

patients with hypogammaglobulinemia. Questions yet to be addressed are how to improve management and eliminate chronic infections.

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THE AMOUNT OF SCURFIN PROTEIN DETERMINES PERIPHERAL T CELL NUMBER AND RESPONSIVENESS

Khatti R, Kasprowicz D, Cox T, et al. *J Immunol.* 2002; 167:6312–6320

Purpose of the Study. The disorder IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) is characterized by enlargement of secondary lymphoid structures, diabetes mellitus beginning in early infancy, and chronic enteropathy. The gene defect was identified in 2001 as *FOXP3* on the X chromosome. The *FOXP3* gene is a member of the forkhead family of transcription factors, however, the basis for IPEX has remained poorly characterized. Previous groups have shown that the immune system is in a state of chronic activation in these patients with overproduction of cytokines and immunoglobulins, but the relationship of these problems to the *FOXP3* mutations has been unclear. This article describes work defining the role of the *FOXP3* protein product, scurfin, to the manifestation of T cell expansion.

Methods. The authors use mouse models including the scurfy mouse, which has an inactive *FOXP3* gene and mice transgenic for overexpression of *FOXP3*. Flow cytometry and histology are used to characterize changes in peripheral T cells and the T cell compartments in secondary lymphoid structures.

Results. The scurfin protein is expressed in the thymus but had no demonstrable effect on the phenotype of the scurfy mouse. Overexpression of scurfin in the thymus in a normal mouse had modest effects on various thymic subsets but did not induce any changes in the periphery. Overexpression of scurfin globally in normal mice caused decreased T cell proliferation and interleukin (IL)-2 production. Similarly, overexpression of scurfin inhibited cytolytic T cell activity.

Conclusions. The function of scurfin appears to regulate the function and size of the peripheral T cell compartment.

Reviewer's Comments. IPEX is an uncommon but nearly always fatal immunodeficiency. Affected boys are often total parenteral nutrition-dependent because of their enteropathy and require very stringent immunosuppression for even short-term survival. Stem cell transplantation may be effective. The importance of this article is in its description of a global overactivity of the T cell compartment. This contributes to our understanding of the pathogenesis of this disorder and reinforces the growing belief that the best management option may be early stem cell transplantation.

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SEVERITY OF MENINGOCOCCAL DISEASE IN CHILDREN AND THE ANGIOTENSIN-CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM

Harding G, Baines PB, Brull D, et al. *Am J Respir Crit Care Med.* 2002;165:1103–1106

Purpose of the Study. The authors sought to establish a correlation between angiotensin-converting enzyme (ACE)

genotypes and outcome from meningococcal sepsis or meningitis. The ACE gene occurs as a D form that lacks a 284 base pair marker and an I form that includes this marker. Individuals with the DD genotype have higher tissue ACE levels than those with at least one I gene.

Study Population. All inpatient cases of meningococcal disease at Royal Liverpool Children's Hospital over a 34-month period were investigated. Consent to study 113 of 142 cases was obtained. Patients were white in 110 cases (55% were male; mean age: 49 months). The distribution of meningococemia, meningitis, and both was 50%, 5%, and 45%, respectively. A control panel of 841 healthy British white children of similar age had ACE genotypes determined as part of another study.

Methods. The severity of illness was graded by the Pediatric Risk of Mortality (PRISM) scale and the Glasgow Meningococcal Septicaemia Prognostic Score (GMSP) on admission. Samples for DNA analysis were blinded to staff who determined ACE genotype with a polymerase chain reaction (PCR) technique.

Results. The distribution of genotypes in the patients and controls was similar: II in 23% of patients, 24% of controls; ID in 46% of patients, 52% of controls; and DD in 31% of patients, 24% of controls. Children with the DD genotype had a statistically significant increase in a number of indicators of severity, including need for mechanical ventilation, need for inotropes, longer pediatric intensive care unit (PICU) stay, and worst GMSP score. Only 1 of 34 DD subjects did not require intensive care unit (ICU) care, compared with 17 of 76 with the other genotypes who did not receive ICU care. DD subjects had a longer PICU stay by approximately 2 days. Of the 11 deaths, 45% were DD, an overrepresentation of this group ($P = .013$).

Conclusions. In children with meningococcal sepsis/meningitis, the presence of the DD genotype of ACE is associated with more severe illness and worse prognosis than the II or ID genotypes. Given the similar distribution of the 3 genotypes in the control population and the children with meningococcal disease, the DD type cannot be shown to be associated with either an increased risk of infection, or a low rate of case ascertainment attributable to rapid death (preventing presentation at the referral center).

Reviewer's Comments. ACE is familiar to immunologist-allergists because of the place of ACE inhibitors in the differential diagnosis of chronic cough, and the occurrence of angioedema in a few percent of patients on ACE inhibitors. The mechanism of these adverse events is incompletely understood, but one suggested cause is inhibition of kininase, which may be synonymous with ACE, leading to an increase of kinins in tissue. The DD genotype of the ACE gene is associated with increased tissue levels of ACE. An increase in this enzyme is proinflammatory in a number of models. Previous searches for factors associated with poor outcome in meningococcal disease had found associations with cytokine genes and with ACE activity. The ACE enzyme system has broad effects in immune and metabolic pathways. Exactly how it is proinflammatory when over expressed is not clear. The occurrence of difficulty both with high levels (DD genotype) and low levels (inhibitor drugs) of ACE activity is disconcerting, but not evidence against the observations. However, such observations will eventually lead us to better understand and manage children whose immune studies are normal at our present level of investigation.

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**SEVERITY OF MENINGOCOCCAL DISEASE IN CHILDREN AND THE
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POLYMORPHISM**

Larry W. Williams
Pediatrics 2003;112;488

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