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The ability to tolerate Candida albicans, a human commensal of the gastrointestinal tract and vagina, implicates that host defense mechanisms of resistance and tolerance cooperate to limit fungal burden and inflammation at the different body sites. We evaluated resistance and tolerance to the fungus in experimental and human vulvovaginal candidiasis (VVC) as well as in recurrent VVC (RVVC). Resistance and tolerance mechanisms were both activated in murine VVC, involving IL-22 and IL-10-producing regulatory T cells, respectively, with a major contribution by the enzyme indoleamine 2,3-dioxygenase 1 (IDO1). IDO1 was responsible for the production of tolerogenic kynurenines, such that replacement therapy with kynurenines restored immunoprotection to VVC. In humans, two functional genetic variants in IL22 and IDO1 genes were found to be associated with heightened resistance to RVVC, and they correlated with increased local expression of IL-22, IDO1 and kynurenines. Thus, IL-22 and IDO1 are crucial in balancing resistance with tolerance to Candida, their deficiencies are risk factors for RVVC, and targeting tolerance via therapeutic kynurenines may benefit patients with RVVC.