Could single-nucleotide polymorphisms (SNPs) affecting the tumour necrosis factor promoter be considered as part of rheumatoid arthritis evolution?

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Abstract

Tumour necrosis factor (TNF), a cytokine mainly produced by macrophages, is associated with a broad spectrum of biological effects, mainly associated with the host defense against microbes. The TNF gene is located on chromosome six within the major histocompatibility complex (MHC). Rheumatoid arthritis (RA) is a systemic autoimmune disease where TNF plays a central role in its etiology and pathogenesis. Written medical evidence of RA can be traced at least as far back as the 17th century, while human paleopathological studies appear to show the presence of RA prior to this period. The fact that RA has experienced an increment both in severity and mortality could be explained by many causes, particularly the crucial role of the immune system.

Single-nucleotide polymorphisms (SNPs) are the most common genetic variations and occur at a frequency of approximately 1 in 1000 bp throughout the genome. The −308 TNF SNP is a mutation that affects the promoter region of the TNF gene. It defines the *TNF1* and *TNF2* alleles, determining low and high levels of TNF expression, respectively. The presence of the *TNF2* allele has also been linked to increased susceptibility to and severity in a variety of autoimmune and inflammatory disorders, including RA, systemic lupus erythematosus, and ankylosing spondylitis. Studies on the functional significance of −308 SNP have detected higher levels of TNF production by cells from *TNF2*-carrying individuals than cells from *TNF1* individuals. This difference does not appear to be due to other genes lying within the MHC region. Since the presence of the *TNF2* allele may increase the host's resistance to local infection, by increasing local production of TNF at the infection site, we may suggest that such a mutation has emerged as a selective advantage to carriers of the *TNF2* allele. This hypothesis may prove itself by observing the high incidence of tuberculosis and other infectious processes in those patients treated with anti-TNF therapy.

Since the human lifespan has increased, the persistence of the *TNF2* allele at high frequency in the population now confers what appears to be a marked survival disadvantage. As a result of the disregulation of the immune system, the genetically-predisposed host expresses larger amounts of TNF, leading to chronic inflammatory processes and

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autoimmune diseases, currently more prevalent. We suggest that RA, a relatively new and increasingly frequent disease, is favored by the presence of the −308 TNF promoter polymorphism, responsible for increased TNF production.

Keywords: Disease association; Polymorphism; Rheumatoid arthritis; TNF

Contents

Introduction

The biological functions of tumour necrosis factor (TNF) are varied, and its mechanism of action is rather complex. TNF, which confers resistance to certain types of infections on the one hand and causes pathological complications on the other, plays contradictory roles (Fiers, 1991). This may be related to the diverse signaling pathways that are activated. TNF produces a broad spectrum of biological effects, as a pivotal cytokine in innate and acquired immunity responses it participates in immuno-stimulation, resistance to infectious agents, resistance to tumours (Aggarwal and Vilcek, 1991; Vilcek and Lee, 1991), sleep regulation (Krueger et al., 1998), and embryonic development (Wride and Sanders, 1995). The cellular effects induced by TNF typically include a broad range of responses such as the release of soluble mediators, the induction of gene expression, growth inhibitory and cytotoxic effects, and the enhancement of cell proliferation. Monocytes and macrophages are the major sources of in vivo TNF synthesis, although many other cell types can produce it under certain circumstances. TNF acts as a co-stimulator for natural killer cells and activates B and T lymphocytes. It enhances the pathogen-directed cytotoxicity of monocytes, neutrophils and eosinophils and is the first factor involved in the cytokine cascade (Tracey and Cerami, 1993).

The stimulatory effects of the vascular bed lining on the endothelial cells are highly important and result in the enhanced surface expression of adhesion molecules and the induction of pro-coagulant activity. The adhesion of neutrophils, lymphocytes and monocytes to the endothelial cells is followed by trans-endothelial cell migration and extravasation. TNF also increases the synthesis of collagenase by fibroblasts and synovial cells, which may be important in the remodeling of joint tissue in arthritis. TNF stimulates osteoclasts and exerts growth inhibitory activity on osteoblasts, resulting in enhanced resorption of bone and articular cartilage (Idriss and Naismith, 2000).

Although TNF plays an important role as a mediator of resistance in parasitic, bacterial, and viral infections, sometimes high TNF circulating levels become pathogenic or fatal in such infections (Hober et al., 1989). It seems that only abnormal situations, such as the overreaction of the host or the dysfunction of natural autoregulatory networks, lead to aforementioned effects (Fiers, 1991).

The TNF gene lies in the class III region of the major histocompatibility complex (MHC), approximately 250 kb centromeric of the human leukocyte antigen (HLA)-B locus and 850 kb telomeric of HLA-DR. Although the circulating TNF levels are highly variable (Aguillón et al., 2001), up-regulation of TNF gene expression has been involved in the pathogenesis of a large variety of illnesses with inflammatory and autoimmune components, some of which are associated with MHC class II molecules, including systemic lupus erythematosus (Jacob et al., 1990), rheumatoid arthritis (RA) (Breunan et al., 1992; Cuenca et al., 2003), inflammatory bowel diseases (Bouma et al., 1996), and ankylosing spondilitis (Rudwaleit et al., 2001). Another group includes acute and chronic infectious processes, such as septic shock syndrome (Tracey and Cerami, 1993), cerebral malaria (McGuire et al., 1994), and acquired immunodeficiency syndrome (Hober et al., 1989).

In this report we review studies that analyze the contribution of TNF and one of its promoter gene polymorphisms to susceptibility to human disease,

specifically to RA. Furthermore, we discuss the historical evolution of RA and hypothesize on the participation of single-nucleotide polymorphisms (SNPs) and their effects on the TNF promoter gene, as an evolutionary element that could mediate increased susceptibility to RA.

Rheumatoid arthritis

RA is a systemic autoimmune disease that affects approximately 1% of the entire world population. It is characterized by chronic synovial joint inflammation and the overgrowth of synoviocytes leading to cartilage and bone destruction. The etiology and pathogenesis of the disease is complex and remains unresolved (Pincus et al., 1994; Breedveld, 1998). Cumulative studies suggest that RA occurs in patients with a genetic background with multiple common inherited genetic risk factors. The genetic contribution for the susceptibility to RA affliction has been demonstrated in family-aggregation and concordance studies, and clinical expression is found to be 3–4 times higher in monozygotic than in dizygotic twins (Aho et al., 1986; Silman et al., 1993). The mode of segregation in the population is best explained by a polygenic background influenced by the right environmental stimuli, suggesting that at least 10 different genetic regions may be linked to susceptibility to this disease (Cornelis et al., 1998). The association of the MHC *DRB1* alleles sharing amino acid sequence at positions 70–74, in the binding groove of the MHC molecule, has been well recognized in Caucasian patients with RA. However, no more than 30% of genetic susceptibility to RA has been attributed to these alleles (Wordsworth et al., 1989; Gregersen et al., 1987; Weynand and Goronzy, 1994).

RA is a heterogeneous disease with a broad spectrum of clinical severity, ranging from mild arthritis to a severe form of the disease, characterized by high serum levels of rheumatoid factor and vital compromise of other organs. Most of the articular destruction occurs in the early years of disease evolution. Diverse clinical, demographic, and genetic conditions have been associated with a more severe evolution of RA, such as a younger age at the time of onset, female sex, positive rheumatoid factor, smoking, the amino acidic conserved sequence of the *HLA-DRB1* alleles (Wicks et al., 1994), and the −308 TNF promoter polymorphism (Cvetkovic et al., 2002).

The role of TNF in rheumatoid arthritis

An accumulation of information reveals that TNF is the central cytokine in the pathogenesis of RA (Breunan et al., 1992), playing a key role in the inflammation and joint damage. High levels of TNF are found in the synovial fluids of patients with RA. In vitro studies indicate that TNF plays a primary role in the cytokine cascade in RA, controlling the production of IL-1 and other pro-inflammatory cytokines, including IL-6 and IL-8 (Butler et al., 1995). TNF mediates joint inflammation and destruction by inducing the synthesis and release of inflammatory metalloproteinases, prostaglandins, and nitric oxide in a variety of cell types, as well as by inhibiting the production of matrix components (Feldmann et al., 1996). Although there is no evidence of a direct TNF cytotoxic effect on the synovial cells, this possibility should not be rejected as part of the deleterious processes involved in RA physiopathology.

Evidence of TNF's role in the pathogenesis of RA has been shown by three important observations (Feldmann, 2001). (1) Plasma, synovial fluid, and tissue from RA patients have been reported to have high concentrations of TNF (Vinasco et al., 1997; Cuenca et al., 2003); (2) transgenic mice that over-express the human TNF gene develop a polyarthritis similar to RA (Keffer et al., 1991), while the administration of human TNF monoclonal antibodies from birth, prevents articular lesions and diminish the incidence of murine arthritis (Williams et al., 1992), and (3) arguably, the most impressive evidence comes from studies demonstrating the clinical benefit observed in RA patients treated with both chimeric (Elliot et al., 1993) and fully human (Kempeni, 1999) anti-TNF monoclonal antibodies or with soluble TNF receptors (Weinblatt et al., 1999; Moreland et al., 1997).

Historical records of rheumatoid arthritis

In contrast to the disease itself, the antiquity of its name *rheumatoid arthritis* is well established. In 1859, Sir Alfred Baring Garrod introduced the term into medical literature in substitution of rheumatic gout. Some descriptions of the clinical entity had been reported previously by Heberden, Haygarth, Charcot and Brodie, and others (Forestier, 1963; Appelboom and Ehrlich, 1998). Earlier authors had referred to forms of arthritis that resemble RA in certain attributes, but they failed to set them off as disease entities and indeed usually confused their description with what are obviously references to gout. The absence of a convincing description of the disease was routinely argued as firm evidence against the existence of RA prior to the 18th century in European populations (Parish, 1963; Short, 1974). Snorrason (1952) concluded that RA was a recent disease, not occurring among European people until the late 18th or early 19th centuries, an opinion

concurred with more recently by studies published in a textbook by Boyle and Buchanan (1971).

It is not only medical theory that has changed over the years, but the way we perceive pathological conditions as well. The power of observation and the importance of physical signs needed to define a specific condition have also varied over time. This is the most plausible explanation to account for the supposed lack of descriptions of RA in medical literature but its antiquity is still a controversial issue.

There is, however, evidence in Asia that suggests the presence of a chronic symmetric polyarthritis in the *Caraka Samhita*, a medical text from India written between 500 BC and 100 AD (Sturrock et al., 1977; Ulrich-Merzenich et al., 1999). The oldest written evidence of a disease similar to modern RA was ascribed to Scribonius Largus, who was probably describing a polyarthritis found in women between 30 and 40 years old (Copeman, 1964). The Roman emperor Constantine IX (980–1055 AD) seems to have been the first famous historical figure who suffered from RA. A brilliant description of his disease is found in the *Chronographia* by Michael Psellus, stressing the recurrent polyarthritis involving the joints of the limbs with severe contractures, deformities in the hands, and consequent disability (Kahn, 1993).

RA is very difficult to find in skeletal remains. In ancient burials and medical museums, bones of hands and feet expected to present the characteristic erosions are usually the least preserved. Reports of human remains of the ancient Egyptians concluded that ankylosing spondylitis, osteoarthritis and gout were identified in remains dating back thousands of years BC, but no unequivocal samples proving peripheric RA have been found (Short, 1974).

Rothschild described a polyarticular erosive symmetrical affliction that cannot be distinguished from modern RA found in more than 900 skeletons from different historical periods ranging from 6500 to 450 BC (Rothschild et al., 1988; Rothschild and Woods, 1990). There is evidence from isolated cases of this disease in skeletons found in Central America between 1400 BC and AD 1550. There are at least five cases of possible RA in Europe prior to 1492, dating between 70 BC and the 15th century (Aceves-Avila et al., 1998, 2001).

It is tempting to assume that ankylosing spondylitis, with or without peripheral joint involvement, existed with some frequency in the ancient world, although different from what we know today as peripheral RA. Because the small bones of the hands and feet have not thus far been as carefully preserved and examined in archaeological studies, roentgenograms may be a more successful means of investigation. However, further study of ancient remains is certainly necessary before reaching this conclusion. The question remaining is whether spondylitis is the original and only form of RA to have appeared through a similar evolutionary process in our history.

Diverse factors contribute to the origin of rheumatoid arthritis

Written medical evidence on RA dates back to at least the 17th century, while human paleopathological studies seem to show the presence of RA prior to this period, although no clear examples of the disease have been determined. RA has certainly increased in both frequency and severity, which could be explained by many causes, particularly the crucial role of the immune system.

There is consensus that RA is the result of a sustained immune response probably triggered by an external antigen in a genetically susceptible host (Moreno-Rodríguez, 1997). The nature of this antigen is still a matter of debate, and there is significant evidence that several antigens are responsible for producing the disease in different individuals (Krause et al., 1996). Pressure imposed on aggressors generates evolutionary processes that are reflected in changes to the aggressor's structural constituents, resulting in structures that are chemically very similar to the human components. For a reason that still remains unknown and due to the similarity between human and microbial structures, the immune system fails in tolerance maintenance leading to an autoimmune reaction.

We should also consider other causes and influences that could have determined an increase in the frequency and severity of this disease. Although RA is defined as an independent pathological entity, this diagnosis may actually encompass a number of different pathological conditions (Arend, 1997). RA can be considered a syndrome: a common pathway of damage produced by the immune system. A single cause can induce different clinical syndromes, depending on environmental influences and the specific characteristics of the host, as described for other infectious conditions (Evans, 1967). Epidemiological evidence suggests that the incidence of RA depends on presently ill-defined host–environment interactions (Silman et al., 1997; Gabriel et al., 1999). Diet and environmental modifications in experimental arthritis models influence the presence and severity of the disease (van der Broek et al., 1992; Hazenberg et al., 1992). Modifications in environment, diet and customs could have influenced the increment of this pathology after the 18th century. In recent years, tobacco has been proposed as an independent risk factor for RA (Saag et al., 1997; Symmons et al., 1997; Karlson et al., 1999; Uhlig et al., 1999).

The high levels of hygiene found in developed countries have also been proposed as responsible for

current increases of some autoimmune conditions (Mason, 1994). There is some evidence pointing to a low prevalence of RA in undeveloped countries (Hall, 1966). As in experimental models of autoimmunity, environmental factors could be fine tuners of the host's response (Wick et al., 1998).

In animal models, cell-mediated autoimmune diseases such as diabetes and adjuvant arthritis can be attenuated and entirely prevented in their hosts by modifying intestinal bacterial flora. Normal bacterial flora protects animals from the disease, while a germ-free environment aggravates the process (Kohashi et al., 1986; Bowman et al., 1994). It seems that a normal intestinal flora assures a wide range of antigenic stimulus for the individual, which diversifies the T cell repertoire and suppresses cell-mediated immunity for antigens encountered this way (Aceves-Avila et al., 2001).

As a consequence of the development of advances in science and technology, the average lifespan has increased considerably. As recently reported, the average lifespan in the USA increased from 77.3 years in 2002 to 77.6 years in 2003 (Centers for Disease Control and Prevention—CDC on-line report at http://www.cdc.gov).

Thus, the progressive aging of population most likely contributes at least in part to the increase in RA, a disease that begins late in life and develops over the course of time. This is consistent with the greater frequency of RA in the Old World.

SNPs the most abundant form of genetic variation

As reviewed by Shastry (2002), 99.9% of the DNA sequence between two randomly selected human genomes is identical. The remaining 0.1% is thought to include some differences or variations in the genome between individuals. This variation, called polymorphism, arises because of mutations. The simplest form of these variations is the substitution of one single nucleotide for another, called SNPs. SNPs are more common than other types of polymorphisms and occur at a frequency of approximately 1 in 1000 bp (Brookes, 1999) throughout the genome (promoter region, coding sequences, and intronic sequences). SNPs can be observed among individuals in a population, may influence promoter activity or DNA and pre-mRNA conformation, and play a direct or indirect role in phenotypic expression (Pitarque et al. 2001; LeVan et al., 2001). Some SNPs are functionally expressed, suggesting that genetic variation is one of the factors associated with susceptibility to many common diseases as well as every human trait such as tallness, curly hair, and individuality (Martin et al., 1997).

SNPs are highly abundant, stable, and distributed throughout the genome. These variations are associated with diversity in the population, individuality, susceptibility to diseases (Cuenca et al., 2003), and differential response to medical treatment (Cuchacovich et al., 2004).

TNF SNPs and rheumatoid arthritis

TNF production may be regulated at the transcriptional, post-transcriptional, and translational levels. Polymorphisms have been described in the promoter region (Jongeneel et al., 1990), the first intron, and 3′ untranslated region of the TNF gene (Beutler and Brown, 1993). It has been suggested that variability in the promoter and coding regions of the TNF gene may modulate the magnitude of the secretory response of this cytokine (Bouma et al., 1996). Of all SNPs affecting the TNF promoter gene, the one located at position −308 seems to be the most related to disease susceptibility. The −308 TNF SNP involves the substitution of guanine (G) for adenine (A), generating *TNF1* and *TNF2* (G/A or A/A genotypes) alleles (Wilson et al., 1992). The polymorphic *TNF2* allele leads to a higher rate of TNF gene transcription than the wild-type *TNF1* allele in in vitro expression studies, and it has been linked to an increased susceptibility to a variety of illnesses (Verwij, 1999; Hajeer and Hutchinson, 2000).

Until now, several studies have reported association of the −308 TNF SNP and susceptibility to RA. Thus, Danis et al. (1995) described that in the Caucasian population the frequency of the *TNF2* allele is 3 times greater in RA patients than in healthy controls. More recently, our group could establish that the *TNF2* allele is present at a frequency 2 times higher in Chilean RA patients than in normal controls (Cuenca et al., 2003). Moreover, carrying the −308 TNF SNP has been associated with more severe forms of disease expression such as the presence of extra-articular manifestations with rheumatic nodules (Vinasco et al., 1997). Additionally, in Swedish patients it has been demonstrated that individuals bearing the heterozygous *TNF2* form develop a more severe disease with an earlier onset (Cvetkovic et al., 2002), while in RA Turkish patients a significant association with bad prognosis of the disease has also been described (Ozen et al., 2002).

Interestingly, the frequency of the −308 TNF polymorphism is higher in the healthy Caucasian population than in other ethnic groups such as Latin-American, Chinese, Japanese or black African populations. Although these frequency distribution differences remain for the G/A genotype the most significant reside in the A/A genotype (Cuenca et al., 2001). On the other hand, results of several incidence and prevalence studies

of RA have been reported during the last decades, indicating a considerable variation of disease occurrence among different populations. Consistent with our proposition, the prevalence estimates for RA suggest that the occurrence of the disease seems to be lower in those ethnic groups with low frequency of the A/A genotype, and higher in individuals bearing this genotype in high proportion, as characteristic for Caucasian groups (Chou et al., 1994; Adebajo and Davis, 1994; Alamanos and Drosos, 2005).

An evolutionary immune adaptation could have led to autoimmunity

In ancestral times, the immune system underwent a continuous adaptation process induced by a high biological pressure from exogenous and endogenous aggressions, increasing its capabilities of activation and synthesis of biological mediators such as cytokines. Specifically, as mentioned previously, the −308 TNF SNP, a mutation that affects the promoter region of the TNF gene, defines the *TNF1* and *TNF2* alleles that determine low and high levels of TNF expression, respectively. Simultaneously, it has been demonstrated that the presence of the *TNF2* allele is also linked to an increased susceptibility to and severity in a variety of autoimmune and inflammatory disorders such as insulin-dependent diabetes mellitus (Pociot et al., 1993a), RA (Brinkman et al., 1997; Cuenca et al., 2003), inflammatory bowel disease (Bouma et al., 1996; Kawasaki et al., 2000), systemic lupus erythematosus (Rood et al., 2000), and ankylosing spondylitis (Rudwaleit et al., 2001).

Prior to the emergence of −308 TNF SNP; it must have been uncommon to detect wide inter-individual differences in the TNF expression as normally occurs today (Aguillón et al., 2001). It has also been demonstrated that the polymorphisms in the human TNF promoter are not all randomly distributed in the promoter, and the available data indicate that indeed such polymorphisms have functional effects that causes their selection and maintenance in the population. Hence, variations affecting the phenotype might be subject to natural selection. Thus, if these variations are retained in the genome over time, they must represent a reproductive advantage for the individual.

Numerous studies on the possible functional relevance of these polymorphisms, as part of transcriptionally functional motifs, have been carried out using transient transfection of reporter genes controlled by allelic variants of the TNF promoter (Wilson et al., 1997; Kroeger et al., 1997), or investigating the expression of TNF by cells derived from individuals with varying TNF promoter genotype (Bouma et al., 1996; Louis et al., 1998). Polymorphisms in the TNF promoter gene may affect transcriptional regulation by modifying the binding site of specific transcription factors or, alternatively, might influence DNA structure in the region (Knight et al., 1999; Udalova et al., 2000). The majority of studies investigating the functional significance of TNF promoter SNP have focused on the SNP at position −308. The reports comparing the TNF production from cells of individuals bearing the *TNF1* allele versus individuals with the rarer *TNF2* allele have generated apparently conflicting results (Uglialoro et al., 1998; Kaijzel et al., 2001; Bayley et al., 2001). Most reports observed higher levels of TNF production in cells from *TNF2* carrying individuals than cells from *TNF1* individuals (Bouma et al., 1996; Wilson et al., 1997; Kroeger et al., 1997; Louis et al., 1998).

Moreover, the difference in TNF production between individuals bearing *TNF1* and *TNF2* alleles does not appear to be due to other genes lying within the MHC. It has been reported that secretion of TNF is elevated in *TNF2* individuals, whether they are HLA-DR3$^+$ or DR3$^-$, indicating that linkage to DR3 is not responsible for the increased TNF expression detected in *TNF2* individuals (Pociot et al., 1993b; Bouma et al., 1996).

Based on the above-mentioned evidence and because the presence of the *TNF2* allele may increase the host resistance to local infection, by increasing local production of TNF at the infection site, such mutations may have emerged as an unrecognized selective advantage to carriers of the *TNF2* allele. This perception is consistent with the fact that in remote times most vertebrates were decimated by a variety of infectious microorganisms, especially intracellular aggressors, known to be susceptible to TNF activity. Therefore, in evolutionary terms, it is likely that in response to the high aggressor's biological pressure, the host's immune system evolved, allowing macrophages, the primary TNF producers, to select this polymorphism. This proposal is consistent with the high incidence of tuberculosis and other infectious processes observed in those patients that have been treated with anti-TNF therapy (Keane et al., 2001).

Intracellular pathogens no longer ravage the population today as they once did, mainly because of introduced chemical and antibiotic therapies. A consequent substantial increase in lifespan is observed, especially in the developed world. At this stage, the fact that the *TNF2* allele continues to persist at such a high frequency seems to be conferring what appears as a marked survival disadvantage, rather than a presently required innate defense against intracellular aggressors.

As a result of the deregulation of the immune system, the genetically-predisposed host expresses higher amounts of TNF, leading to chronic inflammatory processes and to autoimmune diseases, which are currently more prevalent. Considering this evidence, we propose that RA, a relatively new and increasingly

frequent disease, is favored by a specific mutation in the promoter region of the TNF gene. Of all the SNPs that affect the TNF gene, the −308 TNF promoter polymorphism is probably the most relevant for increased TNF production, thus representing a genetic risk factor for RA predisposition.

Finally, a multidisciplinary approach studying different geographical areas with high RA prevalence will generate abundant information on the influence of potential variables on the development of RA. Although RA is considered to be a multifactorial disease, resulting from the interaction of both individual and environmental factors such as sex, age, ethnicity, smoking, infectious agents, hormones, diet and socioeconomic conditions, epidemiological evidence indicates that genetic factors are the most important. Thus, our principal interest is to elucidate the genetic mechanisms modulating the production of inflammatory and anti-inflammatory cytokines, with emphasis on the role of TNF.

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