This Month in the *Journal*

We present four articles this month on the genetics of immune function and inflammation. Boss (p. 279) leads off with a review of the severe immunodeficiency disorder, bare lymphocyte syndrome, in which class II major histocompatibility (MHC) antigens fail to be expressed, because of defects in one of several cell type–specific transcription factors. Cacalano and Johnston (p. 287) discuss the cytokine signaling pathway and its relation to X-linked and autosomal severe combined immunodeficiency in humans and mice. They consider the roles of several novel signaling regulators that interact with interleukin receptor subunits and their associated proteins, many of which could be relevant to human disease pathways. Ruuls and Johnston (p. 294) consider the tumor necrosis factor gene and its relatives, which have been proposed to underlie several autoimmune conditions. It has proved difficult to show this association clearly, because these genes are linked to other strong candidates, including the MHC genes. As the authors argue, this synteny, which is conserved in mice, requires that gene-targeting experiments include unusually rigorous controls. Finally, Broide et al. (p. 302) discuss the role of eosinophils in allergic inflammation and the possibility of therapies that block atopic disease but leave antibacterial defenses intact. Both eosinophils and neutrophils flow in the bloodstream, and the signals on which they rely to adhere to the endothelium and to cross into inflamed tissue are beginning to be understood. One crucial tool in the study of these circulating leukocytes is intravital microscopy; a videomicrograph of this technique is available in the electronic version of this issue.

Mutations in* pNPI *Gene Cause EDS VIIC, *by Colige et al. (p. 308)*

The mechanical strength of skin and other tissues depends greatly on the presence and spatial organization of fibrillar collagens. The connective tissue disorders collectively described as Ehlers-Danlos syndrome (EDS) include defects in procollagen genes and in genes for collagen-modifying factors, such as lysyl hydroxylase. Colige et al. now show that EDS type VIIC is in the latter category. The gene they implicate in this rare recessive disorder, *pNPI,* encodes a metalloproteinase that clips the globular N-terminal propeptide from procollagen types I and II. This cleavage is required if secreted collagen is to form ordered fibrils, as seen in electron-microscopic views of skin from EDS VIIC individuals or from calves with dermatosparaxis, a similar condition. Colige and coworkers identify *pNPI* mutations in all six of the known EDS VIIC patients—most of whom are homozygous for a specific nonsense mutation—and in a dermatosparactic line of cattle. They also explore the alternative splicing of the human pNPI mRNA, showing that a short splicing product that lacks the proteolytic domain is expressed in multiple tissues. The physiological role of this product, if any, remains uncertain, and one individual, who expresses the short but not the longer splicing forms, is as severely affected as other individuals in which all pNPI expression is lost. Because collagen I accumulates in processed form in tissues such as bone and cartilage, there appear to be other enzymes, expressed in tissues other than skin, that can substitute for some of the activities of pNPI.

***Somatic Mutations in* PKD2,** *by Torra et al. (p. 345)*

Polycystic kidney disease is inherited in a dominant fashion, but the characteristic renal and hepatic cysts seen in this disease occur randomly and independently, suggesting that a somatic second hit is required. Two genes, *PKD1* and *PKD2,* have been implicated in this disorder, and, although *PKD1*-linked disease is more severe and occurs earlier than *PKD2*-linked disease, it appears that the two gene products interact. Second hits in the *PKD1* gene have been documented in cyst explant tissue from *PKD1* heterozygotes. However, because residual PKD1 is still expressed in many of the cysts from such individuals, it is uncertain whether loss of heterozygosity (LOH) that is observed is an early or a late event in the disease pathway. Now, Torra and coworkers show that the uncertainties associated with *PKD1* also apply to *PDK2*. In one individual with *PKD2*-linked disease, these authors discover LOH or second site point mutations in a substantial fraction of the cysts. However, because many cysts seem to retain PKD2 protein expression, it appears doubtful that LOH is an obligate early step in cystogenesis. No lesions in either of the *PKD1* alleles are seen in this patient's cysts. Thus, although haploinsufficiency for *PKD2* seems to be permissive for disease progression, the nature of the second event that promotes cyst development remains mysterious.

M-FISH for Diagnostic Applications, *by Uhrig et al. (p. 448)*

Multiplex (M-) FISH is a versatile technique for hybridizing chromosome-specific probes to metaphase spreads,

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allowing each chromosome to fluoresce with a different color. Only five different fluors, combined in varying ratios when they are conjugated to specific probes, are needed to distinguish the 24 human chromosomes. Because it covers the entire genome with a single hybridization step, this technique lends itself to the identification of aneuploidies and translocations, and it can be used instead of Giemsa banding in a variety of diagnostic applications. Uhrig and colleagues have used M-FISH in hundreds of cases in which Giemsa patterns were ambiguous. The authors find that, when applied in aneuploid cells, M-FISH provides clear identities of chromosomal derivatives, and interchromosomal rearrangements can be characterized with greater precision than by standard methods. Some ambiguities still remain, because M-FISH cannot distinguish among long repetitive stretches of DNA from different chromosomes. Uhrig et al. propose that M-FISH be applied as a first step in all analyses, with the initial results guiding the choice of follow-up procedures, such as chromosome bar coding or comparative genomic hybridization.

Mitochondrial Inheritance in ICSI, *by Danan et al.* (*p. 463*)

Intracytoplasmic sperm injection (ICSI) is a robust approach to in vitro fertilization that can be applied even with immature sperm cells or cells that have been killed by freezing and thawing. Because this method circumvents the need for physiologically normal, mature sperm, it is becoming a first choice in idiopathic cases of male infertility. However, doubts linger about the safety of the procedure, and here, Danan et al. explore one such concern: the possibility that paternal mitochondria might persist in the zygote after the sperm cell enters the egg cytoplasm in this unusual manner. Using a PCR-based detection method that is sensitive to paternal mtDNA in amounts as low as 0.02% of total mtDNA, Danan and coworkers find no evidence that newborns who were conceived through ICSI carry any paternally derived mtDNA. This finding suggests that the suppression of paternal mtDNA is highly efficient and raises anew the question of how sperm mitochondria are recognized and destroyed in the zygote or later in development.

A Genomic Screen in Autism, *by Risch et al.* (*p. 493*)

Risch and colleagues have conducted the most comprehensive genome screen yet for autism, a rare disorder of psychological development that appears to be strongly heritable. Monozygotic twins show an extremely high concordance rate for this condition, but other siblings do not; other siblings of affected children are at measurably greater risk than is the general population, but their concordance rate is only 1%–3%. This pattern of inheritance has been interpreted to indicate that multiple loci interact, in a nonadditive fashion, to determine the risk of autistic development. Risch et al. ascertained two groups of sib pairs, consisting mostly of concordant affected children, with some discordant sib pairs and two pairs of affected monozygotic twins. After an initial genomewide screen of 90 families, the authors followed up with a more dense array of markers over eight relatively promising loci on an independent set of 49 families. No strong candidate regions emerged from this analysis, but at least four regions show a modest level of linkage. In addition, the authors have examined the degree of identity-by-descent of different markers among affected sib pairs, and, on this basis, they predict that a large number of loci—perhaps on the order of 20—interact to confer the autistic phenotype.

mtDNA Sequences in the Cayapas, *by Rickards et al.* (*p. 519*)

The Cayapa are an indigenous South American people, now living in northern coastal Ecuador, who are believed to have existed in relative isolation for at least the last 250 years. Rickards et al. have studied the mtDNA distribution of the Cayapa and have compared it to previously reported mtDNA distributions in other Amerind populations, particularly those of the Chibchan linguistic group, to which the Cayapa belong. In addition to the previously identified haplogroups that are common to North and South American indigenous peoples, the Cayapa carry a novel mtDNA hypervariable region haplotype, C10. This haplotype is present in nearly one-third of Cayapans, and the fact that it had never been observed suggests that it must be relatively rare in other related populations. On the basis of their reconstruction of the matrilineal history of the Cayapa, Rickards et al. argue that this group is not monophyletic but is part of a larger "metapopulation" that has restored lineage diversity as intrinsic lineages underwent drift and extinction. If this polyphyletic model applies to other Amerind groupings, the authors argue, the anthropologist's project of reconstructing the timing and size of major dispersal events may become unmanageable.

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