Immunology of chronic mucocutaneous candidiasis

Patients with chronic mucocutaneous candidiasis (CMC) are susceptible to debilitating, persistent, and refractory infections of the skin, nails, and mucous membranes with yeasts of the genus candida, most often by the species *Candida albicans*. The underlying defect is thought to be an impairment of immune defences but the nature of the defect(s) has not been defined.1 *Candida albicans* is an opportunistic yeast inhabiting, as a commensal, the mucous membranes of > 80% of adults, becoming invasive only if the existing balance is disrupted. Various non-immunological factors are known to predispose to candida overgrowth and thrush (diabetes, obesity, systemic antibiotics, systemic and local steroid treatment, dentures, and occlusion—for example, nappies and tight clothing, etc); however, these infections are characteristically resolved as soon as the predisposing factors are removed and should not be confused with a persistent inability to clear candida, as is seen in CMC.2 Patients with CMC do not constitute a homogenous group and numerous classifications have been proposed, mostly based on the presence or absence of endocrinopathy, juvenile or mature onset, and familial or sporadic occurrence.3 Associated findings include alopecia, vitiligo, malabsorption disorders, and infections with encapsulated microorganisms.4 Patients with CMC and endocrinopathy are now frequently referred to as having the APECED (autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome), previously known as APS-1 (autoimmune polyendocrinopathy candidiasis syndrome type 1). In these patients, a genetic defect has recently been identified showing (various) mutations in the AIRE (autoimmune regulator) gene, which probably encodes a DNA transcription factor. The link between the identified gene defect and the inability to clear candida remains unknown. No gene defect has as yet been identified in patients with CMC without endocrinopathy, although there have been occasional reports of such patients where multiple family members through several generations were affected, again suggesting an underlying gene defect.5 Research in this area is currently in progress in our and other laboratories.6

**Immunity to candida**

Protective immunity to candida is complex and includes both the innate response and adaptive cellular and humoral immune responses.7 Data suggest that different mechanisms operate in protection from systemic as opposed to mucocutaneous disease, and indeed disseminated disease is rarely seen in patients with CMC and vice versa. Protection from systemic disease and internal organ spread is mediated primarily by innate immunity, particularly by neutrophils and complement.8 Neutrophil and macrophage function is dependent on antibody and complement opsonisation, as well as pattern recognition receptors such as the mannose and Toll-like receptors.8

Intracellular killing is mediated primarily through oxygen dependent pathways (superoxide anion, myeloperoxidase and reactive nitrogen (NO) production), although oxygen independent pathways (lysozymes) have also been implicated.9 Most at risk from systemic candidiasis are patients who develop granulocytopenia, such as patients on immunosuppressive or cytotoxic treatment for malignancies and other diseases, or patients with inborn phagocytic defects (such as chronic granulomatous disease and hyper-IgE syndrome).10 Interestingly, although complement greatly enhances candida phagocytosis, patients with complement component deficiencies including C3 and C5–9 are not more susceptible.11 Several groups have argued that antibodies to candida are crucial in protection from widespread disease, particularly an antibody specific for a 47 kDa candida protein.12 However, this is difficult to reconcile with the fact that patients with humoral (antibody) immune deficiencies are not particularly prone to infections with fungi, including candida.13 Indeed, patients with CMC have repeatedly been shown to have high amounts of candida specific antibody,14 but are still unable to clear the infection. Interestingly, although the role of T cells is paramount in regulating the humoral and, to a certain degree, the innate immune responses described above, T cell mediated effector mechanisms seem to be crucially important in protection against mucocutaneous rather than systemic spread. Earlier studies showed that candida itself, in particular candida mannan, exerts immunosuppressive properties that result in depressed T cell function.14 Although this might contribute to the immune depression seen in patients with CMC, this is unlikely to play a major role because it is well documented that patients with CMC regularly relapse in spite of candida eradication by vigorous antifungal treatment.15

**Immunity in chronic mucocutaneous candidiasis**

**INNATE IMMUNITY**

Research into the immune defect(s) in patients with CMC over the years mostly demonstrated intact innate immunity to candida, including complement function as well as neutrophil phagocytosis and intracellular killing.7 However, the data on macrophage function are controversial, suggesting subtle impairment of macrophage activation and intracellular killing.16 Most importantly, the regulatory (cytokine producing) role of the macrophage in CMC remains largely unknown.

**HUMORAL IMMUNITY**

Antibody responses in general and specifically to candida have repeatedly been shown to be intact.17 Our own data showed very high titres of IgG1 and IgA candida specific antibodies in all patients. However, recent data suggest that a proportion of patients with CMC may have impaired antibody responses to encapsulated bacteria such as *Haemophilus influenzae* B and *Streptococcus pneumoniae*, with or without accompanying IgG2 subclass deficiency.4

*Because affected families with CMC but without endocrinopathy are extremely rare, it would be much appreciated if any physicians/immunologists seeing or being aware of such patients would contact the authors.*
T CELL MEDIATED IMMUNITY AND CYTOKINES

Protection from mucocutaneous candidiasis has repeatedly been shown to be dependent on cellular immunity and, although the defect remains elusive, it is clear that patients lacking T cells (for example, severe combined immune deficiencies, Di George syndrome), and in particular CD4+ cells (patients with AIDS), will suffer from this form of candidiasis.1,11 In recently identified patients with inborn deficiencies of the receptors for interferon $\gamma$ (IFN-$\gamma$) and interleukin 12 (IL-12) it was shown that, apart from being susceptible to atypical mycobacteria, some also had persistent candidiasis.12 Although our own studies have excluded IFN-$\gamma$ receptor/IL-12 receptor deficiency as a possible cause of susceptibility to chronic candidiasis in patients with CMC (vide infra), it is tempting to speculate that in analogy a rather general immune defect may be underlying the seemingly specific susceptibility to candida. In a series of well designed experiments in animal models, protection against candidiasis was shown to be dependent on a type 1 pattern of cytokine production.13 These studies demonstrated that IFN-$\gamma$ and IL-12 were required for survival and clearance of infection,14 whereas neutralising IL-4 in susceptible strains improved survival.15 However, an animal model of spontaneous CMC is unavailable and the relevance of these findings for CMC in humans remains to be confirmed. In patients with CMC the abnormalities identified were found to affect the cellular arm of the immune response. A spectrum of defects was reported, ranging from no detectable abnormalities through selective absence of cytokine producing cells to generalised absence of cytokine production.16 Cytokine stimulation in response to candida is currently also under investigation in our laboratory. These findings have Bearing not only on understanding the mechanisms involved in CMC itself but also on understanding the mechanisms involved in protective immunity to fungi in general, which are still poorly understood.

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