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“Frontiers in Nitric Oxide and Redox Signaling”

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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.

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