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Short communication

In vitro differentiation of murine hematopoietic progenitor cells toward the myeloid lineage occurs in response to *Staphylococcus aureus* and yeast species

Victoria Maneu [a], Miguel Ángel Estévez [b], Sara de Dios [b], Daniel Gozalbo [b], María Luisa Gil [b], Javier Megías [b,*]

[a] Departamento de Óptica, Farmacología y Anatomía, Universidad de Alicante, Alicante, Spain
[b] Departamento de Microbiología y Ecología, Universitat de València, Burjassot, Spain

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ABSTRACT

We have studied the effect of inactivated microbial stimuli (*Candida albicans, Candida glabrata, Saccharomyces boulardii,* and *Staphylococcus aureus*) on the *in vitro* differentiation of lineage negative (Lin^-) hematopoietic progenitor mouse cells. Purified Lin^- progenitors were co-cultured for 7 days with the stimuli, and cell differentiation was determined by flow cytometry analysis. All the stimuli assayed caused differentiation toward the myeloid lineage. *S. boulardii* and particularly *C. glabrata* were the stimuli that induced in a minor extent differentiation of Lin^- cells, as the major population of differentiated cells corresponded to monocytes, whereas *C. albicans* and *S. aureus* induced differentiation beyond monocytes: to monocyte-derived dendritic cells and macrophages, respectively. Interestingly, signaling through TLR2 by its pure ligand Pam3CSK4 directed differentiation of Lin^- cells almost exclusively to macrophages. These data support the notion that hematopoiesis can be modulated in response to microbial stimuli in a pathogen-dependent manner, being determined by the pathogen-associated molecular patterns and the pattern-recognition receptors involved, in order to generate the populations of mature cells required to deal with the pathogen.

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1. Introduction

Cells of the immune system are prepared for recognizing a variety of pathogen organisms through pattern-recognition receptors (PRRs), which recognize molecular signatures of microbial agents and function as sensors for infection. Toll-like receptors (TLRs) are a family of PRRs that induce the activation of innate immune responses and modulate the subsequent development of adaptive immune responses [1]. Recent studies have indicated that TLRs are not only expressed in mature immune cells, but also in hematopoietic stem and progenitor cells (HSPCs) and their progeny, suggesting a role for them in hematopoiesis during infection [2].

Our group has focused on the involvement of TLRs in the recognition of *Candida albicans*, the most frequent cause of opportunistic human fungal infections, and we have described that inactivated yeasts of *C. albicans* interact *in vivo* with murine HSPCs causing their differentiation toward the myeloid lineage in a TLR2-dependent manner [3–5], and that *in vitro* this differentiation produced monocyte-derived dendritic cells (moDCs), via TLR2- and Dectin-1-dependent pathways [6].

Apart from this, little is known about the effect of other species of yeast and bacterial microbes on the *in vitro* differentiation patterns of hematopoietic progenitor cells (HPCs). For that reason, the objective of the present work has been to study the effect of other microorganisms on *in vitro* differentiation of murine HPCs. In addition to *C. albicans*, we have tested other two yeast and one bacteria species: (a) *Candida glabrata*, the second fungus causing candidiasis worldwide [7]; (b) *Saccharomyces boulardii*, a non-pathogenic yeast used as a probiotic agent against acute gastroenteritis and diarrhea [8] which can produce fungaemia in immunodepressed patients [9,10], and (c) the Gram-positive bacterial species *Staphylococcus aureus*, a relevant pathogen causing a plethora of infections in humans, which is recognized by TLR2 [11].

* Corresponding author. Tel.: +34 61 715 8600; fax: +34 96 354 4570.
E-mail address: javier.megias@uv.es (J. Megías).

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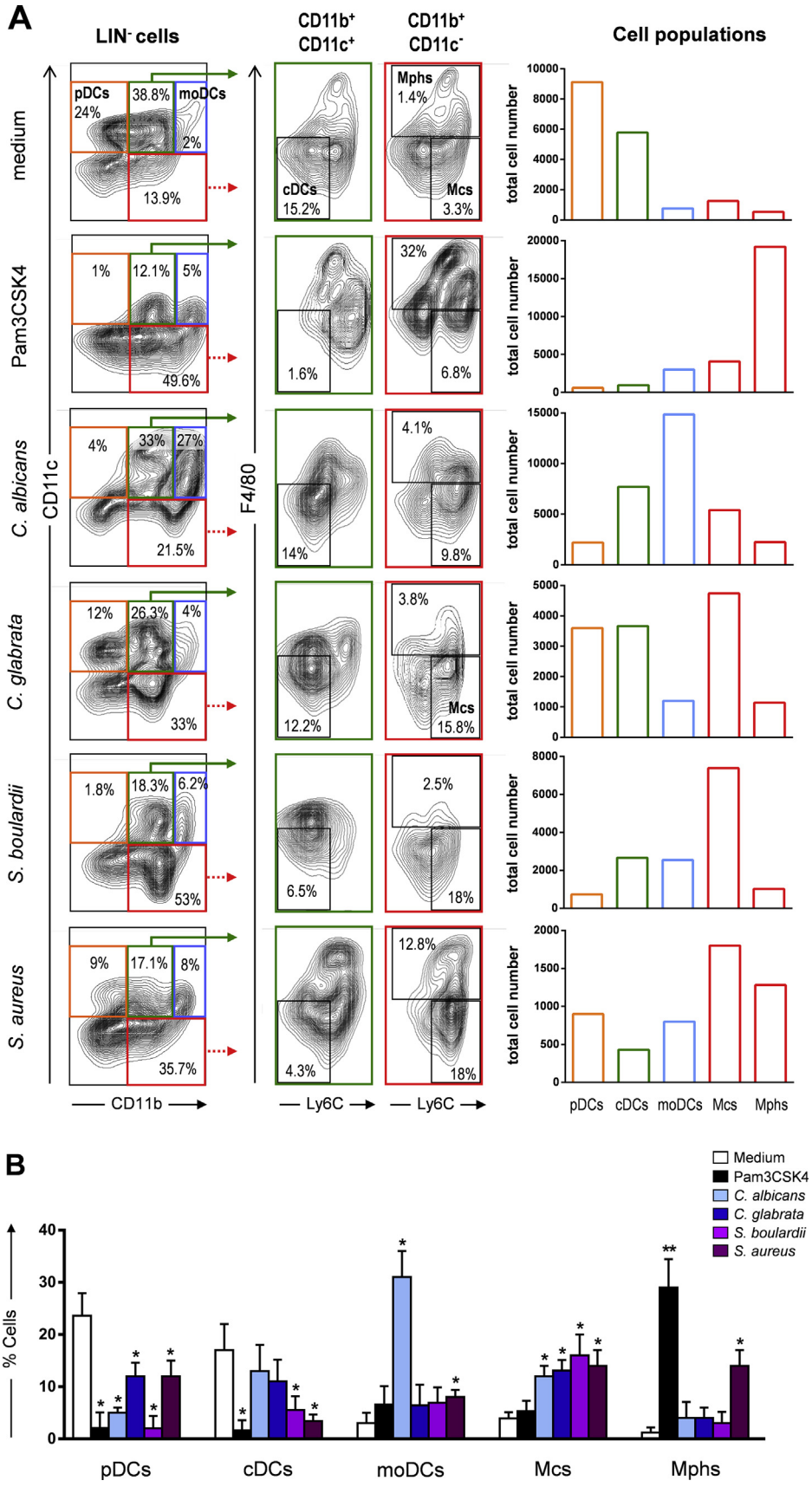
A
LIN- cells
CD11b+ CD11c+
CD11b+ CD11c-
Cell populations
medium
Pam3CSK4
C. albicans
C. glabrata
S. boulardii
S. aureus
CD11c
F4/80
CD11b
Ly6C
Ly6C
pDCs
38.8%
moDCs
2%
13.9%
cDCs
15.2%
Mphs
1.4%
Mcs
3.3%
1%
12.1%
5%
49.6%
1.6%
32%
6.8%
4%
33%
27%
21.5%
14%
4.1%
9.8%
12%
26.3%
4%
33%
12.2%
3.8%
Mcs
15.8%
1.8%
18.3%
6.2%
53%
6.5%
2.5%
18%
9%
17.1%
8%
35.7%
4.3%
12.8%
18%
total cell number
pDCs
cDCs
moDCs
Mcs
Mphs
B
Medium
Pam3CSK4
C. albicans
C. glabrata
S. boulardii
S. aureus
% Cells
pDCs
cDCs
moDCs
Mcs
Mphs

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