Influence of Genetics on Disease Susceptibility and Progression

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For many chronic diseases, the influence of genetics is complex and phenotypes do not conform to simple Mendelian patterns of inheritance. Discussed here are two types of genetic influences on healthy aging. The first involves variation in the gene sequence itself and how this may influence disease susceptibility, progression, and severity, interacting with other recognized risk factors. The second involves epigenetic regulatory mechanisms that may potentially provide insight into how environmental influences affect the expressed genome, thus improving our understanding of the genetic mechanisms underlying multifactorial diseases. The interleukin-1 family of cytokines can be used to illustrate how genetic sequence variation may affect such diseases. This cytokine family plays a key role in mediating inflammation, which is now understood to be a central component of a growing number of chronic diseases. Recent work has revealed many sequence variations in the regulatory DNA of genes encoding important members of the interleukin-1 family, and these variations are associated with differential effects on the inflammatory response. The interactions of environmental factors with both DNA sequence variations and epigenetic modifications are likely to determine the phenotypes of multifactorial diseases of aging as well as the phenotype of healthy aging.

Key words: genetics, epigenetics, single nucleotide polymorphism, allele, haplotype, linkage disequilibrium, inflammation, interleukin-1

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INTRODUCTION

For most common diseases, what is inherited is a higher risk of developing the disease, rather than the certainty of acquiring the disease. Accordingly, genes act as both susceptibility factors and genetic modifiers for various disease states (Figure 1). Recent evidence suggests that components of the cytokine system act as such factors. Cytokines include interleukins, tumor necrosis factors, interferons, lymphocyte growth factors, and hematopoietic growth factors. These polypeptide mediators are central to cell-to-cell communication within the immune system and between the immune system, the vascular system, and tissue cells. Cytokines coordinate the initiation and extent of the inflammatory response to infection and injury—one of the most complex cellular cooperations in the body. Inflammation is also an important component of the susceptibility to, and progression of, a number of disease states; cytokines, for example, have been identified as important mediators in diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease, diabetes, coronary heart disease, and Alzheimer’s disease. The influence of cytokine genetic variations on inflammation and disease provides an example of how variations in gene sequence may be involved in multifactorial diseases of aging.

GENETICS OF INTERLEUKIN-1: VARIATIONS IN DISEASE SUSCEPTIBILITY AND PROGRESSION

Interleukin-1 (IL-1) is actually a family of cytokines of the immune system, and it plays a key role in regulating the acute inflammatory response. One of the oldest cytokines in an evolutionary sense, genetic homologues of IL-1 are present in sponges and other primitive species. For example, the Toll receptor found in the fruit fly, where it controls the induction of potent antimicrobial factors, is related to the IL-1 receptor family in mammals, suggesting this conserved signaling pathway governs an evolutionarily ancient immune response. Not surprisingly, IL-1 also plays a key role in a broad array of inflammatory and autoimmune diseases.
Figure 1. Paradigm describing the interactions between genes and environment in the production of the clinical phenotype for multifactorial diseases.

While the IL-1 family comprises many members, the actions of three main constituents are best understood: the pro-inflammatory IL-1 receptor agonists IL-1β and IL-1α, and the anti-inflammatory antagonist IL-1Ra. Both IL-1β and IL-1α block binding with high affinity to the IL-1 receptor to form a complex. As a result, an intracellular protein (IL-1 receptor-associated protein, IL-1RAcP) binds to the receptor complex, initiating downstream signals to the nucleus to activate transcription factors that, in turn, activate other pro-inflammatory genes. Interleukin-1 receptor antagonist, in contrast, blocks IL-1β and IL-1α actions by binding to the IL-1 receptor with about the same affinity, but acting as a competitive inhibitor because the complex of the receptor with IL-1Ra fails to recruit the IL-1RAcP, and thus does not generate an intracellular signaling response.

Mice lacking the IL-1RN gene (which encodes IL-1Ra) are unable to express the endogenous antagonist, leaving the pro-inflammatory activities of IL-1α and IL-1β unopposed. Here, the homozygous knockouts died much earlier than their heterozygous littermates (who retained one copy of the IL-1RN gene). Of the homozygous knockouts, 93% were dead by the end of the 18-month study while the great majority of the heterozygous knockouts survived for the full term of the study, and remained healthy throughout. Autopsy evidence showed that the homozygous knockouts had florid inflammation of their large arteries, particularly in the aorta and its primary and secondary branches, with evidence of aortic aneurysms, internal hemorrhage, and previous myocardial infarctions. Unexpectedly, when the same experiment was performed in mice of a different genetic background, the arteries of the homozygous IL-1RN knockouts were relatively unaffected, but destructive inflammation of the joints was observed, causing a state of arthritis resembling human rheumatoid arthritis. The results of these studies demonstrate that mice completely lacking the IL-1RN gene spontaneously develop tissue-specific inflammation, but the phenotypic expression of this inflammation differs depending on their genetic backgrounds. This suggests that genetic modifiers other than IL-1RN were involved in the development of these immune-related chronic degenerative diseases.

**SINGLE-NUCLEOTIDE POLYMORPHISMS AND HAPLOTYPES**

The studies described above involved the complete loss of function of a single gene within the IL-1 gene cluster region. However, among variations found in the human genome, the majority are of the single nucleotide polymorphism (SNP) variety. By determining the degree of linkage disequilibrium (LD) among SNPs along a section of chromosome, it is possible to identify haplotypes, or stretches of DNA that tend to be inherited as unitary blocks. If there are different genes within the DNA, those genes will be inherited together. For example, the degree of LD over the IL-1 gene cluster on chromosome 2 is quite high, featuring eight SNPs over a span of 500 kb with several common haplotypes, encompassing the regions that encode IL-1Ra, IL-1β, and IL-1α, suggesting that this region tends to be highly conserved from generation to generation. Further investigations revealed the nature of the LD across the IL-1 gene cluster region. In 25 individuals of diverse ethnicity, DNA was sequenced across their entire IL-1 regions. From this, 40 SNPs of the region were compared in order to determine LD to a high degree of precision. Areas of high LD existed within gene exons and gene promoter regions.

**SEQUENCE VARIATION IN GENE PROMOTER REGIONS**

As genetic variation in the promoter region can affect gene activation (transcription) in different cells and at different phases of development, specific promoter haplotypes within the IL-1 gene cluster may have implications in the inheritance of inflammatory disease susceptibility. There is evidence to support this concept within the IL-1 gene cluster. Using reporter gene assays, four SNPs in the IL-1β promoter region have been identified that influence its activity (Figure 2). The results of this study also demonstrated that a change in allele at the IL-1B(-511) SNP had very different effects on reporter gene function depending on which allele was present at the IL-1B(-31) SNP. In the presence of the wild-type allele 1 at the IL-1B(-511) SNP, changing the IL-1B(-31) SNP from allele 1 to the rarer allele 2 resulted in a moderate reduction in promoter activity (Figure 2, curve A vs. C). In the presence of the rarer allele 2 at IL-1B(-31), however, changing the IL-1B(-511) allele...
had a marked impact, turning the weakest promoter into the most active (Figure 2, curve C vs. D). These data show that the functional effect of a promoter region SNP varies according to the alleles of other linked SNPs within a haplotype.

ASSOCIATION BETWEEN INTERLEUKIN-1 FAMILY GENETIC VARIATION AND DISEASE RISK

What makes this more than just an interesting biochemical observation is the link between different haplotypes of the IL-1 gene region and altered susceptibility to, or severity of, some important inflammatory diseases. For example, in a group of over 500 patients referred for angiography following chest pain upon exertion, the relative risk for coronary artery occlusion was dependent on cholesterol, lipoprotein-A, and smoking, as expected. However, in this study homozygosity for the IL-1B(+3954) allele 2 conferred as much risk as smoking (Figure 3).19 Similarly, there is evidence for linkage of genetic polymorphism within the IL-1 gene region with erosive rheumatoid arthritis,20 and ankylosing spondylitis—an inflammatory arthritis that affects the spinal joints.21 The IL-1 genes may contribute to disease susceptibility as well as acting as genetic modifiers in chronic inflammatory diseases, most of which are likely to be multifactorial in pathogenic terms.

EPIGENETICS: REGULATION AND DISEASE STATE

Epigenetic modifications include methylation of DNA, and methylation and acetylation of histone proteins in chromatin. They are increasingly recognized as being fundamental to development, physiology, tissue specificity, and propensity for diseases.22–24 Defined as heritable changes in genome function that occur in the absence of changes in gene sequence, the role of epigenetic regulation in inflammatory disease is only now beginning to be investigated. While an increasing amount of evidence suggests that environmental influence on disease susceptibility may be mediated via epigenetic mechanisms,25–27 attempts to understand the relative contribution of DNA sequence heritability and epigenetic phenomena to disease pathogenesis have only just begun.28,29 Although promising data have been produced, the full picture of epigenetic regulation in disease states will likely require the development of new high-throughput chemistry technologies. Nonetheless, current research suggests that epigenetic modifications of DNA and the histone proteins found in chromatin may be relevant to the control of the inflammatory and immune

Figure 2. Transcriptional analysis of single versus multiple single nucleotide polymorphism (SNP) allele changes in the IL-1B promoter region on reporter gene expression. For details of transfection conditions, please refer to Chen et al. (2006).18 Transfection sets when comparing the IL-1B promoter constructs, on the left of the figure, showed a reduction in promoter activity when the SNP IL-1B(-31) was changed from allele 1 to allele 2 in the presence of IL-1B(-511) allele 1 (curve A versus C). In the presence of allele 2 at IL-1B(-31), however, changing the IL-1B(-511) allele had a marked impact on promoter activity (curve C versus D). Reprinted from Chen et al.18 (Hum Mol Genet. 2006;15:519–529) with permission from the Oxford University Press.

Figure 3. Odds ratios for risk of coronary artery occlusion associated with cholesterol, lipoprotein-A [Lp(a)], smoking, and IL-1B+3954 allele 2 homozygosity in 504 patients examined for chest pain on exertion. Data from Berger et al. (2000).19
response and/or to inflammatory diseases. For example, it has been reported that certain epigenetic changes are imprinted in memory T cells, and play a key role in maintaining their immediate responsiveness to antigen re-encounter. Similarly, recent evidence suggests that epigenetic regulation occurs at sites where environmental factors impact on the developmental genetic program, determining the activation of nuclear factor-kappaB (NF-kappaB)-dependent genes.

While we have long understood that phenotype was a product of the interaction between genes and environment, only recently have we begun to have insights into the possible biochemical mechanisms underlying this fundamental tenet of biology. The prospect of developing a mechanistic understanding of how the genetic program is affected by factors such as nutrition, medicines, and environmental chemicals, now seems realistic. We must now consider the influence of epigenetics in the pathogenesis of multifactorial diseases, especially those that feature inflammatory responses as a key element (Figure 4).

CONCLUSION

Using the IL-1 gene cluster region as an example, it can be seen how genetic variation may influence the development and progression of common, multifactorial diseases. Identification of specific chromosomal haplotypes across gene clusters or within gene promoters may help elucidate the mechanisms underlying stable differences in gene expression levels between different individuals. Exploiting this genetic information in large population studies, as discussed above, should lead to an improved understanding of the genetic basis of multifactorial diseases. Further, epigenetic modification of DNA and chromatin, as a consequence of interaction between the genome and the environment, may allow a mechanistic understanding of how environmental factors modify the expressed genome, including the modification of genetic susceptibility to diseases. It may, thus, become possible to quantify susceptibility to various diseases in individuals, and to attempt preventive or therapeutic interventions before irreversible tissue damage occurs.

ACKNOWLEDGMENT

Sir Gordon Duff is a consultant to Interleukin Genetics Inc. and owns shares in the company. Interleukin Genetics has patents issued and pending on the use of IL-1 and TNF-alfa genetics as risk factors for various diseases with inflammatory components.

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