species promote TNFa-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases, Cell 120 (2005) 649-661.

[32] N. Iwamoto, D. Sumi, T. Ishii, K. Uchida, A.K. Cho, J.R. Froines, Y. Kumagai, Chemical knockdown of protein-tyrosine phosphatase 1B by 1,2-naphthoquinone through covalent modification causes persistent transactivation of epidermal growth factor receptor, J. Biol. Chem. 282 (2007) 33396-33404.

[33] K. Loh, H. Deng, A. Fukushima, X. Cai, B. Boivin, S. Galic, C. Bruce, B.J. Shields, B. Skiba, L.M. Ooms, N. Stepto, B. Wu, C.A. Mitchell, N.K. Tonks, M.J. Watt, M.A. Febbraio, P.J. Crack, S. Andrikopoulos, T. Tiganis, Reactive oxygen species enhance insulin sensitivity, Cell Metab. 10 (2009) 260-272.

[34] B.C. Dickinson, J. Peltier, D. Stone, D.V. Schaffer, C.J. Chang, Nox2 redox signaling maintains essential cell populations in the brain, Nat. Chem. Biol. 7 (2011) 106-112.

[35] C. Pantano, N.L. Reynaert, A. van der Vliet, Y.M. Janssen-Heininger, Redox-sensitive kinases of the nuclear factor-kB signaling pathway, Antioxid. Redox Signal. 8 (2006) 1791-1806.

[36] R.L. Charles, P. Eaton, Redox signalling in cardiovascular disease, Proteomics

Clin. Appl. 2 (2008) 823-836.

[37] P. Jaspers, J. Kangasjarvi, Reactive oxygen species in abiotic stress signaling, Physiol. Plant 138 (2010) 405-413.

[38] K. Apel, H. Hirt, Reactive oxygen species: metabolism, oxidative stress, and signal transduction, Annu. Rev. Plant Biol. 55 (2004) 373-399.

[39] M. Dewaele, H. Maes, P. Agostinis, ROS-mediated mechanisms of autophagy stimulation and their relevance in cancer therapy, Autophagy 6 (2010) 838-854.

[40] F. Martinon, Signaling by ROS drives inflammasome activation, Eur. J. Immunol. 40 (2010) 616-619.