Candida Albicans in Psoriasis

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Contributor: Carmen de Jesús Gil

Psoriasis is a T cell-mediated skin disease resulting from epithelial and immunological cells' interactions, which affects around 2% of the population worldwide. Its onset is influenced by genetic and environmental factors, particularly infections among which *Streptococcus pyogenes* is the best characterized. However, the commensal fungus *Candida albicans* has been also associated to triggering psoriasis. Here we discuss what it is known about the link betweeen *Candida* and psoriasis pathogenesis.

psoriasis Candida albicans IL-17 plaque psoriasis

1. Introduction

Candida albicans infections have been associated to psoriasis flares over time[1]. However, the insights of this relationship is poorly characterized. Several studies have confirmed increased *Candida albicans* colonization of the oral[2][3][4][5][6] and gut[2][6] mucosa in psoriasis patients compared to healthy individuals, which have been confirmed by a recent meta-analysis too. Nonetheless, whereas some authors revealed an association between *C. albicans* existence at mucosal sites and psoriasis severity[2][4][6], others did not find such correlation[3][7][8]. Likewise, the presence of *Candida albicans* at cutaneous levels is still controversial. Most skin mycobiome studies have not revealed differences between psoriasis and healthy individuals' *Candida spp*. levels[3][9][10][11][12][13][14][15]. However, Sarvtin T. and colleges found elevated *C. albicans* in lesional skin from the trunk compared to either adjacent normal skin or healthy controls' skin[5]. Furthermore, Salem I. et al. recently reported the presence of higher *C. albicans* in non-lesional skin swabs[16].

Introduced in the early eighties, the role of the skin as a peripheral lymphoid organ has been dissected ever since[17]. The Cutaneous Lymphocyte-associated Antigen (CLA) identifies a subpopulation of memory T cells with skin tropism. It is expressed in more than 90% of cutaneous T cells whereas only in 15-20% of T cells in peripheral blood. Once in the skin, these cells can go back to systemic circulation though the lymphatic system, meaning that they recirculate back and forth between both tissue compartments. Of important note, the phenotype, antigen specificity and effector function of circulating CLA+ T lymphocytes reflect the mechanisms taking place at cutaneous levels, consequently they are consider good peripheral biomarkers for T cell mediated skin conditions such as psoriasis or atopic dermatitis[18][19]. Here we explore how this subset of skin tropic lymphocytes respond to *C. albicans* in coculture with autologous epidermals cells from psoriasis patients compared to healthy controls.

2. Exploring *C. albicans* humoral and cellular responses in psoriasis

Currently, the evidence of microbes' presence in psoriatic patients is focused on complex DNA-based technologies[20]. However, specific immunoglobulins assess environmental microorganism exposure and the isotypes observed in immunoglobulins can elucidate the mechanisms of antigen encounters[21]. Initial studies of anti-Candida antibody levels did not observe differences between patients with psoriasis and healthy individuals[9][22]. Recently, however, Liang YS et al. showed increased anti-whole cell antigen IgG and decreased anti-soluble antigen IgA and IgM in serum from psoriasis patients versus healthy individuals[23]. Whilst, Sarvtin MT et al. reported decreased anti-*Candida* IgM, IgA and IgG levels in psoriasis patients compared to controls[5]. As such, the humoral response against *Candida albicans* in psoriasis patients remains controversial.

To evaluate *C. albicans* exposure, we assessed fungus-specific IgA and IgG (including all subtypes) in plasmas from plaque and guttate psoriasis patients, as well as healthy controls. Significantly increased levels of anti-CA IgA and IgG were found in plaque psoriasis, with particularly higher disease severity, whereas similar antibody response was found in guttate psoriasis as to healthy controls. Importantly, active *Candida* infection was not observed in any subject, according to an ELISA diagnostic kit.

C. albicans T cell response in our ex vivo model of psoriasis in a small cohort of patients had been previously explored, showing primarily CD4+ T cell activity [24]. In this study, preferential CLA+ T cell response to *C. albicans* was confirmed, dominated by IL-17F production, in a larger cohort of psoriasis patients but also in control subjects. Even if similar CA-induced cytokine profile is observed, we found overall increased cytokine response in guttate versus plaque psoriasis patients. Interestingly, although *C. albicans* induction of IL-9 by CLA+ T cells was already shown in healthy donors[25], we observed significantly increased CA-induced IL-9 in psoriasis patients compared to controls.

Considering the distinct exposure to *C. albicans* within psoriasis, we believed patients with high anti-CA IgA levels may carry pathophysiological peculiarities that could be responsible for their clinical course of disease. An extensive proteomic profile was performed in plasma from non-treated psoriasis patients. Interestingly, patients with high anti-CA IgA displayed generally increased proteins involved in antimicrobial humoral response, cell chemotaxis and inflammatory immune response. Based on their functions, several proteins were selected for further validation via ELISA in psoriasis and healthy samples, such as: RNASE3, azurocidin, CCL18 and CHI3L1. Increased CHI3L1, AZU1 and CCL18 levels were present in plasma from plaque psoriasis patients compared to guttate psoriasis and healthy subjects; whilst RNASE3 was similarly increased in plaque and guttate psoriasis as to controls. These proteins are associated to anti-candidal activity, are able to attract CLA+ T cells and have been described to be increased in periodontal disease lately. Notably, increased prevalence of periodontal disease has been reported in psoriasis patients[26]. Our data regarding plasma levels of these proteins in psoriasis support this link, although longitudinal follow-up studies are required to better establish a causal relationship.

3. Conclusions

In light of our findings, the association of *C. albicans* and psoriasis is reinforced. The presence of IgA against *Candida albicans* in plasma from plaque psoriasis patients without clinical signs of infection identifies subjects that

have been exposed to this microbe, which preferentially activates skin-homing T cells to secrete IL-17 cytokines. We consider that *C. albicans* exposure may affect psoriasis evolution, and eventually response to therapies. Assessing anti-CA IgA levels may be beneficial to better evaluate and stratify psoriasis patients. However, the role of this commensal fungus in psoriasis pathogenesis remains to be fully understood and important questions persist. Th17 response is required for fighting against *C. albicans* infection, as demonstrated by defects in the IL-17/IL-17R axis that are associated to chronic mucocutaneous candidiasis[27]. Therefore, it could be hypothesized that our observation could be related to treatment approaches for psoriasis. Effective therapies in psoriasis reduce Th17 response, facilitating fungal colonization that subsequently promotes IL-17 response fueling psoriasis pathogenesis in a vicious circle. However, predisposing background to increased response to *C. albicans* cannot be ruled out. Single nucleotide polymorphisms (SNPs) on IL-23 and IL-17 related genes are described as psoriasis genetic risk markers [28]. Some of these SNPs could be associated to altered response to *C. albicans* in psoriasis patients, a matter that remains unexplored to our knowledge.

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