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A non-human primate model of lyme disease

Tick-borne spirochetes of the *Borrelia bugdorferi* group are the causative agents of Lyme disease. This multisystem disorder may involve the central and peripheral nervous systems and produce symptoms referable to nerve roots of the spinal cord and their coverings. However, only rare autopsy reports describe the human pathology of Lyme meningoradiculitis and the inflammatory changes are rather nonspecific. Animal models are virtually nonexistent because rodents infected with pathogenic *Borrelia* species rarely develop nervous system disease. Hence, very little is known about the pathogenesis of Lyme neuroborreliosis. In this issue, **Bai *et al*** (p. 160) present the first detailed analysis of experimental spinal cord involvement by Lyme borreliosis in a nonhuman primate model. The investigators were able to produce meningoradiculitis in one of 25 macaques (*Macaca mulatta*). The pathologic features and characteristics of the immune reaction of the affected animal were extensively studied. Interestingly, the experimentally induced nervous system changes were similar to European Lyme borreliosis, in which the second most common clinical manifestation is a meningoradiculitis. This model may be helpful to better understand the inconsistent response to therapy for many patients and provide further insights into the pathogenesis of neuroborreliosis.

Expanding the spectrum of spectrinopathies

Spectrin is the principal structural protein of the erythrocyte membrane, and is composed of two subunits, alpha- and beta-spectrin, which are encoded by separate genes. Hydrophobic interactions between the subunits are critical for the formation of functional teramers and oligomers. Prior analyses of spectrin mutations have provided insights into the molecular pathogenesis of hereditary disorders of the red blood cell. In this issue, **Gallagher *et al*** (p. 229) identify a novel point mutation, Ile24Thr, in an infant with neonatal hemolytic anemia and father, both of whom have elliptocytosis/poikilocytosis. This mutation occurs in a highly conserved region of the alpha-spectrin gene and results in the replacement of a hydrophobic isoleucine with a hydrophilic threonine in the major binding site of alpha–beta-spectrin self-association. Molecular modeling revealed that a heterozygous mutation disrupts highly conserved hydrophobic interactions in the interior of the spectrin triple helix that are critical for structure and function. This paper expands the spectrum of hereditary 'spectrinopathies' and provides further clues regarding their pathogenesis.

Holding court in the liver: increased appreciation for portal tract fibroblasts

The last 30 years have seen the coronation of the perisinusoidal hepatic stellate cell (HSC) as the key cell responsible for liver fibrogenesis. In the setting of liver injury, HSC undergo activation, whereby they lose their characteristic lipid-storing phenotype and acquire a contractile myofibroblast phenotype. Such activation includes a considerable capacity for proliferation and migration. Hence, to HSC is ascribed the dominant role in liver fibrogenesis, leading eventually to the establishment of cirrhosis. However, a nagging issue has been the source of portal tract-based and pericentral fibrosis: are HSC responsible for all fibrosis in the liver? The answer is assuredly 'No', since there is an additional population of normal mesenchymal fibroblasts that reside within portal tracts, around hepatic veins, and in the subcapsular region. This population of cells appears to be heterogeneous, including bona fide fibroblasts in the portal tract mesenchyme and subcapsular mesenchyme, fibroblasts around bile ducts, and fibroblasts in the second cell layer around hepatic veins. A limited but critically important series of animal studies over the past 15 years have clearly established that these non-HSC mesenchymal cells proliferate, acquire their own smooth muscle actin-positive myofibroblast phenotype, and contribute significantly to the deposition of extracellular matrix. All of these cell types deposit fibrillin-1 during fibrogenesis. In this issue, **Lorena *et al*** (p. 203) utilize the differential deposition of elastin by non-HSC myofibroblasts in rats to demonstrate that biliary tract fibrosis is accompanied by substantive deposition of fibrillin-1 and elastin-positive extracellular matrix, whereas carbon tetrachloride-induced fibrosis engenders predominantly elastin-negative extracellular matrix. They go on to demonstrate that mechanical stress within the tissue influences the extent of cellular fibrillin-1 deposition and whether an aberrant ECM is established. These studies further strengthen the argument that attention must be given to the role of non-HSC mesenchymal cells in the generation of liver fibrosis. In a companion Minireview in this issue, **Ramadori and Saile** (p. 153) discuss the scientific journey that has led to the strong emphasis on the HSC and relative underappreciation of non-HSC mesenchymal cells in liver

fibrogenesis. They conclude that the pathogenesis of liver fibrosis is more likely a democracy than a regency.

Tumor subspecies: divergent clones in lymphoma

The concept of subspeciation is well established in the realm of microbiology. Key examples in human disease are the emergence within one patient of new strains of hepatitis C virus or human immunodeficiency virus, owing to the infidelity of RNA virus replication. The analogy applies to human malignancies as well, since somatic mutation within malignant tumors also leads to the emergence of subclones. In most instances, discussion centers around the 'more aggressive' nature of the subclones, leading to invasion and distant metastasis of solid tumors or acute transformation of previously less aggressive hematopoietic malignancies. Less clear is the role of 'subspeciation' in leading to two anatomically different malignancies. In the current issue, **Rosenquist *et al*** (p. 253) utilize micromanipulation of single cells and molecular analysis of V gene rearrangements to demonstrate elegantly that somatic hypermutation from a common precursor gave rise to a composite diffuse large B-cell lymphoma and Hodgkin lymphoma within the same patient. What distinguishes this report from previous such demonstrations is the thoroughness of the molecular archaeology. This study supports the concept that sustained somatic hypermutation after malignant transformation many have critically important implications for management of human malignancies, regardless of whether the pathologist can identify 'subspeciation' of the malignancy by more routine techniques.