Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging[1–3]

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ABSTRACT

Inflammation plays a central role in many diseases of aging, and genetic differences in the inflammatory response appear to influence different disease courses among individuals. Variations in the genes for the family of interleukin 1 (IL-1) proteins are inherited together in a small set of patterns and provide an example of the role of inflammatory genetics as a modifier of diseases of aging. The IL-1 genetic variations are associated with variation in both the inflammatory response and the clinical presentation of a range of diseases, including coronary artery disease, Alzheimer disease, gastric cancer, and periodontitis. This growing understanding of the role of genetic variation in inflammation and chronic disease presents opportunities to identify healthy persons who are at increased risk of disease and to potentially modify the trajectory of disease to prolong healthy aging. Nutrition represents one of the promising approaches to modulation of the risk of diseases of aging because of the effects of certain nutrients on gene expression. One of the most practical applications of nutritional modulation of chronic disease may be nutrients that regulate the expression of key inflammatory genes. *Am J Clin Nutr* 2006;83(suppl):475S–83S.

KEY WORDS Coronary artery disease, Alzheimer disease, cancer, periodontitis, nutrigenetics

INTRODUCTION

Inflammation is now well established as a central component of several chronic diseases. Overtly healthy persons have been shown to have a broad range of expression of inflammatory mediators, and some persons are consistently in the higher part of the range for certain mediators, such as C-reactive protein (CRP) (1–6). In both population studies and controlled clinical trials, some variables, such as smoking, body mass index, and hormone replacement therapy, have been shown to influence concentrations of inflammatory mediators (7–13), but it remains unclear why some persons have consistently elevated systemic inflammatory responses. It seems reasonable, therefore, to determine whether genetic differences contribute to the variance in inflammatory mediator expression and whether that genetic effect influences an individual's risk of chronic diseases. This information may then be used to develop approaches to reduce the morbidity of diseases of aging.

When we consider how the genetics of inflammation may affect common chronic diseases as we age, 3 primary questions arise: Are genetic variations commonly found in the population that influence inflammation in a substantial way? Is that influence powerful enough to be clinically meaningful? Does this information suggest potential approaches to prevent the clinical implications of individual genetic differences in inflammatory mechanisms?

It is well known that complex chronic diseases, such as cardiovascular or neurodegenerative diseases, have a variety of component causes, of which inflammation is but one (14–16). Also, these causal factors interact to determine the level of inflammatory response to a particular stimulus, and those interactions most certainly change over time.

The genetics of the interleukin 1 (IL-1) system will be discussed as one example of how commonly occurring genetic differences among individuals may interweave with other factors to influence chronic inflammatory processes. Most importantly, these genetic variations appear to exert a sufficiently powerful effect to alter the progression of certain chronic diseases.

Genetic influences on the inflammatory component of complex disease expression may manifest themselves in multiple ways. We have tested the hypothesis that different persons have different expressions of inflammatory processes and that over long periods of time, ie, not weeks or months but years, this different expression pattern is sufficient to change the trajectory of disease. It should be emphasized that the genetic factors are not operating in this hypothesis as a "cause" of the disease but rather as a disease modifier. The clinical disease expression may therefore only be evident when *1*) the individual has been exposed to one of the causative factors, and *2*) the individual is susceptible (**Figure 1**). The susceptibility condition by itself is insufficient for the disease, but the onset and progression of disease may be earlier and faster in susceptible persons than in others.

If the hypothesis is correct, then those persons with genetic variations that alter the inflammatory response may have a different trajectory of certain diseases as they age and may benefit from manipulation of the inflammatory response to lower the disease trajectory or from more aggressive control of the causative factors of the disease. Our goals should be to develop the necessary technology to identify persons with increased susceptibility and to identify the necessary pharmaceutical, nutritional, or lifestyle interventions to slow the onset and progression of chronic diseases in this susceptible population. Because we

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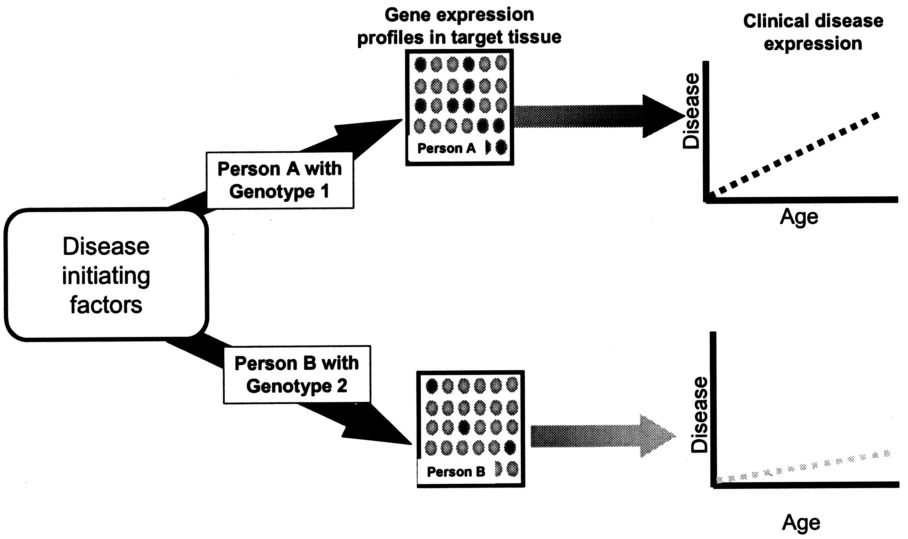

FIGURE 1. Interactions between modifying genes and disease initiating factors in the production of the clinical phenotype for multifactorial diseases. Genetic factors that modify disease do not initiate pathology but may alter disease expression.

would identify healthy persons with different genetically determined biological responses, the management of their disease predisposition should ideally be through modulation of the specific gene expression that is different in those persons. Nutrients that modulate gene expression in key regulatory pathways may provide great potential to alter the health-disease trajectory of persons with genetic variations in chronic disease risk. IL-1 biological activity is one of the key regulators of inflammation, and IL-1 genetic variations represent one potential opportunity for nutritional intervention to influence chronic diseases.

INTERLEUKIN 1 IS A CRITICAL COMPONENT OF INFLAMMATION

The rapid, generalized inflammatory processes that occur in response to an infection with a microbial pathogen are well coordinated and involve the migration of blood leukocytes to specific tissues and the activation of leukocytes and resident tissue cells to guide cascades of biochemical and cellular events. This host response involves a complex array of soluble mediators that are released initially from local tissue cells at the challenge site to recruit leukocytes out of the vascular space. Additional mediators originate from the freshly recruited leukocytes and then from distant cells, such as hepatocytes, which are activated to release mediators into the systemic circulation to help amplify or dampen the cascades and protect the well-being of the entire system. Once the leukocytes reach the local site, cytokines that communicate among cells orchestrate a finely tuned series of processes to eradicate pathogens and repair damaged tissues and protect the integrity of the host. The immuno-inflammatory responses that follow a microbial challenge are well documented, and the body's response to nonmicrobial challenges, such as oxidized LDL cholesterol, is very similar. These common responses are mediated through highly conserved pattern-recognition receptors, such as Toll-like receptors, which recognize a limited set of ligands on pathogens, called pathogen-associated molecular patterns (17, 18). It is now known that certain nonmicrobial molecules, such as specific epitopes on oxidized LDL cholesterol mimic the molecular patterns on pathogens that are innately recognized by the host as part of the differentiation of self from nonself (19). Thus, microbial and certain nonmicrobial challenges to the body activate similar host protective mechanisms.

Some of the same mechanisms that guide clearance or control of the challenge also lead to remodeling of the local tissues to facilitate cell migration and ultimately tissue repair. Because these mechanisms are critical to survival of the host, many of the same chemical mediators that activate the inflammatory cascades also regulate specific elements of metabolism to mobilize energy reserves to support the immuno-inflammatory response. Thus, fever, loss of appetite, and wasting of tissues are characteristic features of both severe infection and severe injury.

The inflammatory response system is relatively easy to describe in broad terms as it relates to an acute challenge, but the response to a chronic challenge is less easily outlined. System failure, in which tissue damage accumulates and results in organ damage, likely involves failure to eliminate the challenge, as with excess cholesterol, or subtle individual differences in the balance of regulating chemicals. Dysregulated inflammation has long been implicated in classic inflammatory diseases, such as rheumatoid arthritis, but in recent years specific components of the inflammatory process have been found to underlie several major diseases that are not routinely classified as inflammatory conditions, such as cardiovascular disease (15) and Alzheimer disease (20, 21).

Although extensive arrays of chemical mediators are involved in these processes, not all mediators influence the outcomes equally. The initial response to a challenge must be rapid, so it entails many cascades that both amplify and broaden the response after the activation of a few immediate-response genes. Because the gene products at the heads of the cascades have great leverage, they must also have redundant control mechanisms with substantial feedback to shape the response.

Among the first genes activated with almost any challenge to a tissue are the genes for IL-1 and tumor necrosis factor α (TNF-α), the products of which are at the head of the amplifying cascades. The critical and hierarchical role of these specific cytokines are shown by the fact that recombinant drugs that block

TABLE 1
Interleukin 1 (IL-1) single-nucleotide polymorphisms commonly reported in the literature

	IL-1A	*IL-1B*		*IL-1RN*
IL-1 cluster haplotype	(+4845) or (−889)[1]	(+3954)	(−511) or (−31)[2]	(+2018) or VNTR[3]
1	2	2	1	1
2	1	1	2	1
2b	1	1	2	2
3	1	1	1	1

[1] *IL-1A*(+4845) and *IL-1A*(−889) are essentially 100% concordant in whites (25).
[2] *IL-1B*(−511) and *IL-1B*(−31) are essentially 100% concordant in whites (24).
[3] The *IL-1RN* variable number tandem repeat (VNTR) is a penta-allelic system, with alleles 3, 4, and 5 being very uncommon. If the VNTR is collapsed to a bi-allelic system with alleles 2–5 scored as allele 2, it is highly concordant with *IL-1RN*(+2018) in whites.

the activity of either TNF-α [etanercept (Enbrel; Amgen, Thousand Oaks, CA); infliximab (Remicade; Centocor, Horsham, PA)] or IL-1 [anakinra (Kineret; Amgen)] are successful in the clinical control of inflammation in many patients with rheumatoid arthritis.

INTERLEUKIN 1 GENE VARIATIONS ARE COMMON IN THE POPULATION

The 9 genes of the IL-1 family, including the 3 well-defined IL-1A, IL-1B, and IL-1RN (receptor antagonist) genes, have all been mapped to a 430-kb section of DNA on the long arm of human chromosome 2 (22). Of the gene products, IL-1α and IL-1β are agonists, whereas IL-1Ra is a competitive antagonist for the IL-1 receptor and is therefore a primary negative regulator of the proinflammatory IL-1 response. These genes have been extensively studied, and between 1995 and 2005, >400 articles were published on the role of IL-1 gene polymorphisms in human clinical disease expression. Although many single-nucleotide polymorphisms (SNPs) have been identified in the coding and regulatory regions of the IL-1 genes (23, 24), most of the clinical studies used 1–3 of the SNPs that are commonly reported in whites (**Table 1**).

A high degree of linkage disequilibrium exists across the IL-1 gene region (26) and this has allowed the identification of groups of SNPs that are inherited together in blocks (ie, haplotypes) (24, 26). In whites, 3 common haplotypes have been identified (24, 26; Table 1). Persons with the IL-1 cluster haplotype 1, for example, are carriers of allele 2 at *IL-1A*(+4845) and *IL-1B*(+3954). Haplotype 2 genotype is defined primarily by *IL-1B*(−511) allele 2 and pattern 3 genotype by carriage of allele 1 at the IL-1A and IL-1B markers. Carriage of IL-1RN allele 2 has been reported to modify IL-1 biological activity, mostly in the context of haplotype 2 (27–29).

PERSONS WITH DIFFERENT INTERLEUKIN 1 GENETIC VARIATIONS HAVE DIFFERENT INFLAMMATORY RESPONSES

Persons with different IL-1 genetic patterns have consistently been shown to vary in their inflammatory responses. Because investigators have used very different systems to study the genetic effects, however, the specific findings must be evaluated relative to the experimental system. Many of the studies that specifically addressed the associations between IL-1 gene variations and various inflammatory mediators are listed in **Table 2** (29–38).

TABLE 2
Studies addressing associations between interleukin 1 (IL-1) gene variations and various inflammatory mediators

Mediator and mediator source	Disease exposure[1]	IL-1 haplotype associated with elevated mediator concentrations[2]	Reference
IL-1β protein			
Plasma	None	Haplotype 1	Hurme and Santtila (31)
PBMCs[3]	Pancreatic cancer	Haplotype 1	Barber et al (32)
PBMCs	None	Haplotype 1	Iacoviello et al (30)
Gingival fluid	Periodontitis	Haplotype 1	Engebretson et al (33)
PBMCs	None	Haplotype 2	Hall et al (34)
IL-1α protein			
Gingival fluid	Periodontitis	Haplotype 1	Shirodaria et al (35)
CRP[4]			
Serum	Pancreatic cancer	Haplotype 1	Barber et al (32)
Serum	Coronary artery disease	Haplotype 1	Berger et al (36)
Serum	Periodontitis	Haplotype 1	D'Aiuto et al (37)
Serum	Coronary artery disease	Haplotype 1	Latkovskis et al (29)
Serum	None	Haplotype 2	Eklund et al (38)
Tissue factor			
PBMCs	None	Haplotype 1	Iacoviello et al (30)

[1] Subjects in the study had the listed condition.
[2] Haplotypes as defined in Table 1.
[3] Peripheral blood mononuclear cells.
[4] C-reactive protein.

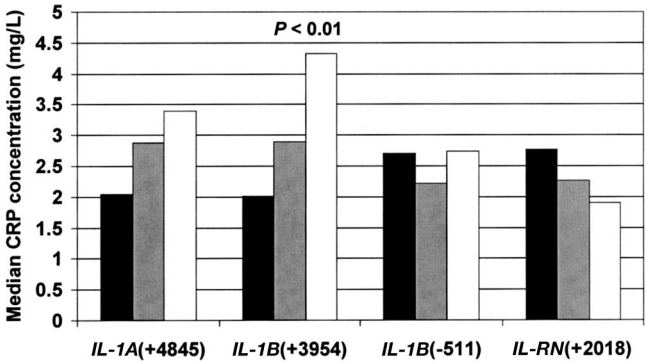

FIGURE 2. Median plasma C-reactive protein (CRP) concentrations according to interleukin 1 (IL-1) genotype in patients undergoing angiography. ■, genotype = allele 1.1; ▨, genotype = 1.2; □, genotype = 2.2. Data are from Berger et al (36).

In general, of the predominant IL-1 haplotypes, persons carrying alleles that are consistent with haplotype 1 have been reported to have significantly higher concentrations of IL-1β protein in plasma and higher concentrations of both IL-1α and IL-1β in gingival fluid. Stimulated peripheral blood mononuclear cells from these persons also produce IL-1β in greater quantities than seen in cells from carriers of other alleles. The same IL-1 gene variations have been associated with higher concentrations of CRP and tissue factor in plasma and serum.

Most of the studies involved persons exposed to some disease challenge, eg, they had documented coronary artery stenosis or periodontitis. For example, in patients undergoing coronary angiography for various indications, those who were homozygous for the *IL-1B*(+3954) allele 2 (ie, haplotype 1) polymorphism had twice the median CRP concentration of those who were homozygous for the other genotypes (**Figure 2**; 36).

In other studies involving overtly healthy persons, mediator expression tended to be lower than in the diseased persons, but those with haplotype 2 or haplotype 3 appeared to have greater levels of mediator expression than did those with haplotype 1 (34, 38, 39). These findings suggest that persons with the IL-1 haplotype 1 are more responsive to a challenge than are persons with the other haplotypes. Thus, the literature supports the conclusion that for persons who are exposed to a challenge that activates the host response, those with genotypes consistent with haplotype 1 will have a more exuberant response that leads to higher mediator levels than seen in persons with other IL-1 genotypes.

PERSONS WITH DIFFERENT INTERLEUKIN 1 GENETIC VARIATIONS HAVE DIFFERENT CLINICAL TRAJECTORIES OF CERTAIN DISEASES

Complex diseases are characterized by interactions among multiple genes and environmental factors and clinical endpoints that may be achieved by various combinations of component causes and modifiers. The critical question relative to genetics of complex diseases is whether gene variations have sufficient biological effects to alter clinically measurable outcomes. IL-1 expression is a characteristic of the pathogenesis of several diseases, including rheumatoid arthritis, inflammatory bowel disease, cardiovascular disease, chronic periodontitis, and osteoporosis (40).

In the past 10 y, IL-1 gene variations have been associated with earlier onset or more severe disease expression of Alzheimer disease (41), cardiovascular disease (42; S Offenbacher, JD Beck, J Pankow, et al, unpublished observations, 2004), periodontitis (43, 44), osteoporosis (45–47), and others (48). Other studies, however, failed to show any such correlations (50, 51). The interpretation of studies of associations between candidate gene variations and clinical disease is complicated, often due to the use of SNPs that do not adequately represent the variation in the candidate gene and the use of imprecise clinical endpoints.

This review will consider the IL-1 genetic data for 3 conditions: periodontitis, cardiovascular disease, and gastric cancer. It should be emphasized that we must assume that there will be ethnic differences in genetic associations unless proven otherwise. Most studies of IL-1 genetics and disease have been in whites. The exception is gastric cancer, for which several studies have been conducted in Japanese, Koreans, and Chinese.

INTERLEUKIN 1 GENETIC VARIATIONS ARE ASSOCIATED WITH SEVERE PERIODONTITIS

Periodontitis is a chronic inflammatory disease initiated by specific bacteria that activate host mechanisms that destroy the bone and connective tissues that support the teeth. Studies in nonhuman primates have shown that drugs that specifically block IL-1 and TNF-α dramatically and significantly reduce the tissue destruction even when the bacterial challenge is not reduced (51).

About 8–13% of the adult population has severe generalized periodontitis, and twin studies indicate that the heritability for periodontitis is high, with one-half of the variation in clinical expression explainable solely by genetic factors (52). Indeed, even in the absence of conventional oral hygiene to control the bacterial challenge, the progression of periodontitis can vary significantly (53). Substantial data support the current concept that specific bacteria are essential to the initiation and progression of chronic periodontitis (54), but the rate of progression and disease severity are determined by host modifiers such as smoking, diabetes, and genetic influences.

In 1997 we reported that persons with IL-1 genotypes that are consistent with haplotype 1, ie, carriage of allele 2 at both *IL-1A*(−889) and *IL-1B*(+3953), had an increased risk of severe periodontitis (43). Since then, 17 studies have been published that evaluated the association of IL-1 genotypes with severity of periodontal disease in white adults (43, 44, 55–69). Fourteen of those reported statistically significant associations, whereas 3 failed to show any association between IL-1 gene variations and the severity of disease.

For example, Axelsson (70) and coworkers conducted a 10-y longitudinal study of 320 persons randomly selected by postal code from the county of Värmland, Sweden. Importantly, all subjects were 50 y old to avoid the age effects that are known to complicate data interpretation. For 10 y, these persons were placed in a specific prevention program that followed well-established periodontitis prevention protocols (70). Two factors, smoking and IL-1 genotype, significantly increased the risk of progression of alveolar bone loss and tooth loss due to progressive periodontitis. Moreover, the effect was synergistic: 41% of the IL-1 genotype-positive smokers lost >2 teeth, compared with roughly 11% of those who had only one of the risk factors.

INTERLEUKIN 1 GENETIC VARIATIONS ARE ASSOCIATED WITH CARDIOVASCULAR DISEASE

Persons who are overtly healthy but have elevated inflammatory mediators, such as CRP, have a significant increase in risk of cardiovascular disease (71–75). In fact, in patients with a prior history of cardiovascular disease, decreasing CRP reduces the incidence of subsequent cardiovascular events comparable to lowering LDL-cholesterol concentrations, and there is an additive effect to lowering both (76). To design strategies for reducing inflammation, it is important to understand the factors that contribute to elevated inflammation in persons with no evidence of chronic inflammatory disease.

IL-1 has been implicated in various processes involved in atherosclerosis and cardiovascular disease (77–79). The critical role of IL-1 is clearly evident in hypercholesterolemic mouse models, in which there is less atherosclerosis in animals with reduced IL-1β biological activity, achieved by either knocking out the IL-1β activity (80) or enhancing IL-1Ra activity (81). In addition, mice with greater IL-1 activity as a result of knockout of the endogenous antiinflammatory IL-1Ra develop spontaneous transmural infiltration of inflammatory cells in the large arteries, especially at branch points (82).

IL-1 genetic variations have been associated with acute coronary events (30, 83, 84) and coronary artery stenosis (42), although not all studies have found significant associations (49, 85). For example, in patients with an early (men $<$ 45 y; women $<$ 50 y) myocardial infarction or ischemic stroke, those with IL-1 genetic variations consistent with haplotype 2 were significantly protected from both myocardial infarction (odds ratio = 0.36; 95% CI: 0.20, 0.64) and stroke (odds ratio = 0.32; 95% CI: 0.13, 0.81) (30). In this study, adjustments for fibrinogen and CRP did not modify the association. In other studies, IL-1 genetic variations that are markers of haplotype 1 were significantly associated with ischemic stroke (86) and first cardiovascular events (S Offenbacher, JD Beck, J Pankow, et al, unpublished observations, 2004). Other studies have shown a significant IL-1 genetic influence on responses to various cardiovascular treatments, including responses to drug therapy (87) and coronary angioplasty and stenting procedures (88).

Current data appear to support the conclusion that IL-1 gene variations that are associated with overexpression of inflammatory mediators are also associated with increased risk of cardiovascular events. Additional studies are needed to resolve some of the conflicting findings, to clarify the magnitude of effect, and to determine the role of IL-1 genetics in cardiovascular disease in other ethnic populations.

INTERLEUKIN 1 GENETIC VARIATIONS ARE ASSOCIATED WITH GASTRIC CANCER

The gastrointestinal disorders of chronic gastritis, peptic ulcers, and gastric cancer are initiated by *Helicobacter pylori*, a Gram-negative microorganism. Although *H. pylori* is an essential requirement for the development of gastric cancer, disease appears to require a susceptible host. Between 2000 and mid-2005, 26 studies on the association of IL-1 genetics and gastric cancer were published, of which 21 found significant positive associations with IL-1 genotype, although the specific genotypes differed somewhat in whites and Asians (89–114). Most of the studies evaluated the influence of IL-1 genetics in persons with documented *H. pylori* infection. For example, in a Portuguese population of 221 patients with chronic gastritis and 222 patients with gastric cancer, persons who had IL-1 genotypes consistent with carrying IL-1 haplotype 2b had an increased risk of cancer (odds ratio = 3.3; 95% CI: 1.3, 8.2) (105).

The studies of IL-1 genetics in gastric cancer in Asian populations have been less clear (97, 106) and may involve SNPs and haplotypes other than those that have been studied in whites (98). In general, current studies in both Asian and white populations indicate that SNPs that are part of the IL-1 haplotype 2 are involved in the increased host susceptibility to gastric cancer in persons infected with *H. pylori*.

CERTAIN NUTRIENTS CAN INTERACT WITH INFLAMMATORY GENE VARIATIONS TO MODULATE RISK

Great interest currently exists in the use of genetic information to guide the use of drugs in patients who are most likely to have a favorable response. Pharmacogenetics may involve an individual's likelihood of toxicity as influenced by variations in drug metabolism genes or may involve an individual's likelihood of enhanced drug action as the result of genetic differences in the drug target. It is now well established that certain nutrients have direct effects on gene expression through both epigenetic mechanisms and modification of transcription factors (115). This information may also be used, as in pharmacogenetics, to identify a subset of persons who receive special benefit from specific nutrients.

Some nutrients bind to, or in some way directly activate, specific transcription factors (115), which then regulate the activation of specific sets of genes. Polyunsaturated fatty acids (PUFAs) are one example of nutrients that directly alter transcription factors through the nuclear peroxisome proliferator-activated receptors (PPARs). These receptors bind to fatty acid ligands and then form a heterodimer complex with another nuclear receptor, retinoid-X-receptors. This heterodimer complex binds to specific DNA sequences to regulate gene expression. PPAR activation has been shown to modulate inflammation, including the inhibition of secretion of IL-1, IL-6, and TNF-α by stimulated monocytes (116–118).

Other nutrients alter the oxidation-reduction status of the cell to indirectly influence transcription factor activity. Many antioxidants will alter the activation status of the transcription factor nuclear factor κB, which is a key regulator of many genes, such as those involved in several aspects of the inflammatory response. Nutritional compounds, such as n$-$3 fatty acids and isoflavones, have been shown to alter genes that code for cytokines, growth factors, cholesterol-metabolizing enzymes, and lipoproteins (119–121).

Therefore, if gene variations alter the DNA sequence of a transcription factor binding site, the gene regulation by a specific nutrient may differ among persons with the different gene variations. A recent study provided support for this concept (122). One polymorphism in the inflammatory gene arachidonate 5-lipoxygenase (5-LOX) has been associated with risk of cardiovascular disease. Data show that persons who are homozygous for the 5-LOX polymorphism have a greater thickness of the carotid arterial wall, which is one indicator of the extent of

atherosclerosis. There was, however, a strong interaction between the dietary intake of PUFAs and the 5-LOX polymorphism. Dietary intake of arachidonic acid, an n−6 PUFA, had no association with carotid wall thickness in subjects without the 5-LOX polymorphism, but in persons with the 5-LOX polymorphism, increasing dietary intake of n−6 PUFAs was significantly associated with increasing carotid wall thickness. Also, low amounts of n−3 PUFAs were associated with increased carotid wall thickness only in persons with the 5-LOX polymorphism. PUFAs are known to regulate the expression of several inflammatory genes. It is reasonable to conclude from this study that the n−6 PUFAs activated the 5-LOX gene to a greater extent in persons with the polymorphism than in those without the polymorphism, thereby increasing the risk of atherosclerosis in some persons based on the presence of both dietary components and specific gene polymorphisms.

Although the PUFA and 5-LOX data are from an epidemiologic association study and not from a randomized controlled clinical trial, the implications are clear. We should be able to use polymorphisms in gene families that are at major biological control points of inflammation to identify persons with a higher risk of chronic diseases of aging. That appears to be possible with IL-1 gene polymorphisms and a few other genetic variations involved in inflammation. Because some of the IL-1 gene polymorphisms are in regulatory sequences, it seems reasonable to search for nutrients that have differential effects on gene expression in the different IL-1 genotypes and to test those nutrients for differential clinical benefits in persons with the IL-1 gene variations.

CONCLUSIONS

Although many genetic factors may be involved in inflammation, those at the head of powerful biological cascades, such as IL-1 and TNF-α, appear to have strong potential to affect a broad range of biological mechanisms. Substantial data exist showing that persons with different IL-1 gene variations have different inflammatory responses. Data also exist indicating that for some complex diseases, such as periodontal disease, cardiovascular disease, and gastric cancer, the IL-1 genetic effect is sufficiently strong to alter the trajectory of clinical outcomes.

The primary objective of identifying risk factors is to prevent disease and ideally to do so before irreversible morbidity occurs. The most widespread application of risk factors has been in a public health model, in which lifestyle factors such as smoking are addressed in a public education campaign. There are a few examples of widespread use of risk factor identification for individual patient management, such as medical management of elevated cholesterol. These approaches have been primarily driven by the availability of drugs to modify the risk. In those situations, the pharmaceutical industry invested in education of the public and medical communities to encourage early risk identification and preventive therapy to reduce a risk factor.

Genetic risk factors for common chronic diseases offer the opportunity to identify at-risk persons well before disease initiation is evident. This raises multiple issues, including *1*) how to achieve a reasonable benefit-to-cost ratio for genetic testing in asymptomatic persons and *2*) how to accomplish effective primary prevention for at-risk persons. Because certain nutrients are known to alter transcription factors and gene expression, nutrients that specifically target the biological activities that are influenced by variations in key inflammatory genes may offer great potential to modulate the clinical expression of some chronic diseases. These issues and opportunities are significant and may represent the great challenges of how to utilize the tremendous potential of genomics to meet the desire of many persons to prolong healthy aging.

KS Kornman is a full-time employee and shareholder of Interleukin Genetics Inc. Interleukin Genetics has patents issued and pending on the use of IL-1 and TNF-α genetics as risk factor tests for various diseases with inflammatory components.

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