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# In Vivo Role of Myeloperoxidase for the Host Defense

Yasuaki Aratani*, Fumiaki Kura[1], Haruo Watanabe[1], Hisayoshi Akagawa[2], Yukie Takano[2], Kazuo Suzuki[2], Mary C. Dinauer[3], Nobuyo Maeda[4] and Hideki Koyama

*Kihara Institute for Biological Research, Yokohama City University, Yokohama, [1]Department of Bacteriology and [2]Department of Bioactive Molecules, National Institute of Infectious Diseases, Tokyo, Japan; [3]Indiana University, Indiana, [4]University of North Carolina, North Carolina, USA*

**SUMMARY**: Myeloperoxidase (MPO) is located within neutrophils capable of producing HOCl. To define the in vivo role of MPO, we have generated MPO-knockout (MPO-KO) mice. The mice without MPO developed normally. However, MPO-KO mice showed severely reduced cytotoxicity to various microorganisms such as *Candida albicans*, *Aspergillus fumigatus*, and *Klebsiella pneumoniae*, demonstrating that MPO-dependent oxidative system is important for host defense against fungi and bacteria, although the effect varies from species to species of pathogens. To compare the importance of MPO and NADPH-oxidase for host defense, MPO-KO and chronic granulomatous disease (CGD) mice were infected with different doses of *C. albicans*, and their infection severity was analyzed. CGD mice exhibited increased mortality and tissue fungal burden in a dose-dependent manner, whereas normal mice showed no symptoms. Interestingly, at the highest dose, the mortality of MPO-KO mice was comparable to CGD mice, but was the same as normal mice at the lowest dose. These results suggest that MPO and NADPH-oxidase are equally important for early host defense against a large inocula of *Candida*.

Neutrophils are believed to be the first line of defense against invading microorganisms, but in vivo roles of reactive oxygens produced by neutrophils are not well known. Myeloperoxidase (MPO) catalyzes reaction of hydrogen peroxide with chloride ion to produce hypochlorous acid that is used for microbial killing by phagocytic cells. To define the in vivo role of MPO, we have generated mice having no peroxidase activity in their neutrophils and monocytes (1). MPO-deficient (MPO-KO) mice showed severely reduced cytotoxicity to *Candida albicans*, *Aspergillus fumigatus*, *Trichosporon asahii*, and *Pseudomonas aeruginosa*, and others (Table 1) (1-3), demonstrating that MPO-dependent oxidative system is important for host defense against fungi and bacteria.

However, the significance of MPO compared to the NADPH-oxidase is still unclear because individuals with MPO deficiency are usually healthy in contrast to the patients with chronic granulomatous disease (CGD) who present clinical symptoms early in life and die with recurrent infections during childhood. To better understand the contributions of MPO and NADPH-oxidase to antifungal defense mechanisms, we compared the susceptibility of MPO-KO mice and CGD mice to the infections with *C. albicans*. Interestingly, at the highest dose, the mortality of MPO-KO mice was comparable to CGD mice, but was the same as normal mice at the lowest dose (Fig. 1). At the middle dose, the number of fungi disseminated into various organs of the MPO-KO mice was comparable to the CGD mice in one week after infection, but it was significantly lower in 2 weeks (4). These results suggest that MPO and NADPH-oxidase are equally important for early host defense against a large inocula of *Candida*.

Table 1. Recovery of fungi and bacteria from the lungs of wild-type and MPO-KO mice after intranasal inoculation

| Organism | log CFU/lung | | | B/A |
|---|---|---|---|---|
| | 0.5 h | 48 h | | |
| | | (A) Wild type | (B) Mutant | |
| *Candida albicans* | 6.7 | 4.8 ± 0.2 | 6.3 ± 0.2 | 30.1 |
| | 5.7 | 3.6 ± 0.2 | 5.4 ± 0.1 | 66.1 |
| *Cadida tropicalis* | 6.0 | 4.1 ± 0.2 | 5.6 ± 0.1 | 33.1 |
| | 5.1 | 3.0 ± 0.2 | 3.5 ± 0.1 | 3.0 |
| *Trichosporon asahii* | 6.0 | 4.7 ± 0.1 | 6.1 ± 0.1 | 26.3 |
| | 5.1 | 3.6 ± 0.2 | 4.2 ± 0.1 | 3.9 |
| *Aspergillus fumigatus* | 5.7 | 2.2 ± 0.2 | 3.6 ± 0.2 | 22.9 |
| | 5.2 | 1.8 ± 0.5 | 2.9 ± 0.2 | 12.9 |
| *Pseudomonas aeruginosa* | 5.8 | 3.5 ± 0.3 | 6.3 ± 0.3 | 550.0 |
| | 5.0 | 2.8 ± 0.1 | 2.9 ± 0.2 | 1.3 |
| *Klebsiella pneumoniae* | 6.8 | 3.3 ± 0.3 | 4.3 ± 0.3 | 9.3 |
| | 5.2 | <1.0 | 1.9 ± 0.9 | >8.1 |

CFU of inoculated fungi and bacteria in mouse lungs was assessed at indicated times.

*Corresponding author: E-mail: yaratani@yokohama-cu.ac.jp

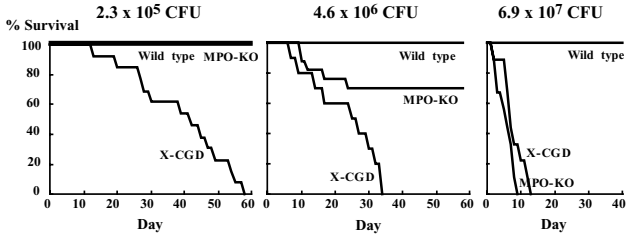


Fig. 1. Survival of mice after *C. albicans* infection. Wild-type, MPO-KO, and X-CGD mice were intraperitoneally infected with the indicated doses of *Candida*.

Hereditary MPO deficiency is a common neutrophil defect with estimated incidence of 1 in 2,000 in the United States, and of 1 in 50,000 in Japan. Our present results suggest that MPO-deficient individuals could exhibit similar problems as CGD patients if exposed to a large amount of microorganisms.

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