Jpn. J. Infect. Dis., 57, 2004

Contribution of Peroxidases in Host-Defense, Diseases and Cellular Functions

Kazuo Suzuki*, Eri Muso[1] and William M. Nauseef[2]

National Institute of Infectious Diseases, Tokyo, [1]Kitano Hospital Medical Research Institute, Osaka, Japan; [2]University of Iowa and Veterans Administration Medical Center, Iowa, USA

SUMMARY: Peroxidases figure prominently in biology and contribute significantly to cell biology, host defense against infection, and pathogenesis of several inflammatory diseases. These varied and diverse aspects of peroxidase biochemistry and its clinical implications will be the subjects of in-depth analysis at the 4th International peroxidase meeting held in Kyoto. Specific topics range from the molecular basis of peroxidase structure and function to the clinical consequences of autoantibodies generated against myeloperoxidase (MPO), the peroxidase present in circulating neutrophils. Consideration of novel aspects of peroxidase biology, both unanticipated biochemical properties of MPO and the potential role of MPO in the pathogenesis of inflammatory diseases such as atherosclerosis, will also be included. In addition to peroxidases, the newly expanded family of NADPH oxidases will be discussed. We hope that this collection of scientists who share a common interest in peroxidase biology but each possess expertise in distinctly different aspects of the subject will provide a setting for spirited discussion and a lively exchange of views to yield advances in understanding and to create new applications of those insights to benefit clinical medicine, agriculture and industry.

1. Peroxidase and related oxidase studies

In 2000, a book entitled "The peroxidase multigene family of enzymes" (1) updated the peroxidase field and summarized the proceedings of the 2nd International Peroxidases Meeting held in Chiemsee and organized by Drs. Petro Petrides and William Nauseef. However since that time, several advances in the peroxidase field have occurred. Recent work has uncovered novel biochemistry, new gene families, and knock-out animals have been used to address important and unanswered questions. We convene now in Kyoto peroxidase scientists from around the world to discuss ongoing studies and share new insights into the biology of this important protein family.

Myeloperoxidase (MPO): The organizing principle of the first peroxidase meeting was an interest in myeloperoxidase, the family member expressed in exclusively in cells of a neutrophilic or monocytic lineage. As neutrophils are the dominant cellular component of the human innate immune system and the oxygen-dependent antimicrobial system of neutrophils is the most efficient defense against microbes, MPO has a central place in neutrophil microbicidal action. Unique among the animal peroxidase family, MPO catalyzes the two electron oxidation of chloride ion in the presence of hydrogen peroxide to generate hypochlorous acid, a potent antimicrobial agent. The MPO-hydrogen peroxide-chloride system is responsible for microbicidal activity against a wide range of organisms and has served as the paradigm for neutrophil oxidative killing of bacteria.

Dysfunction of host-defense due to MPO-deficiency in human: Despite its central role in normal host defense, the phenotype of inherited deficiency of MPO has not been clearly demonstrated as increased risk for infectious complications. Four allelic mutations resulting in inherited MPO deficiency have been previously reported (2-5) R569W, Y173C and M251T and G501S. The defect mechanisms and manner of inheritance has been described in detail (3). The prevalence of complete MPO deficiency in Japan is estimated to be 1.75/100,000, a value 14- to 28-fold lower than that of the United States and Europe, respectively (1,6). The molecular basis of deficiencies in Japan and their relation to the genotypes seen elsewhere are the subject of ongoing study.

MPO-deficient mice: Whereas population studies on the prevalence of complications among human with inherited MPO deficiency have been of limited use, the application of molecular techniques to generate mice deficient in MPO has proven a useful experimental tool. The earlier reports of the clinical consequences of MPO deficiency described the increased risk in affected individuals for disseminated and often fatal candidiasis. This association between MPO activity and host defense against Candida was recapitulated in the mouse model by Aratani et al. (7). The availability of the MPO knock-out mouse also makes possible testing novel hypotheses regarding the role of MPO in pathogenesis of diseases unrelated to infection. Unexpectedly MPO-deficient mice show an increase in experimentally induced atherosclerosis (8), perhaps highlighting important species differences between mouse and man. Nonetheless, the mouse model will provide important and novel insights into MPO biology.

Peroxidase related to Disease Activity: MPO-ANCA related diseases: In addition to host-defense function, MPO is also a target molecule of MPO-specific anti-neutrophil cytoplasmic autoantibody (MPO-ANCA). Antibodies directed against cytoplasmic constituents of the neutrophil, specifically MPO and proteinase 3, have been extensively described as markers for systemic vasculitis and crescentic glomerulonephritis. Evidence further indicates that MPO and the MPO-ANCA are risk factors for the development of immune-mediated renal disease, as the sera of patients with microscopic polyangiitis and crescentic glomerulonephritis (CrGN), high titers of MPO-ANCA are frequently detected. Studies in the mouse model promise to provide important insights into the pathogenesis of this vasculitic disease.

Immunomodulatory therapy for MPO-ANCA related diseases: Many therapeutic trials for MPO-ANCA related diseases have been performed, especially those for rapidly progressive glomerulonephritis (RPGN) due to CrGN. Among the various interventions tested, intravenous immunoglobulin (IVIg) has improved the outcome of this highly life-threatening disease in Europe. Although there are many potential mechanisms underlying the beneficial effect of IVIg, one may be the suppression of the presentation of MPO to stimulated neutrophils. In addition other immunomodulatory effects including the correction of abnormally deviated Th1/Th2 balance and suppression of the highly elevated cytokine activity may play a role (submitted). The favorable outcome of the IVIg for MPO-ANCA related RPGN in Japan and the partial elucidation of the mechanism of action will be presented.

NOX family: MPO action requires hydrogen peroxide and in stimulated neutrophils, the NADPH oxidase generates reactive oxygen species, including hydrogen peroxide, from molecular oxygen. The phagocyte NADPH oxidase is a multicomponent enzyme containing membrane and cytosolic components that assemble at the membrane when neutrophils are stimulated by an appropriate agonist. The membrane component of the NADPH oxidase is a heterodimeric protein composed of gp91*phox* and p22*phox*. Recently homologues of gp91*phox* have been described, giving birth to the NOX (NADPH oxidase) protein family. Previously work from the laboratories of Krause and of Sumimoto were presented at 6th MPO meeting at Atami in 2000 (Abstract Book). As the family grows and new data emerge, it seems that the NOX enzymes have two physiological functions: 1) Host defense, typified by the phagocyte NADPH oxidase and indirectly suggested for NOX1, DUOX1, and DUOX2.

*Corresponding author: E-mail: ksuzuki@nih.go.jp

and 2) Biosynthetic processes, as seen with for DUOX enzymes, implicated in biosynthesis of thyroid hormone in mammals and in the crosslinking of extracellular matrix in *C. elegans*. In addition, NOX enzymes are involved in signaling function of ROS and new information will be presented at the meeting.

2. Role of the International Peroxidase Meeting

Drs. Suzuki and Nauseef have organized this international meeting to extend insights into role of MPO and other peroxidases, as originally intended at the first peroxidase meeting. The first meeting on myeloperoxidase was inspired and organized by Dr. Dolphe Kutter and held in Luxemburg in 1996. It was a small meeting but served to confirm the need for an international meeting where investigators, clinical and basic, who shared an interest in the biology of MPO could come together to discuss important aspects of its biology and role in health and disease. The second meeting was convened to meet this charge and was held in a Benedictine Abbey on Fraueninsel in Lake Chiemsee, in Bavaria, Germany. Organized by Petro Petrides from Munich, Germany and William Nauseef from the University of Iowa, USA, the meeting in 1998 was a great success, generating the publication of a book "The peroxidase multigene family of enzymes: Biochemical basis and clinical applications" and setting the stage for future meetings. The 3rd conference was held in Vienna, Austria in 2002 and was organized by Christian Obinger. Christian expanded the chemistry component of the meeting and expanded the format to include not only other animal peroxidases but also peroxidases from the plant world.

The 4th International Peroxidase Meeting: The 4th International Peroxidase Meeting is held on October 27 - 30, 2004, Kyoto Palulu Plaza (www.nih.go.jp/MPO/). Based on the background of International Peroxidase Meeting, we will organize the 4th International Peroxidase Meeting joined with the 10th MPO meeting organized by Muso, Kitano Hospital. The MPO meeting has been held in Japan since 1995, making this the 10th anniversary MPO Meeting. Thus it seems appropriate celebrate this special milestone by joining with the 4th International Peroxidase Meeting. The program for the meeting has been organized around the following format: Opening Lecture: Contribution of MPO in vasculitis development by K. Suzuki, and Plenary Lecture: Lessons from MPO deficiency about functionally important structural features by W. Nauseef will be announced. Special lectures-1. Clinical treatment for patients with MPO-ANCA by D. Jayne, E. Muso, and Y. Aratani, and -2. New aspects of peroxidases and oxidases: Nox/Duox family NADPH oxidases: expression patterns and possible physiological functions by K-H Krause will be presented. In addition, five sessions: MPO-ANCA-related diseases, action and molecular aspects of peroxidases, inflammation and peroxidaserelated diseases, peroxidases and NADPH oxidases, and reaction of MPO will be joined with poster presentations. Conferees registered are from Austria, France, Germany, Italy, New Zealand, Russia, Spain, Sweden, Switzerland, UK, and USA in addition to Japan.

Thus, we will have presentations of various peroxidases and other oxidases in this meeting. We intend to provide a venue at these sessions for discussion of all aspects of peroxidase biology. Finally, we hope that the insights and information provided at the meeting will reveal new roles for the peroxidases and other oxidases in health and disease.

The next meeting: The 5th meeting will be held in Christchurch in New Zealand and organized by Dr. Tony Kettle in The Christchurch Medical School.

ACKNOWLEDGMENTS

We thank to all local and international organizers and advisory organizers, speakers, conferees in poster presentation, staffs and the editorial office of Japanese Journal of Infectious Diseases. Also, we represent appreciation to grant supports by 78 companies, which belong to The Pharmaceutical Manufacturers' Associations of Japan, Inoue Foundation for Science, Exoxemis Co., in USA, and all cooperative companies.

REFERENCES

1. Petrides, P. E. and Nauseef, W. M. (eds.) (2000): The Peroxidase Multigene Family of Enzymes. Springer-Verlag, Berlin.
2. Nauseef, W. M., Brigham, S. and Cogley, M. (1994): Hereditary myeloperoxidase deficiency due to a missense mutation of arginine, 569, to tryptophan. J. Biol. Chem., 269, 1212-1216.
3. DeLeo, F. R., Goedken, M., McCormick, S. J. and Nauseef, W. M. (1998): A novel form of hereditary myeloperoxidase deficiency linked to endoplasmic reticulum/proteasome degradation. J. Clin. Invest., 101, 2900-2909.
4. Romano, M., Dri, P., Dadalt, L., Patriarca, P. and Baralle, F. E. (1997): Biochemical and molecular characterization of hereditary myeloproliferative deficiency. Blood, 90, 4126-4134.
5. Ohashi, Y.Y., Kameoka, Y., Persad, A.S., Kohi, F., Yamagoe, S., Hashimoto, K. and Suzuki, K. (2004): Novel missense mutation found in Japanese patient with myeloperoxidase deficiency. Gene, 327, 195-200.
6. Nunoi, H., Kohi, F., Kajiwara, H. and Suzuki, K. (2003): Prevalence of inherited myeloperoxidase deficiency in Japan. Microbiol. Immunol., 47, 527-531.
7. Aratani, Y., Koyama, H., Nyui, S., Suzuki, K., Kura, F. and Maeda, N. (1999): Severe impairment in early host defense against *Candida albicans* in mice deficient in myeloperoxidase. Infect. Immun., 67, 1828-1836.
8. Brennan, M. L., Anderson, M. M., Shih, D. M., Qu XD, Wang X., Mehta, A. C., Lim, L. L, Shi, W., Hazen, S. L., Jacob, J. S., Crowley, J. R., Heinecke, J. W. and Lusis, A. J. (2001): Increased atherosclerosis in myeloperoxidase-deficient mice. J. Clin. Invest., 107, 419-430.