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Gastrointestinal colonisation and systemic spread of *Candida albicans* in mice treated with antibiotics and prednisolone

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ABSTRACT

Normally, *Candida albicans* is a commensal microbe that resides in the human oral cavity, gut and vagina. However, the fungus can cause mucosal and systemic infections in immunocompromised individuals. The mechanism by which local mucosal infections progress to systemic candidiasis is poorly understood. Here, a murine model of gastrointestinal (GI) candidiasis was developed by inoculation of the oral cavity, followed by treatment with tetracycline (TC) and prednisolone (PSL). Temporal progression from a local infection of the oral cavity to a systemic infection was then monitored. Histological analysis of tissues from mice treated with both TC and PSL revealed massive infiltration of the tongue and stomach by hyphae. PSL increased the fungal burden in the tongue, stomach and small intestine, and facilitated dissemination to the spleen, kidney and liver within 3 days post-infection. Treatment with both TC and PSL supressed interferon (IFN)-γ and interleukin (IL)-17 (cytokines that play key roles in host defence against fungal infection) levels in the tongue, which were induced by *C. albicans* infection. In addition, the mucosal layer of the small intestine of mice treated with both TC and PSL was almost destroyed by the fungal infection; this may be a critical event that allows passage of the fungus across the mucosa and into the systemic circulation. Thus, this mouse model is useful for studying mechanisms underlying progression of *C. albicans* from a local infection of the oral cavity to a systemic infection in immunocompromised individuals.

1. Introduction

Candida species are commensal organisms that commonly reside in humans [1]. They are present in the gut microflora, oral cavity and vagina, and behave like commensal microbes in hosts with normal innate immune system function [2,3]. Although these fungi do not normally cause disease, alterations in the normal microbiota due to compromised immunity mean that the fungi can become pathogenic [3]. *Candida albicans* is one of the most common causes of oral cavity candidiasis, an opportunistic and typically superficial infection [1,4]. However, the microbe can also cause systemic candidiasis, which is associated with high mortality [5,6]. People at risk for serious candidiasis include patients with a compromised immune system and/or normal bacterial flora that have been disrupted by antibiotics. Broad-spectrum antibiotics suppress commensal bacteria in the gastrointestinal (GI) tract, thereby facilitating *C. albicans* colonisation and potentially leading to disseminated candidiasis [7]. Host immune status is another factor that may contribute to overgrowth of *C. albicans* [8]. Mutations in genes encoding host cytokines such as interleukin (IL)-17, IL-22 and interferon (IFN)-γ increase the susceptibility of both mice and humans to mucosal candidiasis [8–11]. In addition, immunosuppressive treatment (e.g., cytotoxic chemotherapy or bone marrow ablation before transplantation) or systemic disorders (e.g., HIV infection or leukaemia) promote overgrowth of *C. albicans* [8,12].

C. albicans uses various strategies to proliferate in response to local environmental conditions. Changes in gene expression allow the fungi to adapt rapidly to differences in pH, oxygen content and nutrient levels in the human GI tract [13–16]. Furthermore, *C. albicans* is a dimorphic fungus; the morphological transition between the yeast and the hyphal forms during adaptation to local environmental conditions is one of its main virulence factors [15,17]. However, information about how the fungi adapt and spread to different organs is limited.

Here, we orally inoculated ICR mice with *C. albicans* to develop an experimental model for GI and disseminated candidiasis; the mice were treated with antibiotics (tetracycline; TC) and the immunosuppressive agent prednisolone (PSL) to disrupt the microbiota and supress the immune system, respectively [4,18]. Several studies of candidiasis used the GI candidiasis mouse model induced by corticoids [19–22]. PSL is a classic intermediate-acting glucocorticoid and is used to treat a wide range of health issues; it effectively reduces inflammation by inducing

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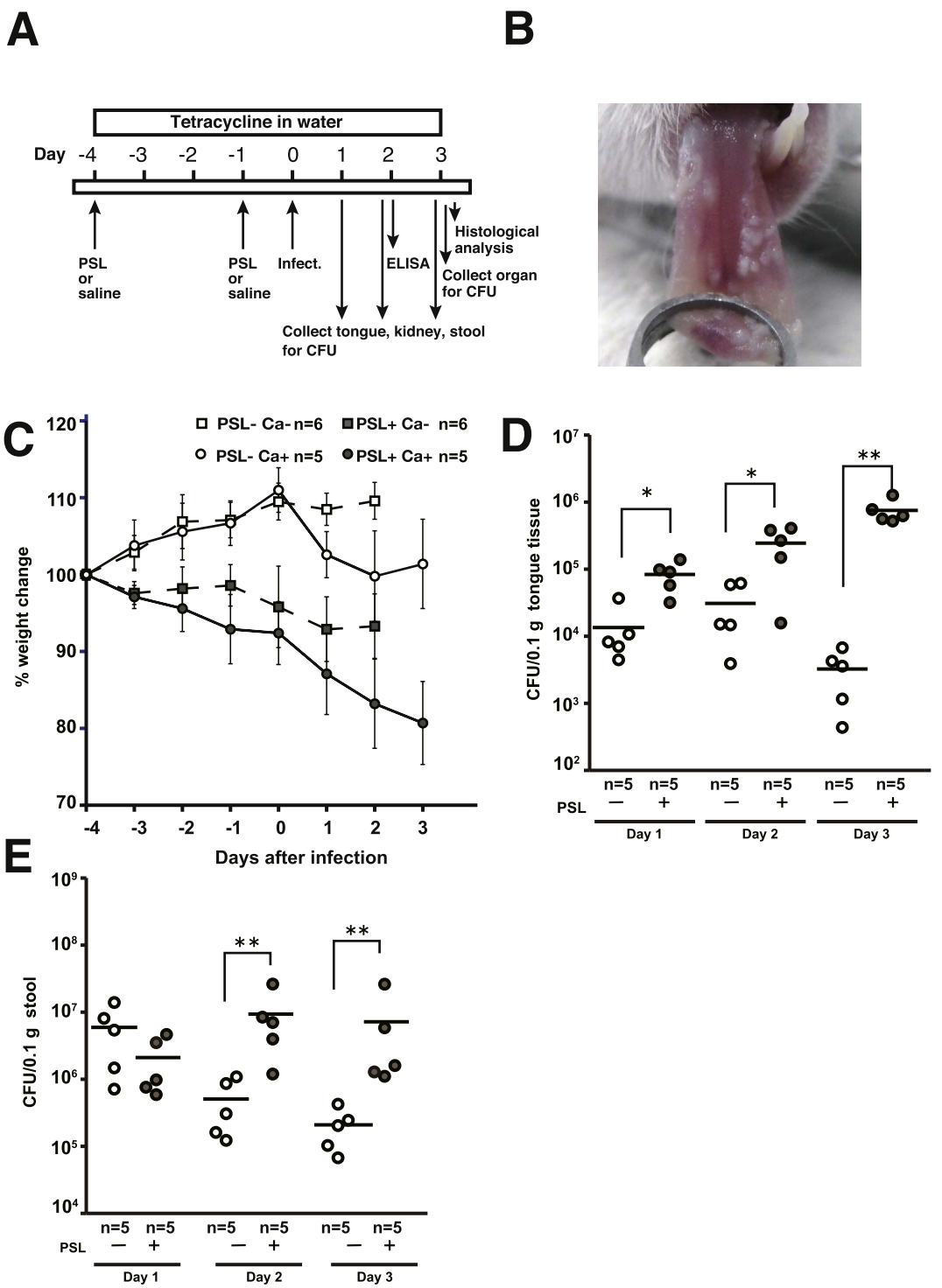

Fig. 1. Effect of prednisolone (PSL) on murine gastrointestinal colonisation by *Candida albicans*.
(A) Timeline of infection.
(B)Macroscopic features on Day 3 post-inoculation with *C. albicans*. Fungal lesions on the tongue of mice treated with PSL.
(C) PSL treatment and/or *C. albicans* infection induces weight loss. Weight was assessed daily and plotted as a percent of the starting weight. Open symbols indicate PSL non-treatment and closed symbols indicate PSL treatment. Squares indicate uninfected (Ca-; n = 5) and circles indicate infected (Ca+; n = 6) mice.
(D) ICR mice were treated (PSL+, closed circles; n = 5) or not (PSL-, open circles; n = 5) with PSL and infected orally with *C. albicans*. The fungal burden (CFU/0.1 g of tongue tissue) was then assessed on the indicated days. Time course data are representative of a single experiment.
(E) The fungal burden in the stool (CFU/0.1 g) of PSL-untreated (PSL-, open circles; n = 5) or PSL-treated (PSL+, closed circles; n = 5) mice infected orally with *C. albicans* was assessed on the indicated days. Data are representative of three independent experiments. Bars represent mean values. $P^* < 0.05$ and $P^{**} < 0.01$.

immunosuppression [23–25].

We examined fungal burden (in the tongue, stomach and small intestine) and translocation in experimental GI candidiasis model mice and analysed local production of cytokines (IL-17A and IFN-γ) at the early stage of infection. The data will help us to better understand how fungal growth is regulated in target organs, and the mechanisms that allow passage of fungus across the gut mucosa.