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Immunity and tolerance to infections in experimental hematopoietic transplantation

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Resistance and tolerance are two types of host defense mechanisms that increase fitness in response to fungi. Several genetic polymorphisms in pattern recognition receptors, most remarkably Toll-like receptors (TLRs), have been described to influence resistance and tolerance to aspergillosis in distinct clinical settings. TLRs on dendritic cells pivotally contribute in determining the balance between immunopathology and protective immunity to the fungus. Epithelial cells also contribute to this balance via selected TLRs converging on indoleamine-2,3-dioxygenase (IDO). Studies in experimental hematopoietic transplantation confirmed the dichotomy of pathways leading to resistance and tolerance to the fungus providing new insights on the relative contribution of the hematopoietic/nonhematopoietic compartments.

Hematopoietic stem cell transplantation (HSCT) has been proven an effective therapeutic strategy for hematological malignancies and immune disorders. Despite the significant advances witnessed in the technique of transplantation and in therapies to avoid rejection episodes, this practice is nonetheless prone to the harmful consequences of the nonspecific immunosuppression required for survival of the allograft. In order to minimize these severe side effects, research is focusing on the exploitation of therapies leading to tolerance induction and immune homeostasis.

Fungal infections remain nowadays a major cause of transplant-related morbidity and mortality in the HSCT setting [1]. One of the most important risk factors for fungal infections in HSCT has historically

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been neutropenia. However, a predominance of aspergillosis cases occurring in the post-engraftment rather than the neutropenic period in transplant recipients has been described [2]. This suggests that host immunity is crucial in eradicating infection, but an overzealous immune recovery can also be harmful and may contribute toward worsening disease. Therefore, proper immunotherapies restraining deregulated innate and adaptive responses could provide control of immune overreactions in fungal infections [3].

In this review, we shall consider the interplay between recipient- and donor-dependent mechanisms of protection that are coordinately induced for optimal anti-microbial resistance with minimum histopathology (otherwise referred to as protective tolerance). In experimental candidiasis and aspergillosis, the balance between Th1 cells (that provide antifungal resistance) and regulatory T cells (Tregs) that limit the consequences of the associated inflammatory pathology may provide the basis for the occurrence of functionally distinct modules of immunity for resistance and tolerance [4]. Specifically, we will discuss the role of these protective mechanisms in antifungal immunity and how these can be successfully exploited to elicit anti-microbial immunity and concomitant tolerance. Resistance and tolerance are two types of host defense mechanisms that increase fitness in response to fungi [4].

Inflammation and immunity in fungal infections: the current view

The current understanding of the pathophysiology underlying fungal infection and disease fits with the bipolar nature of the inflammatory process in infection [3,5]. In order to achieve the best-fitted form of antifungal resistance, innate responses interplay with adaptive immunity, preserving the precarious balance between the opposing effects of inflammation on infection. Inflammation is in part required for protection – particularly in mucosal tissues – during the transitional response occurring temporally in the bridging between innate and adaptive responses. However, uncontrolled inflammation may eventually aggravate disease and ultimately oppose pathogen eradication. In this context, taming overzealous and exaggerated inflammatory responses has been shown to rely on indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme in the tryptophan catabolism involved in the inhibition of cell proliferation, including that of potentially harmful activated T cells [6], tryptophan catabolites and Treg function. In contrast, IL-23 and the Th17 pathway, by down-regulating tryptophan catabolism, may instead favor pathology and serve to accommodate the apparently paradoxical association of chronic inflammation with fungal persistence [7]. It is of interest that the IL-23/Th17 pathway has been recently acknowledged to play an important role in transplant rejection and tolerance [8]. In this regard, strategies antagonizing IL-23/IL-17, including the administration of synthetic kynurenines, could represent a means of harnessing progressive or potentially harmful inflammation [3,5]. Similarly, we have recently found that blocking inflammatory pathways *in vivo* could also be exploited for the development of siRNA therapeutics to attenuate inflammation in aspergillosis [9].

The above findings may assist in explaining the fact that, despite humans being constantly exposed to fungi, fungal diseases are relatively rare. This implies that the continuous coexistence between fungi and their mammalian hosts plays an underrated contribution to the plasticity of the immune system. In fact, recent evidence supports that the unremitting integration of pro- and anti-inflammatory signals in response to fungi is critical for a proper control of infection and T-cell homeostasis. In this context, IDO and tryptophan catabolites are major determinants of this delicate balance, by providing the host with immune mechanisms adequate for protection without necessarily eliminating fungal pathogens – which would impair immune memory – or causing unacceptable levels of tissue damage [3,5]. Ultimately, the mechanism used by the immune system for suppressing autoreactive responses could conceivably be employed for therapeutic purposes in transplantation.

Resistance and tolerance to fungi in HSCT

Dendritic cells provide antifungal immune resistance and tolerance

Dendritic cells (DCs) orchestrate the adaptive immune responses to *Aspergillus* [9,10]. The plasticity of fungus-pulsed DCs in initiating disparate Th cell responses largely relies upon the specialization and cooperation between distinct DC subsets and the discriminative recognition of fungal morphotypes by