Candida albicans INDUCES THE ACTIVATION OF THE ARGINASE PATHWAY IN THE HUMAN MONOCYTE CELL LINE (U937)

Icely, PA, Renna, MS, Sotomayor, CE*
CIBICI-CONICET. Facultad de Ciencias Químicas. Universidad Nacional de Córdoba
Haya de la Torre y Medina Allende, Ciudad Universitaria, Córdoba-Argentina (CP5000).

INTRODUCTION
The phagocytes including Monocytes and Macrophages, play an important role in the defence mechanism against the infection with C. albicans. In the metabolism of the L-arginine, the balance between the activation of the inducible Nitric Oxide Sintetase(iNOS) pathway and the arginase pathway, promotes in these cells two alternative states that have been associated with different immune response in the host. The “in vitro” host-pathogen models are a powerfull tool to explore particular interaction and their modulation by therapeutic agents. In the present work we evaluated the activation of L-arginine pathway in a human monocyte cell line(U937), in order to validate previous results obtained with purified human cells(PHC), and to explore the effect of antifungal treatment in the balance of this metabolic pathway. Two antifungal agents used frequently in the treatment of this micosis, Fluconazole and Amphotericine B, were included in this study.

MATERIAL AND METHODS
We used the patogenic C.albicans strain 387 as previously described(1); Fluconazole and Amphotericine B as antifungal agents; different stimulants for the macrophagic cell as LPS from Escherichia coli serotype 055:B5 and PMA from Sigma.
The monocyte cell line U937 was cultured at a density of 3x10^5 cell/mL and incubated with C.albicans, in the absense or presense of the different stimulants or the different antifungal agents single or in combination with C.albicans. The supernatants were removed and used to determine nitric oxide and the monolayer was used to determine arginase activity(2).

RESULTS
The contact of C.albicans with U937 induces the activation of L-arginine pathway in a dose dependent manner(p<0,05). Although the NO production was absent, the balance between both pathways favored the production of arginase. The level of stimulation was higher and the value obtained after fungus stimulation at 5:1(E:T) was similar to the classic activator PMA(p<0,05). It has been described that antimicrobial drugs may have broad immunomodulatory properties besides their antifungal activity. In the present study, neither Amphotericine B nor Fluconazole induce the NO production, but when the activation of arginase pathway was evaluted only in presence of Fluconazole, the U937 cells produce arginase. When the cells were cocultured with C.albicans and the antifungal agents, the same profile was observed.

CONCLUSIONS
In several host-pathogen interactions, mean the classic Mo/MØ activation is associated with the pathogen control, the alternative Mo/MØ way is considered to favored growth and establishment of infection. The relevance of balance of MØ activation pathway against C.albicans is not completly understood and in vitro approach could contribute to explore this field. Here in we provide evidence of the ability of fungus to trigger the L-arginine pathway and favored the alternative activation of U937. These cells present the same profile of response that PHC, indicating that U937 could be used as a valid model to evaluate the molecular mechanism triggered by the pathogen during the host interaction. Interestingly the arginase pathway could be modulated in different manners depending on antifungal agents.

REFERENCES

*Sotomayor, CE. TEL +54 351 4344976; FAX +54 351 4333048; e-mail: csotomay@mail.fcq.unc.edu.ar