workshop a2: friday, march 10

Genetic Factors in Human Infection

The genetics of resistance and susceptibility to HIV-1 infection.
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Polymorphisms in two human gene systems have been convincingly shown to alter susceptibility to HIV-1 infection and/or the pace at which immunodeficiency develops. Genes encoding certain cell-surface receptors for chemokines also regulate attachment and penetration of HIV-1. The receptor gene *CCR5* is truncated by a 32bp deletion (Δ32) in the code for a transmembrane portion. Individuals homozygous for this deletion show strong protection against HIV-1 infection, and infected heterozygotes show modest but consistent deceleration of the disease process. Combinations of single nucleotide variants in the region of the *CCR5* promoter further modulate the response to HIV-1. *CCR5* variants appear to influence the success of antiretroviral treatment. Allele frequencies differ substantially among ethnic groups. The human leukocyte antigen (*HLA*) system for antigen processing and presentation may alter acquisition of HIV-1 infection. In infected but untreated individuals multiple *HLA* class I markers clearly interact to determine the ultimate outcome. Heterozygosity at class I but not at class II loci confers an unequivocal advantage. The effects of the chemokine receptor and the *HLA* gene systems are apparent rather early in the course of infection. Other markers (e.g. in chemokine and tumor necrosis factor promoter genes) have shown less compelling relationships or have been less carefully scrutinized. These discoveries have been made in sets of individuals carefully categorized for intensity of exposure to the virus, viral clade, and onset and course of infection. Recognizing additional host influences and attributing the pathogenetic events to increasingly complex genetic interrelationships, with HIV-1 infection as with any chronic disease, will likely require comprehensive efforts in large populations.

Nramp proteins, susceptibility to infection and divalent cations transport. V. Picard[1] F. Canonne-Hergaux[1], M. Cellier[2], and P. Gros[1]. [1]Biochemistry, McGill Univ., Montreal. [2]Armand Frappier Inst., Laval, QC, Canada.

Our laboratory has used the mouse as a model organism to study the genetic basis of susceptibility to infectious diseases. In inbred mouse strains, susceptibility to infection with intracellular parasites such as *Salmonella*, *Mycobacterium* and *Leishmania* is controlled by the chromosome 1 locus *Ity/Bcg/Lsh*. Positional cloning was used to identify the *Nramp1* gene, and study of animals bearing loss of function and gain of function mutations confirmed that *Nramp1* is allelic with *Ity/Bcg/Lsh*. Parallel case control and linkage studies in humans have shown that susceptibility to tuberculosis and leprosy is associated with *NRAMP1* alleles on 2q in populations from endemic areas of disease. *Nramp1* codes for an integral membrane phosphoglycoprotein with 12 transmembrane domains expressed exclusively in the lysosomal compartment of macrophages and in neutrophils. It is rapidly recruited to the membrane of the phagosome where it may affect microbial replication. *Nramp1* defines a super-family of membrane proteins that have been highly conserved in evolution from bacteria to man, and some of these homologs have been recently shown to function as pH-dependent divalent cations transporters. Most notably, the close mammalian Nramp1 homolog Nramp2 is expressed at the brush border of the duodenum, is regulated by dietary iron and is mutated in anemic *mk* mice and *Belgrade* rats. Additional transport studies using radiolabeled ligands and fluorescent probes identify Nramp2 as the major transferrin-independent intestinal iron uptake system. Nramp2 is also expressed in recycling endosomes, co-localizing with transferrin suggesting that Nramp2 also transport iron into the cytoplasm from acidified endosomes. These results suggest that Nramp1 may also function as a divalent cation transporter across the phagosomal membrane, thus removing from that space nutrients essential for microbial replication. Recently, functional Nramp transporters have been identified in a number of bacterial species, suggesting that both the mammalian and bacterial Nramp proteins may work in opposite orientation competing for acquisition of divalent cations in the phagosomal microenvironment.