borne in mind that although uninfected transgenic mice do not develop diabetes they do show substantial insulitis, a process which itself may be the result of antigen presentation/recognition proceeding in the islets (even in the absence of viral destruction). In fact, transfer of activated transgenic T cells into uninfected recipient mice produces insulitis but not diabetes, indicating that *de novo* presentation of 'sequestered' autoantigen alone cannot explain the development of diabetes following virus infection. An alternative, but not mutually exclusive, mechanism is that Coxsackie B4 virus infection could indeed create a proinflammatory, 'hot' milieu favoring either the differentiation of destructive Th1 cells (which could then directly attack the target tissue) or the recruitment of accessory effector cells such as macrophages[6]. Indeed, in IDDM lesions, proinflammatory cytokines (such as IL-12), which are capable of activating Th1 cells and/or macrophages, are abundant[5]. Further studies of cytokine expression in the Coxsackie mouse model of IDDM are required to clarify this issue.

Finally, could local activation of pathogenic T cells be an important factor in other autoimmune disorders? Presumably the answer is no in MS and other inflammatory demyelinating brain diseases. We know that only freshly activated but not resting T cells (naive or memory) are capable of passing through the endothelial blood-brain barrier separating circulating blood from brain parenchyma[14]. Therefore, activation of encephalitogenic T cells most likely occurs within the peripheral immune system rather than in the brain itself.

The Horwitz study emphasizes the complexity of the interplay between immune responses to infection and autoimmune disease. Clearly their strategy will help us to better understand the etiology of autoimmune disease and hopefully will enable us to design better and more specific therapies.

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All in the p53 family

Tumor suppressor genes commonly belong to families but for years *p53* was believed to be the exception to this rule as all attempts to find its siblings failed. So there was great excitement when p73, p53's big brother, was accidentally discovered last year. Now, David Sidransky's group from the Johns Hopkins Medical Institutions and Ikawa and colleagues from Tohoku University report in this issue (pages 747 and 839) that they have discovered another sibling for p53, clearly showing that a bona fide p53 family does exist. Both groups used degenerate primers and the polymerase chain reaction (PCR) to isolate a gene with high homology to *p53*, *p73* and the rat gene, *ket*.

Sidransky's group isolated their clone, p40, from a human prostate cDNA library using primers designed against p53's DNA binding portion. 'We were actually surprised when we looked at the sequence,' says Sidransky. "We said 'Hey! There really is a family of genes!' " Northern analysis indicated that p40 is predominantly expressed in bladder and kidney, and Sidransky believes it could be involved in bladder and prostate tumor development. In contrast, the p53 homologue identified by Ikawa's group, p51, was highly expressed in skeletal muscle and placenta, and appeared to bear more similarity to p73 than to p53.

It is yet to be determined whether p51 and p40, like p53, respond to stress or DNA damage by regulating the cell cycle and inducing apoptosis. Ikawa's group demonstrated that expression of p51 (see photograph; red) in a p53-deficient osteogenic sarcoma cell line induced these cells to undergo apoptosis, detected by the TUNEL assay (green).

It will also be important to determine whether mutations in these genes are associated with tumorigenicity. Ikawa's group observed a p51 mutation in 1 of 66 human primary tumors and also in two tumor cell lines. Both p51 and p40 mapped to human chromosome 3q, a region where deletions are commonly associated with bladder and other types of cancer. Sidransky points out that it will be particularly interesting to look for mutations in this new p53 family member in patients with Li-Fraumeni syndrome, a disorder in which a variety of malignancies result from p53 germline mutations.

The implications of a p53 family of proteins are intriguing. Researchers are anxious to learn whether members are involved in the same pathway, serving as backup genes for one another. 'Identifying the downstream targets of these genes will be fascinating,' says Sidransky, 'p51 does not have a lot of similarity with p53's activation domain, so it might have a totally different function.'

Finally, the possibility exists that other p53 family members are still out there. Sidransky admits that his group's PCR screen has yielded several DNA fragments that await further analysis. Because they are using primers against p53's DNA binding site as probes, he considers the possibility that there could be proteins with homology to the p53 DNA binding domain but without other sequence similarity to p53. As Sidransky puts it, 'The family might get more complicated, but it will also get more interesting.'

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