Editorial

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 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 ectodermal dystrophy) syndrome.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 ectodermal dystrophy) 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.7 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 9 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.12 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).13 Interestingly, although complement greatly enhances candida phagocytosis, patients with complement component deficiencies including C3 and C5–9 are not more susceptible.14 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.15 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.16 Indeed, patients with CMC have repeatedly been shown to have high amounts of candida specific antibody,17 18 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.19 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.20

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.21 However, the data on macrophage function are controversial, suggesting subtle impairment of macrophage activation and intracellular killing.22 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.23 24 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.25

*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.
infection, whereas neutralising IL-4 in susceptible strains inhibited the CD4+ subset, and a data suggested that the defect in CMC was at the level of cell design experiments in animal models, protection against accordingly specific susceptibility to candida. In a series of well-vide infra), it is tempting to speculate that in analogy a case of our patients expressed normal amounts of receptor for IFN-γ and IL-12 (T Lammas, personal communication, 2000). At this point, it is impossible to say whether the defect primarily lies with the T cells as type 1 cytokine producers or whether the fault lies further “upstream”, involving accessory cells (macrophages?), which fail to produce adequate amounts of type 1 inducing cytokines, such as IL-12. Although the mechanisms are unclear, our data suggest that patients with CMC may also have a problem in the recruitment/maturation of candida specific CD3+CD4+ cells, which fail to switch from CD45RA+ to CD45RO+ after culture with candida antigens (our data, unpublished, 2000). This work was supported by registered charity Action Research. Thanks to J H Robinson and M Abinun for helpful suggestions and C Corlott for expert technical assistance.

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