festation of in vivo anti-candidal activity.

Our previous hypothesis considered that macrophages activated primarily or secondarily by BRMs may play an important role in anti-candidal activity.[13] Since GM-CSF was originally known to stimulate macrophages, the activation of macrophages appears to be a direct result of this cytokine effect. Antifungal activity and mechanisms of activated macrophages are still controversial and speculative, making further detailed studies on the mechanisms of increased resistance of carrageenan-sensitive effectors of great interest. Furthermore, we have indicated that γ-IFN plays a key role in the manifestation of in vivo anti-candidal activity.

Most BRMs have been thought to be effective only when given prophylactically.[4] In addition to macrophages, potent candicidal activity by neutrophils has also been demonstrated in various experimental infection models.[26] Therefore, in this study, the protection induced by GM-CSF appears to be due to its direct effect on macrophage activation. The therapeutic potential of cytokine may be limited by the degree of its toxicity,[27] the brief duration of its activating effect on tissue, and our inability to selectively deliver the molecule to the appropriate effector cells. However, it is possible that these limitations may be overcome by the use of various drug delivery systems. Liposomal GM-CSF is one of the methods considered. On the other hand, new combinations of GM-CSF with new antifungal agents such as amphotericin B[28] and fluconazole[29] have also recently been studied, and their clinical applications are now being developed.

One of the present authors[5,13] found that γ-IFN plays a key role in the manifestation of in vivo anti-candidal activity in most biological response modifiers (BRMs). Therefore it may be reasonable to assume that γ-IFN plays an important role as one of the factors in protecting mice against candidiasis.

REFERENCES

1. Gorensek, M.J. The immunocompromised host. *Dermatol. Clin.* 1989; **7**: 353-367.
2. Cryz, S.J. Jr., Furer, E., Germanier, R. Simple model for the study of *Pseudomonas aeruginosa* infections in leukopenic mice. *Infect. Immunol.* 1983; **39**: 1067-1071.
3. Deepe, G.S., Bullock, W.E. Immunological aspects of fungal pathogenesis. *Eur. J. Clin. Microbiol. Infect. Dis.* 1990; **9**: 567-579.
4. Talmadge, J.E., Herberman, R.B. The preclinical screening laboratory: evaluation of immunomodulatory and therapeutic properties of biological response modifiers. *Cancer Treatment Rep.* 1986; **70**: 171-182.
5. Chen, H.Y., Chen, C.H., Mikami, Y., Yeh, M.Y., Wu., J.S. Comparison of in vivo protective activity of interleukin-1" with that of interferon and tumor necrosis factor against systemic *candida albicans* infection in mice. *J. Interferon Res.* 1993; **12(S1)**: S110.
6. Sakamoto, K.M., Golde, D.W., Gasson, J.C. The biology and clinical applications of granulocyte-macrophage colony-stimulating factor. *J. Pediat.* 1991; **118**: S17-S20.
7. Bodey, B., Bodey, B. Jr., Siegel, S. E., Kaiser, H. E. Molecular ontogenesis of the thymic reticulo-epithelial cell network during the organization of the cellular microenvironment. In vivo. 1999; **13**: 267-294.
8. Marodi, L., Tournay, C., Kaposzta, R., Johnston, R.B. Jr., Moguilevsky, N. Augmentation of human macrophage candidacidal capacity by recombinant human myeloperoxidase and granulocyte-macrophage colony-stimulating factor. *Infect. Immunol.* 1998; **66**: 2750-2754.
9. Eckert, J., Ramp, T. Cryopreservation of *Echinococcus multiocularis* metacestodes and subsequent proliferation in rodents (Meriones). *Zeitschrift Parasitenkunde* 1985; **71**: 777-787.
10. Chen, H.Y., Chen, C.H., Yeh, M.Y., Wu, J.S., Yazawa, K., Mikami, Y. In vivo anti-candidal activity induced by a traditional Chinese herbal medicine, Ganoderma Lucidum. *Jpn. J. Med. Mycol.* 1992; **33**: 505-512.
11. Wright, S.C., Bonavida, B. YAC-1 variant clones selected for resistance to natural killer cytotoxic factors are also resistant to natural killer cell-mediated cytotoxicity. *Proc. Natl. Acad. Sci. USA.* 1983; **80**: 1688-1692.
12. Blot, C., Lebrec, H., Roger R., Bohuon, R., Pallardy, M. Immune parameters are affected differently after cyclosporine A exposure in Fischer 344 rats and B6C3F1 mice: implications for immunotoxicology. *Toxicology.* 1994; **94**: 231-245.