EDITORIALS

GENETIC MODELLING IN RHEUMATOID ARTHRITIS: CAT WALK OR TIGHT ROPE?

Interest in the genetic basis of human disease has been greatly stimulated in recent years by a plethora of fascinating discoveries in the field of monogenic disorders. Some of these observations have potentially important implications for diagnosis, prognosis and therapy while others have raised controversial ethical issues. Previously unsuspected and sometimes highly surprising pathogenetic mechanisms have been revealed; maternally inherited mitochondrial DNA-related diseases [1], unstable segments of DNA (e.g. myotonic dystrophy, fragile X syndrome and Huntington's chorea) [2, 3], somatic mosaicism (e.g. osteogenesis imperfecta and the Marfan syndrome) [4, 5] and imprinting of parental genes, initially in a number of rare disorders (Beckwith-Wiedemann, Prader-Willi, Angelman syndromes) [6] but, more recently in atopy, one of the commonest diseases with a strong genetic component [7]. In addition, it is well-recognized that similar phenotypes may arise from mutations in quite different genes (phenocopies) and variable penetrance, of dominant effects in particular, is common. All this in monogenic disorders—as if this were not enough attention has now turned to the (even) more complex disorders in which the genetic component (frequently polygenic) interacts with non-genetic influences to cause disease.

RA, of course, is a classic multifactorial disease but attempts even to estimate its genetic component have been hindered by what at first glance appear to be quite trivial considerations, such as 'what is RA?'. For example, those time-honoured indicators of the genetic contribution to RA, such as sibling recurrence risk and concordance rates in monozygotic (MZ) twins, are influenced strongly by the severity of the disease in the proband. Lawrence's classic studies revealed that the risk of RA in the siblings of probands with seropositive, erosive RA was three times greater than in the siblings of probands with mild, non-erosive disease, in whom the risk of RA was barely greater than in the general population [8]. A similar, approximately threelfold greater recurrence risk, has been reported in MZ twins selected for seropositive, erosive disease (30%) [8] compared to studies that also include milder index twins (12%) [9]. Although the best estimates of the total genetic contribution to RA probably come from twin studies these are nevertheless beset by numerous potential confounding factors such as ascertainment bias, cross-sectional study design and definition of disease [10]. There is even substantial debate about how similar identical twins actually are, in part because of differences in their in utero environments [11]. Consequently even the best twins studies can only be regarded as giving rough estimates of the genetic contribution to RA. Since this represents the most basic forth of genetic modelling it is obvious that attempts at more complex modelling may be perilous.

Even when assessing the best characterized genetic component of RA, that linked to the HLA-DRB1 locus, there is scope for many different interpretations. There is compelling evidence for the direct involvement of HLA-DR genes themselves [12] but linked gene hypotheses have not been entirely discarded and there is considerable uncertainty about the mode of inheritance of HLA-DR linked susceptibility. For example, since the DR4 phenotype alone is strongly associated with the disease a simple dominant model would appear to explain susceptibility [10, 12] but homozygosity for DR4 seems even more important, particularly in severe RA [13]. Population and family studies appear to confirm that both haplotypes are important in determining outcome [13, 14] but it remains to be clarified which aspect of severity (intra-articular, extra-articular, young onset etc.) is most closely correlated with HLA-DR [15]. Recessive inheritance of the HLA-DR contribution has been suggested by some authors on the basis of the excess sharing of two rather than one HLA haplotype by affected pairs of siblings [14]. The shared epitope hypothesis of RA, championed by many [10, 12, 14], has also come under scrutiny by the modellers. One study rejected this in favour of a simple recessive HLA-DR linked model [16], probably erroneously since these authors failed to take account of the markedly different susceptibility to RA dependent on whether the QKRAA motif appeared in the context of DR1 or DR4 (Dw14).

Estimates of the HLA-linked contribution to the genetic component of RA have been derived by several authors using a variety of methods [10, 14, 17, 18] with the consensus that it accounts for about 30%. However, these estimates are again dependent to a great extent on figures such as sibling recurrence risk, population prevalence of RA and concordance rates in MZ twins that are not totally reliable so that a degree of scepticism is allowable. Strenuous efforts are now being made to map the genes accounting for the rest of this susceptibility using multcase sibships and DNA microsatellite markers [18]. It is tempting to suggest that in time as we identify other genes involved in RA we may learn more about our models than the models we have really taught us to date.

It is against this background that an article appearing in this edition of the Journal must be assessed [19]. Pritchard has analysed the family history of RA amongst over 700 patients attending hospital clinics in Wales. From these results he proposes the existence of a major non-HLA susceptibility gene transmission of which from an affected father enhances susceptibility.
to RA in the offspring. The hypothesis is an exciting one which is worth exploring further but it relies critically on the observation that among 84 probands there were 33 with affected fathers compared to an expected number of 21. As super-models know taking to the catwalk can be hugely rewarding but, in a field where numbers can be fickle creatures, the catwalk is more akin to a tightrope and much more work will be necessary before this hypothesis can be generally accepted.

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INDUCIBLE CYCLOOXYGENASE (COX-2): A SAFER THERAPEUTIC TARGET?

It has been estimated that NSAIDs are used by over 13 million Americans a day, with an annual cost in excess of $1 billion [1]. This makes them one of the largest and most competitive areas of pharmaceutical research. The basis for the mechanism of action of NSAIDs is due to inhibition of the enzyme cyclooxygenase (COX) [2].

Cyclooxygenase is responsible for the elaboration of the biologically active thromboxanes (TXs) and prostaglandins (PGs). Recently, two isoforms of COX have been identified, sequenced and cloned. The constitutive isoform, COX-1, encodes a 2.8 kb mRNA and the primary structure of the enzyme has been determined from the cDNA of sheep [3, 4] and humans [5]. The second, mitogen inducible isoform, COX-2, encodes a 4 kb mRNA and has been reported in Rous sarcoma virus transformed chick embryo fibroblasts and phorbol myristate acetate stimulated 3T3 fibroblasts, see [6].

It is well established that COX from various tissues is differentially inhibited by NSAIDs both in vitro [7] and in vivo [8]. If this is re-evaluated in respect to the finding that there are now two COXs, it may mean that depending on the ratio of the COX isoforms in each tissue the effects of a particular NSAID may vary. In addition, NSAIDs may also show selectivity for the different COX isoforms. For example, aspirin is more selective for COX-1 than COX-2 [9]. Thus, an NSAID may have different effects depending on which enzyme it preferentially inhibits and also which enzyme is the predominant isoform in the various tissues or pathologies. It is hence imperative that the relative contribution of COX-1 and COX-2 in all stages of inflammation be determined.

We have tried to address some of these questions by measuring the levels of COX-1 and COX-2 protein and relating this to the profile of COX activity, during the formation of a murine model of chronic granulomatous inflammation [10]. Throughout all stages of the inflammatory response the predominant COX isoform was