**EDITORIAL**

*Candida albicans* triggers a differential profile of microRNAs depending on its growing form

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*Candida albicans* is a polymorphic fungus capable of growing in yeast, pseudohyphal and hyphal forms, being the latter associated with its pathogenic capacity.1 This fungus belongs to the commensal microbiota but becomes an opportunistic systemic pathogen in certain circumstances of immunosuppression such as HIV infection, transplants or neutropenia. Despite the advances in antifungal therapies, mortality rates in systemically infected patients can rise up to 60 %.2 Considering that, much effort is being devoted to understand the cellular and molecular events triggered by this pathogen when detected by different components of the immune system.

Immune cells such as macrophages, dendritic cells, neutrophils or γδT cells can recognize *Candida albicans* by means of a plethora of pattern-recognition receptors (PRRs) including Toll-like receptors (TLRs) or C-type lectin receptors (CLRs). Dectin-1 is one of the most relevant CLRs involved in *Candida* recognition, responsible for triggering many antifungal responses such as phagocytosis, generation of reactive oxygen species (ROS) and cytokine production.3

In this issue, D. Agustinho and colleagues4 report that certain sets of microARNs (miR) are differentially induced in mouse macrophages depending on the morphology of *Candida albicans* that is recognized. Due to its relevance in immune responses, authors performed a more detailed study of miR155 expression. Their data indicate that miR155 induction by *Candida albicans* hyphae is fully dependent on Dectin-1. At the signaling level, Dectin-1-mediated miR155 expression relies on the proximal adaptor Syk, with no role for Raf-1.

Although induction of miRs in response to *Candida albicans* in macrophages has been already described,5 Agustinho’s work provides the important notion of a defined expression profile of miRs induced by different morphologies of the fungus. This aspect is not trivial as it could stand on the base of how the immune system successfully discriminates between yeast and hyphal forms of *C. albicans*, controlling the transition from commensalism to pathogenicity.6 Structural particularities on surface glucans7 or recognition by different populations of immune cells8 have been described as potential mechanisms responsible for this morphologic discrimination. Showing that, it is tempting to speculate that different expression patterns of miRs can be also found in other immune cell types depending on the *Candida* morphology. Regarding this issue, dendritic cells are of special interest as master antigen presenting cells.

An important concern raised by Agustinho’s work is the relevance of the mouse background for the study of Dectin-1-triggered responses against *Candida albicans*. Their data suggest that different mouse strains could influence the variations in the expression of miRNAs. It is important to remember that the first description of Dectin-1 contribution in the response against *Candida* was controversial: Brown’s group stated that Dectin-1 was critical to control disseminated candidiasis9 while Iwakura’s research proposed that it was redundant.10 Nowadays it is mostly accepted that different backgrounds of the mouse strains used between labs would explain this discrepancy. The same fact could explicate inconsistent results obtained regarding the relevance of Dectin-1 in “trained immunity.” This process consists in a boosted inflammatory response in monocytes after a first exposition to *Candida albicans*, generating protection against a secondary reinfection.11 However, it has also been proposed that Dectin-1 is redundant in this process.12 As suggested by Agustinho and colleagues,
these discrepancies could be due to the use of different mouse backgrounds. Much attention should be paid to this issue in the future in order to avoid misinterpretations.

Looking at the general picture, it is interesting to see that most of the miRNAs analyzed are induced after a certain time of stimulation (up to 8 hours), in accordance with previous data. This clearly supports the regulatory role of miRNAs in response to Dectin-1, not being part of the primary response, as it is for example the case of TNFα. It is also noteworthy that hyphae recognition induced higher levels of nearly all miRNAs. Taking into account that the hyphal form is associated with the capacity of tissue invasion, one could speculate that the hyphae-induced miRNA profile is an alternative pathogenicity mechanism. Generation of Candida mutants that selectively lack the capacity to induce these miRNAs would help to elucidate their functional relevance.

The authors focused on the induction of miR155 because of its known relevance in the regulation of immune responses. They established a correlation between miR155 detection and reduced mRNA expression of some of its known targets such as MyD88, SHIP-1, SOCS1 and IKKα. Experiments of loss-of-function and/or gain-of-function are demanded to clarify the specific role of this miRNA in macrophages after Dectin-1 engagement.

Still, it is interesting that the 2 analyzed targets with well-recognized regulatory functions such as SHIP-1 and SOCS1 have been implicated in the molecular signaling triggered by Dectin-1. In this context, SHIP-1 regulates ROS production and SOCS1 mitigates the inflammatory responses triggered by TLR9. On the other hand, MyD88 has been implicated in the cytokine production triggered by Candida albicans infection. Keeping that in mind and as indicated by the authors, it is difficult to isolate the global effects of miR155.

However, mice overexpressing miR155 showed a myeloproliferative disorder, resembling the phenotype observed in SHIP-1 deficient mice. In addition, mice lacking miR155 showed increased SHIP-1 and SOCS1 expression with dampened inflammatory responses. All together it would allow venturing that 2 of the most representative targets for miR155 are SHIP-1 and SOCS1. If so, the functional consequence of miR155 induction downstream Dectin-1 would be boosting or maintaining the inflammatory response against Candida hyphae. It could be envisioned as a mechanism to reinforce the killing of the pathogenic form of the fungus.

Finally, Agustinho’s data show that miR155 expression induced by Candida albicans hyphae is completely dependent on Dectin-1 and Syk but at the same time, miR155 is further increased in the absence of both TLR2 and TLR4. The crosstalk between different families of PRRs has been documented as evasion strategy used by microbial pathogens or alternatively, as an immune mechanism to increase the inflammatory response against those pathogens. Of particular interest for this work, it has been described that Dectin-1 inhibits TLR4 signaling by reducing TLR4 expression in the context of sterile hepatic inflammation. Altogether, one may wonder whether there is a regulatory feedback loop between these receptors in a way that one controls the expression of the other. An easy approach to address this point would be the analysis of Dectin-1 expression on macrophages lacking both TLR2 and TLR4.

In summary, this work opens new interesting avenues of research in the field of the immune response against Candida albicans. Possible arising questions are: which are the functional consequences of the differential miRNA expression induced by the hyphal form? Is it beneficial for the host or for the pathogen? Which are the molecular targets in this context? Eventually, can we manipulate this process in order to improve our fight versus this infection?

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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