Immunogenetics

Safety in numbers

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A recent report from Enrique Gonzalez *et al*[1] provides a striking example of the influence that duplications of immune receptor genes can have on HIV susceptibility and progression to AIDS.

The HIV virus utilises three major receptors of the immune system to beat this system from within. These are the CD4 coreceptor on CD4+ T-helper cells, the CCR5 chemokine receptor on T-cells and the DC sign receptor on antigen-presenting dendritic cells (DCs). The virus utilises these receptors to attack to, penetrate into and replicate in mainly CD4+ T cells and it eventually destroys and depletes them. In the case of DC sign, this appears to allow DCs to transport HIV towards central lymphoid organs to gain better access to T lymphocytes.

Polymorphisms in the HIV components that interact with these receptors and polymorphisms in the host receptors themselves, as well as duplications of these genes can therefore be expected to influence susceptibility to HIV infection and progression to AIDS.

In this new study, the authors show that duplications of the gene that encodes CCL3L1, the most potent known ligand for CCR5, confers marked resistance to HIV infection and progression towards AIDS, independent of ethnic background. CCL3L1 presumably has potent anti-HIV activity because its chemokine activity might block the interaction between HIV gp120 envelope protein and CCR5. As the authors speculate, another alternative is that CCL3L1 may induce ligand-mediated internalisation of CCR5, thereby reducing its availability for use by gp120.

More research is obviously needed to clarify the precise mechanism(s) by which CCL3L1 low copy number predisposes to HIV persistence following infection and to progression towards AIDS in those persistently infected.

Not surprisingly, CCL3L1 copy number and CCR5 genotypes were shown to have interactive effects. Earlier work had shown before that CCR5 haplotypes, including CCR5 promoter polymorphisms as well as coding polymorphisms in CCR2 (CCR2-V64I) and CCR5 (Δ32), influence the risk of acquiring HIV and the rate of disease progression.[2–5] In the current work, CCR5 detrimental (det), that is, disease accelerating and nondetrimental (non-det) CCR5 genotypes, were further analysed with respect to low or high CCL3L1 copies ($CCL3L1^{low}$ or $CCL3L1^{high}$) in an HIV-positive adult cohort. This analysis allowed this cohort to be stratified into four mutually exclusive genetic risk groups. Interestingly, the theoretically highest risk group ($CCL3L1^{low}$ $CCR5^{det}$) showed a greater than three-fold greater risk of progressing rapidly to eight of 12 AIDS-defining illnesses.[1]

The important role that genetics has in susceptibility to retrovirus-induced disease has been well-known for decades, ever since the pioneering work of Frank Lilly and co-workers[6–8] on murine viral leukemogenesis. The genes involved were found to affect viral host range and replication as well as the immune response. The earliest gene locus (cluster) found to affect susceptibility to murine viral leukemogenesis was in fact MHC.[6] Even at this early stage, a gene dose effect was evident, because in animals with homozygous MHC-resistant haplotypes a protection against viral leukemogenesis was more profound than in heterozygous animals with a single MHC-resistant haplotype.[9]

MHC haplotypes are known to affect a variety of specific immune responses, including antiviral antibodies, CD4+ T-helper cell responses and cytotoxic T lymphocyte (CTL) responses. For example, the HLA B*5701 allele frequently shows up in cohorts of long-term asymptomatic HIV-infected individuals: a pattern that probably reflects CTL recognition of dominant and conserved HIV peptides that HLA B*5701 presents.[10,11]

In most individuals infected with HIV, the virus manages to immuno-escape from CTL responses by generating mutations in the viral peptides presented by HLA molecules. Viral structural constraints in the conserved HIV peptides presented by HLA B*5701 apparently do not allow the virus to escape from immune attack by mutations in these particular sequences.

So now we have a good idea of the importance of polymorphisms in CCR5, CCL3L1 and HLA genes for susceptibility to retroviral diseases. However, many more genetic effects are lurking in the dark, awaiting exploration. Nonetheless, the susceptibility loci that have already been identified point towards the mechanisms that underlie this susceptibility and, moreover, suggest ways of therapeutically exploiting the chemokine and chemokine receptor pathways. Also, in vaccine design experience with the HLA B57 resistance allele indicates that HIV vaccines should aim at induction of T-cell responses against conserved epitopes that the HIV virus cannot afford to evade by generating escape mutants. Clearly, the challenges for geneticists, virologists and immunologists alike are enormous, to not only further document genetic control of HIV infection and progression towards AIDS, but also to design novel therapeutic interventions based on these insights■

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X Chromosome Inactivation

No longer 'all-or-none'

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Exciting new data indicate that X-chromosome inactivation (XCI) is very far from the 'all-or-none' phenomenon that we thought it was when it was first discovered.

When XCI was first described, it was thought that one X-chromosome in somatic cells of female mammals was fully actively transcribed (Xa) and the other was completely inactive (Xi). This was seen as a dosage compensation mechanism, that is, a mechanism that ensured that XX females and XY males would have equal dosages of X-linked gene products.

Very quickly, however, it was suggested that X-linked genes with homologues on the Y-chromosome would escape inactivation as they would not require dosage compensation. While the suggestion that genes with Y-chromosome homologues would escape from inactivation was found to be true, other genes without Y-chromosome homologues were also found to escape XCI.[1,2] Thus the phenomenon was no longer all-or-none, in the sense of a whole chromosome being inactive or active. Nonetheless, the all-or-none concept of XCI persisted in that individual genes were thought either to escape fully or to undergo complete inactivation.

An exciting outcome of the human gene-sequencing project is that it has enabled much more detailed studies of the X-chromosome and XCI. A total of 1098 genes have now been identified on the human X-chromosome,[3] and Laura Carrel and Hunt Willard, in a recent *Nature* paper,[4] have been able to study escape from XCI in all of these genes that are expressed in cultured skin fibroblasts (over 600).

A striking and exciting feature of their results was that XCI was not all-or-none for every gene. About 20% of genes were inactivated in some but not all samples, and thus were expressed in either one or two doses in different samples. A further 15% escaped XCI completely, and so were expressed in two doses, and only 65% were fully silenced, and were thus expressed in the expected one dose only.

If these results with cultured cells reflect the situation *in vivo*, then Carrel and Willard's findings have important implications for clinical genetics. Genes without Y-chromosome homologues that escape XCI will have unequal dosages of their gene products in males and females. This could underlie some of the phenotypic differences between normal males and females. Genes with variable escape from XCI are also likely to underlie previously unexplained variation among females, either normal females or those heterozygous for X-linked disease genes. In the latter case, in addition to variation in the percent of cells having the mutant X-chromosome inactive, there will also be variation in the proportion of those cells in which the mutant gene is silenced.

These new results also provide increased understanding of the phenotypic abnormalities in individuals with X-chromosome anomalies, particularly those who are X0 or have partial deletions of the X-chromosome. For the escaping genes, the expression of two gene doses from the two X-chromosomes is normal. Females with deletions or who are X0 will have a deficit of the gene products of these genes in the deleted region. Escaping genes are not evenly distributed along the X-chromosome, but tend to be clustered,[4] notably in the distal region of Xp, and also in some other spots in Xp and in Xq. The concentration of escaping genes in Xp is consistent with the more severe effect of deletions of Xp than of Xq, since there are more genes in Xp for which expression of two doses is the normal state.

It will be fascinating to see how generally applicable these results in cultured cells are to cells *in vivo*. In addition to skin fibroblasts, the authors studied rodent–human somatic cell hybrids, in which XCI