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Review

Receptor polymorphisms and diseases

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Abstract

The aim of our review is to summarize common genetic variations of some receptors associated with clinical consequences, which were not outlined in the previous special issue of this journal. Because of the multiple pathomechanisms of diseases, a set of genetic variation can play a role in the development of pathological conditions. From the data available three articles would merit a greater interest. In systemic lupus erythematosus the associations related to some polymorphisms of Fc-, tumor necrosis factor (TNF) α- and interferon receptor may explore new autoimmunological and inflammatorical pathomechanisms. In the endocrinology, the androgen receptor repeat polymorphism will exert significant aspects in the development of prostate cancer. The pleoitropic responsibility of vitamin D3 receptor polymorphism in the pathogenesis of immunological disorders (primary biliary cirrhosis, inflammatory bowel disease, type 1 diabetes mellitus) and of malignancies (malignant melanoma, breast cancer) shed light on the importance of common nuclear receptors. Nevertheless, in the future studies a more consistent approach minimizing requirement bias in the selection of patients will approve our understanding the role of genetic influence on the pathogenesis of diseases.

Keywords: Disease; Endocrinology; Gene

1. Introduction

Cells in a multicellular organism need to communicate in order to coordinate their function. Animal cells produce signaling molecules that influence other cells. Alternatively, they form gap junctions for direct cytoplasmatic interaction. One type of signaling molecule binds with high affinity to specific receptor proteins on the surface or inside of the target cells they influence. The receptors convert this interaction into one or more intracellular signals. The other form of receptors, the intracellular type, is located in the cytosol or in the nucleus. They are in an inactive state and the coupling of a signal molecule as activation gives rise to the capacity to bind to specific genes in the nucleus and regulate their transcription. Unlike intracellular receptors, cell surface receptors do not regulate gene expression directly. Receptor–ligand interaction leads to the initiation of various intracellullar signal-transduction mechanisms. The cell surface receptors differ basically as to the conformational change induced by the binding of an extracellular ligand. Based on the transduction mechanisms, the receptors can be divided into three classes: channel-linked, G-protein and catalytic. The channel type of signaling between electrically excitable cells is mediated by a small number of neurotransmitters that transiently open or close ion channels and changes the permeability of the plasma membrane. Catalytic receptors operate as enzymes. The function of the cytoplasmatic domain of the transmembrane part is a tyrosine-specific kinase. GTP binding regulatory proteins mediate the interaction of G-protein-linked receptors with enzymes or ion channels. The interaction activates a chain of events that alters the concentration of small intracellular signaling molecules, cAMP, and Ca^{2+}. Receptors play a crucial role in the regulation of cellular function and small changes in their structure might gradually influence the quality of the response. Changes in protein composition can be caused by genetic variability among individuals. Genetic polymorphism is defined by the frequency of occurrence of two or more alleles at a certain genetic locus. The frequency has to be greater than the occurrence of spontaneous mutation. Genetic marker is one type of polymorphism that can be easily detected, but it is not essentially in regulatory (causal) association with the coding part of the given gene.

Discovering the major susceptibility locus can be the key to advances in understanding the causes of a disease. In general, we use association studies to test whether a

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genetic marker (polymorphism) occurs more frequently in the cases studied than in the controls. If linkage with the disease or with an intermediate phenotype of the disease emerges from linkage studies this finding would strongly support the idea that the candidate gene is in some way involved with the disease. Clinicians should know that association of polymorphisms with complex diseases at best generates hypotheses as to how this relation is accomplished and may induce further molecular genetic studies (positional cloning, transgenic models, etc.).

2. Receptor variants and diseases

We discuss receptor polymorphisms arranged in major pathophysiological chapters without mentioning polymorphisms detailed in the articles in the special issue on Pharmacogenomics (410 (2000) 2–3).

2.1. Immunology

2.1.1. Interferon-γ receptor and systemic lupus erythematosus

Systemic lupus erythematosus is characterized by multisystem inflammation and the production of autoantibodies by activated B-lymphocytes, and by decreased cellular immune responses related to dysregulation of T lymphocytes. Autoantibodies can generate immune complexes and may cause tissue damage. Interferon-γ as well as interleukin-2 is mainly responsible for the T helper cell type1 response, the cell-mediated immunity (Tanaka et al., 1999). Interferon-γ is a secretory protein produced by activated T lymphocytes and natural killer cells. It binds to a specific cell surface receptor complex that consists of an interferon-γ receptor ligand-binding chain and an interferon-γ receptor signal-transducing chain (Tanaka et al., 1999). Genetic polymorphism of A839G within interferon-γ receptor 2 was found. As described earlier, this polymorphism leads to amino acid substitution of arginine for glutamine (Gln64Arg) in interferon-γ receptor 2 (Nakashima et al., 1999). Genetic polymorphism (Val14Met) in interferon-γ receptor 1 has also been reported (Tanaka et al., 1999).

There are a number of reports concerning the role of allelism within the major histocompatibility complex for susceptibility to systemic lupus erythematosus. In Caucasians, association of human leukocyte antigen DRB1∗0301 and DRB1∗1501 was reported while, in the Japanese group only the association with DRB1∗1501 was observed (Hashimoto et al., 1994). The involvement of other genes outside the major histocompatibility complex is not clear. The association of systemic lupus erythematosus with autoimmunity and inflammation suggests the importance of genes involved in the cytokine network (Alarcon-Valera and Alarcon-Segovia, 1982). Therefore, the relationship of the genotypic combination of these interferon-γ receptor polymorphisms and systemic lupus erythematosus has been studied intensively. Interferon-γ binds a receptor on B cells and induces HLA-DR antigen expression on the cell surface. As activated B cells play a major role in the pathogenesis of systemic lupus erythematosus, a high induction of HLA-DR expression may reflect disease activity. B cells bearing the variant receptor (Met14/Val14) show a significantly reduced induction compared with that of B cells with a normal receptor. In another study the risk of systemic lupus erythematosus associated with the interferon-γ receptor 1 Met14/Val14 genotype was confined to individuals whose interferon-γ receptor 2 genotypes were Gln64/Gln64 (odds ratio = 9.6 in Gln64/Gln64 vs. odds ratio = 3.6 in Arg64/Arg64) (Nakashima et al., 1999). Although there was no difference in receptor function concerning HLA-DR expression, i.e., in the induction of B cells between Gln64 interferon-γ receptor 2 and Arg64 interferon-γ receptor 2, but the function of B cells bearing variant interferon-γ receptor 1 (Met14/Val14) was significantly reduced compared with that of normal receptor B cells (Val14/Val14) (Nakashima et al., 1999). The combination of interferon-γ receptor 1 (Met14/Val14) and interferon-γ receptor 2 (Gln64/Gln64) may induce synergistic dysfunction of the receptor. It was considered that these polymorphisms do not play a direct role in the pathogenesis of systemic lupus erythematosus but are some of the genetic factors that may induce the development of this disease by combination with other loci or other circumstances.

2.1.2. Tumor necrosis factor (TNF) receptor 2 and systemic lupus erythematosus

Tumor necrosis factor is a pleiotropic cytokine whose biological effects include induction of apoptosis or stimulation of the target cells through activation of the transcription factor NF-[κ]β. Some of the lupus-prone mice were shown to have reduced production of TNF-α and treatment with recombinant TNF-α resulted in significant protection from disease development (Jacob et al., 1996). It is of interest, that one of the genome-wide scans suggested the chromosomal position 1p36 as a candidate region where the gene coding for TNF receptor 2 is located (Gaffney et al., 1998). Based on these findings, TNF receptor 2 was considered to be a strong candidate as susceptibility gene for systemic lupus erythematosus. Although a number of possible polymorphic sites have been reported in the entire TNF receptor 2 gene, only three of such variations in exons 4, 6 and 9 result in the amino acid change (Santee and Owen-Schaub, 1996). A polymorphism within TNF receptor 2 exon 6, leading to a non-conservative amino acid change, is significantly associated with susceptibility to systemic lupus erythematosus. The odds ratio of individuals carrying the 196R allele for developing systemic lupus erythematosus was close to that of HLA-DRB1∗1501, which is one of the few established genetic risk factors for systemic lupus erythematosus in the

Japanese population (Hashimoto et al., 1994). There are two distinct receptors for TNF-α, TNF receptor 1 (TNF-R55, CD120a) and TNF receptor 2 (TNF-R75, CD120b) (Komata et al., 1999). Although the extracellular domains of TNF receptor 1 and TNF receptor 2 share 28% identity, no homology is present between the intracellular domains of the two receptors. An increased induction of serum TNF by stimulation with lipopolysaccharide suggests that TNF receptor 2 may have a regulatory role in the suppression of inflammatory responses mediated by TNF receptor 1 in certain circumstances. Such a role could suggest that 196R is a loss-of-function substitution, resulting in an excessive immune response and enhanced apoptosis in individuals carrying this allele. The finding of elevated levels of soluble TNF receptor 2 in patients with systemic lupus erythematosus may also support this possibility (Gabay et al., 1997). TNF receptor 2 196 M/R is located in the fourth extracellular domain close to one of the two *N*-glycosylation sites. Little is known about the relationship between structure and function of TNF receptor 2, including the exact ligand-binding site. Finally, it remains to be determined whether the polymorphism at codon 196 is primarily responsible for the pathogenesis or whether it only represents linkage disequilibrium with other polymorphic sites of primary significance.

2.1.3. Fc receptors and systemic lupus erythematosus

The genetic polymorphism of human Fc receptor IIa and Fc receptor IIIb has been characterized and associated with certain diseases.

The two allelic forms of Fc receptor IIa differ by two nucleotides, one is in the first extracellular immunglobulin (Ig)-like domain (EC1) predicting a glutamine to tryptophan at position 27 and one is in the second extracellular Ig-like domain (EC2) predicting an arginine to histidine at position 131. The change at position 131 markedly alters the ability of the receptor to bind human IgG2, and this polymorphism has been associated with certain bacterial infections (Sanders et al., 1994) and with systemic lupus erythematosus (Salmon et al., 1996). The association of receptor IIa polymorphism with the susceptibility to, or clinical features of systemic lupus erythematosus was shown in African Americans, Caucasians and Koreans, but was not observed in the United Kingdom or in Greece. The two allelic forms of neutrophil-specific Fc receptor IIIb differ by five nucleotides, which results in four amino acid differences in EC1. Although binding of IgG does not seem to be affected, these two allelic forms do have different levels of quantitative function, and one allele has been associated with severe renal disease in certain systemic vasculitides (Wainstein et al., 1996).

More recently, de Haas et al. (1996) have described a triallelic sequence polymorphism at nt 230 in Fc receptor IIIa. This single nucleotide substitution in the third exon encoding EC1 predicts an amino acid change from leucine to arginine or from leucine to histidine and reportedly influences the binding of human IgG and several anti-CD16 monoclonal antibodies (De Haas et al., 1996). Such structural variants of Fc receptor IIIa, recognized by altered patterns of anti-CD16 monoclonal antibodies binding, may be related to a clinical phenotype of repeated infections. An another polymorphism at nt 559 was found and this non-conservative T to G substitution predicts a change of phenylalanine into valine at position 176 in the membrane-proximal EC2 (Wu et al., 1997). Compared with phenylalanine/phenylalanine homozygotes, Fc receptor IIIa expressed in valine/valine homozygotes bound more IgG1 and IgG3 despite identical levels of receptor expression. These observations indicate that the sequence polymorphism at nucleotide position 559 alters the apparent affinity of Fc receptor IIIa on both natural killer cells and monocytes for IgG. This difference affects the ability of the receptor to initiate a range of cell programs in response to a standard stimulus and underlies the previously described variation in natural killer Fc receptor IIIa function. Initial analysis of 200 patients with systemic lupus erythematosus indicates a strong association of the low-binding phenotype with disease, especially nephritis. A corresponding under representation of the homozygous high-binding phenotype receptor IIIa polymorphism was also shown to be associated with systemic lupus erythematosus in a study with patients and controls of diverse ethnic origin including in Caucasians.

2.1.4. T-cell receptor and immunoglobulin A nephropathy

T-cell activation and antigen recognition involve the T-cell receptor. Along with human leukocyte antigens, complement factors, immunglobulins, and cytokines, the T-cell receptor gene was listed among the candidates related to faulty immune regulation in patients with immunoglobulin A (IgA) nephropathy, which is the most common glomerulonephritis worldwide, representing an important cause of end-stage renal failure. Although the exact pathogenesis of the disease remains unclear, various disturbances of cellular and humoral immunity have been recognized. Hyperactivity of T helper cells and altered cytokine production were found in patients with IgA nephropathy. The data implied a possible role of the germline T-cell receptor constant region in determining susceptibility to the development and/or prognosis of IgA nephropathy. The complete T-cell receptor chain locus spans approximately 1 Mb in the human genome at position 14q 11–12 and is encoded by three gene segments: variable, joining, and constant. The search for genetic markers within human T-cell receptor genes has been prompted by the idea that these genes might influence the susceptibility to human leukocyte antigen-associated diseases because of the functional relationship between major histocompatibility complex and T-cell receptor molecules. The *Taq*I polymorphic site here is located between the joining and constant regions of the T-cell receptor, at 575 base pair (bp) 5′ of the C 1 exon. A rearrangement in the

noncoding region of the gene might be in linkage disequilibrium with variations in the structure or regulatory elements of the T-cell receptor.

The prevalence of the TT or Tt genotypes (*Taq*I site) among patients with IgA nephropathy with chronic renal failure (89.3% in progressive vs. 74.5% in stable state; $p = 0.01$) is of interest but additional investigations are needed to clarify the underlying mechanism (Deenitchina et al., 1999). It seems that the presence or absence of the T allele might modify the clinical course of IgA nephropathy. The relative risk for the T allele carriers from the two groups (progressive and stable) to develop renal failure was relatively low in one study (odds ratio: 2.7; 95% CI 1.1–6.3; $p < 0.05$) (Deenitchina et al., 1999).

2.1.5. Chemokine receptors, sarcoidosis and diabetes mellitus

Following the discovery that a mutation in chemokine receptor 5 can render a cell resistant to HIV infection, there was a rush to find how many in the high risk, but infection-free community was homozygous for the mutated allele. The 32-bp mutation fell within the coding region and gave rise to a non-functional protein. A mutation in the minor coreceptor chemokine receptor 2 influenced disease progression, although no effect on incidence was revealed. The mutation (64I) was found at allele frequencies of up to 15%, suggesting that an effect could be widespread. It is also difficult to imagine why an effect on disease progression would be found in the absence of an effect on transmission.

There is increasing evidence that chemokines participate in the differentiation of lymphocytes toward the T1 or T2 phenotype. Transient upregulation of chemokine receptors on leukocytes allows for the selective amplification of either a cell-mediated Th1-type immune response or an allergic Th2-type response. In sarcoidosis, it appears likely that genetically predisposed hosts are exposed to unknown antigens that trigger an exaggerated cellular immune response and the formation of granulomas. It is assumed that T lymphocytes in sarcoidosis are of the T helper cell type 1-like phenotype. Furthermore, monocyte chemotactic protein-1, macrophage inflammatory protein-1, and RANTES ("regulated on activation, normal T-cell expressed and secreted") have been identified as being released by alveolar macrophages in sarcoidosis. Chemokine receptor 2 is a receptor for monocyte chemotactic protein-1, whereas several others (monocyte chemotactic protein-2, -3, -4, and -5) are close to structural homologues of monocyte chemotactic protein-1.

In addition to human leukocyte antigen regions considered in the search for genes that may confer susceptibility to sarcoidosis, chemokine receptor-2-64I is one of the genetic variations that could influence the development of sarcoidosis. A recent study revealed that the presence of chemokine receptor-2-64I conferred a lower risk of sarcoidosis (Tien-Jyun et al., 2000a,b). The adjusted odds ratio was as low as 0.369 (95% CI 0.203–0.673), suggesting that chemokine receptor 2 polymorphism was an independent associative factor for the development of sarcoidosis.

Interestingly, chemokine receptor $2-/-$ mice have significant defects in delayed-type hypersensitivity responses, production of Th1-type cytokines, and monocyte extravasation, findings, which indicate that the presence of chemokine receptor-2-64I may lead to attenuation of the exaggerated Th1-type immune response to unknown antigens in sarcoidosis. However, the detailed mechanism by which the point mutation in the chemokine receptor 2 gene mediates protection against sarcoidosis is still unknown.

Given the high prevalence of sarcoidosis in Africans, it is possible that chemokine receptor-2-64I has different genetic effects according to race.

Insulin-dependent diabetes mellitus (IDDM) in animal models is T-cell-mediated and requires the participation of both CD8+ class I major histocompatibility complex restricted and CD4+ class II major histocompatibility complex restricted T-cells (Wicker and Peterson, 1995). Studies have shown the substantial roles of several regulatory and proinflammatory cytokines. Because, basically, IDDM is determined by genetic factors, we analyzed chemokine genes as candidates for susceptibility loci of IDDM. We found no differences in the frequency of chemokine receptor 5 $\Delta 32$ mutations between IDDM children and non-diabetic individuals, suggesting that there is no association between the deletion and IDDM (Szalai et al., 1999). In contrast, the chemokine receptor-2-64I allele frequency was significantly higher in children from the IDDM group than in the control group (Szalai et al., 1999). The importance of this mutation in IDDM cannot be explained as yet but since chemokine receptor 2 mediates the chemotaxis of CD4+ and CD8+ T-cells to areas of inflammation, and since these cells play important roles in insulitis, a mutation in the chemokine receptor 2 gene may contribute to the susceptibility to emergence of the disease.

3. Endocrinology and metabolic disorders

3.1. Estrogen receptor and atherosclerosis

The gene for human oestrogen receptor contains a polymorphism in the regulatory (upstream) region of the gene. This polymorphism consists of a dinucleotide (thymine and adenine) repeat, the length of which has been associated with bone mineral density, suggesting an effect on oestrogen receptor transcription (Ogawa et al., 2000).

In a coronarographic study, the median number of the repeat ($n = 19$) was used to categorize the population into three groups: those with short allele genotypes (both alleles of < 19 repeats), those with long allele genotypes (both alleles of ≥ 19 repeats), and those with mixed genotypes (one short and one long allele). Men with long allele genotypes had a significantly greater number of

severely narrowed coronary arteries ($p = 0.009$), larger areas of complicated lesions ($p = 0.008$), and more calcification of the coronary arteries ($p = 0.01$) than men with short alleles (Kunnas et al., 2000). It was speculated that carriers of the long repeat variants have lower expression of the oestrogen receptor gene and benefit less from the cardiovascular protective effect of oestrogen receptors.

3.2. Androgen receptor and prostate cancer

The growth and development of the human prostate gland as well as the maintenance of its function in adults is dependent on the presence of circulating androgens and intact intracellular steroid signaling pathways. Androgen stimulation is also required during the initial stages of prostate cancer development. During this period, androgen withdrawal induces tumor shrinkage as the inhibition by androgens of normal apoptotic pathways present in primary and metastatic prostate cancer has been turned off. While early prostate cancer is dependent on an androgenic environment, in its advanced stages the disease invariably becomes unresponsive to steroid regulation by one or more presently unknown mechanisms.

It is of great interest that dietary and other environmental factors have been associated with the incidence of prostate cancer. It has also been suggested that the metabolic link between fat intake and prostate cancer risk may involve androgen hormone pathways also influenced by some genetic polymorphism.

The gene of the androgen receptor, a ligand-activated transcription factor that mediates the androgenic response, is located at chromosome Xq11–12 and consists of eight exons. Androgen receptor defines three major protein functional domains: a C-terminal ligand-binding domain, a central DNA-recognition and -binding domain, and an N-terminal transcription–activation domain. Within the latter domain are 2 single-amino acid repeat length polymorphisms. The first, a polyglutamine tract, is coded by a repeated CAG, the second, a variable number of glycine residues, is coded by a tandem array of GGC sequences (Sleddens et al., 1993). Case-control studies have found associations between prostate cancer risk and one or both of the androgen receptor trinucleotide repeat polymorphisms. The risks have tended to be strongest for men with shorter $(CAG)_n$ alleles presenting higher clinical stage and tumor grade, i.e., more aggressive tumor (Irvine et al., 1995). Hakimi et al. (1997) observed that the frequency of shorter $(CAG)_n$ alleles was also substantially higher in patients with unsuspected metastatic disease identified as lymph node-positive prostate cancer. Differences in the average $(CAG)_n$ repeat length have been found to exist among ethnic groups and could be correlated with the prostate cancer risk among these populations (Irvine et al., 1995). In vitro investigations have suggested that variation in $(CAG)_n$ length affects the androgen receptor capacity to stimulate transcription at target gene promoters (Kazemi-Esfarjani et al., 1995). These functional results indicate that fewer CAG triplets result in a more active receptor under controlled conditions, and are correlated with ethnic variations in prostate cancer risk. Length variation of the $(GGC)_n$ sequence has been less widely studied, resulting in a possibly biased assessment of risk.

$(GGC)_n$ variation was significantly related to disease-free survival and overall survival (Edwards et al., 1999). Longer alleles (i.e., those with 17 or more repeats) were associated with shorter time to relapse and poor overall survival. This $(GGC)_n$ correlation is a new finding and it is much stronger than the association with $(CAG)_n$ variation. These results indicate that the androgen receptor polyglycine tract may have a functional role at least in the regulation of tumor growth. A role in normal prostate physiology is also likely. The short glycine repeats may identify men who develop prostate cancer but with decreased aggressiveness. Only two studies have reported a functional role of the polyglycine tract in vitro: Jenster et al. (1994) found that complete deletion of the $(GGC)_n$ sequence had no substantial effect on the activity of the hormone-regulated androgen receptor, whereas Gao et al. (1996) found that the same mutation resulted in a diminished capacity to activate the mouse mammary tumor virus luciferase gene. It was suggested that the role of $(GGC)_n$ in regulating tumor growth is likely to be relevant only for a limited time period in the multistep tumor progression process.

Several other studies failed to reveal an overall significant genotype-specific prostate cancer risk in connection with either the $(CAG)_n$ or the $(GGC)_n$ polymorphism as compared with control groups (Irvine et al., 1995).

Numerous investigators have used polymerase chain reaction—single-strand conformation polymorphism of DNA extracted from foci of prostate cancer to search for other androgen receptor variants both in clinically detectable disease and in latent prostate cancer. To date 581 cases of clinically detectable prostate cancer have been analyzed at the molecular level for the presence of androgen receptor mutations and a total of 47 mutations (frequency 8%) causing an amino acid change or addition have been detected. (Marcelli et al., 2000). Therefore, androgen receptor mutations are quite rare in patients with clinically localized disease and usually do not play a role in the initial phases of prostatic carcinogenesis. The data obtained suggest that androgen receptor is not responsible for the initiation of prostate cancer and serves only as a normal signaling molecule. Conversely, a relatively high number of mutations were detected in metastatic tissue, arguing for a contribution by variant androgen receptor molecules to the development of metastatic disease and/or androgen-independent growth.

3.3. Insulin receptor mutations and diabetes mellitus

Insulin resistance confers increased susceptibility to non-insulin-dependent diabetes mellitus (NIDDM), athero-

sclerotic cardiovascular disease, ovarian hyperandrogenism, and possibly hypertension. Insulin resistance is largely inherited as a complex trait. Insulin action is a multistep process that involves numerous molecules including those that mediate insulin's cellular signals and proteins that catalyze glucose uptake and metabolism. Thus, there is a broad array of genes that might harbor mutations conferring impaired insulin sensitivity (Moller et al., 1996).

Studies of cells from patients with several syndromes of extreme insulin resistance led to the discovery of functional defects involving the insulin receptor. Subsequently, a number of specific mutations in the insulin receptor gene were identified. To date, more than 35 different mutations have been described, leading mostly to one of three unusual syndromes: type A syndrome, Rabson Mendenhall syndrome, and leprechaunism (Moller and O'Rahilly, 1993). Although receptor mutations probably account for all cases of leprechaunism (and the Rabson Mendenhall syndrome), only a subset of insulin-resistant subjects with features of type A syndrome have mutations in this gene. Furthermore, receptor mutations are rarely present in patients with common NIDDM (O'Rahilly et al., 1991). Nevertheless, insulin receptor mutations represent the only clearly defined genetic cause of insulin resistance in humans.

Current knowledge of the pathophysiology of common forms of insulin resistance suggests the existence of defects that involve either (1) glucose transport and/or phosphorylation or (2) non-oxidative glucose storage as glycogen. Therefore, apart from work on the insulin receptor, recent attention has focused on the genes encoding molecules such as glucose transporters 4, hexokinase II, and glycogen synthase. In addition, genes for specific signaling molecules such as insulin-stimulated protein kinase-1 and protein phosphatase-1 that are implicated in the regulation of glycogen synthase have been investigated. Despite intensive efforts, the results of such studies have been relatively disappointing so far.

3.4. PPAR-γ and obesity

There is increasing evidence of genetic factors in obesity but the exact genes involved have not been identified. The nuclear receptor, peroxisome proliferator-activated receptor-γ (PPAR-γ), has a key role in lipid and glucose metabolism and is implicated in metabolic disorders predisposing to atherosclerosis such as dyslipidemia and diabetes mellitus.

PPAR-γ is a transcription factor and is an important regulator of adipogenesis and a modulator of intracellular insulin-signaling events. PPAR-γ mRNA expression in both skeletal muscle and adipose tissue is induced by insulin in vitro. In skeletal muscle of obese subjects, PPAR-γ mRNA is elevated in direct relation to body mass index and fasting insulinemia (Park et al., 1997).

PPAR-γ is encoded by a single gene that gives rise to two isoforms by alternative splicing, γ-1 and γ-2, which are transcribed from different promoters and differ in their first exons (A1 and A2 for PPAR-γ1; B for PPAR-γ2). The two forms differ in that PPAR-γ2 has an NH_2-terminal extension of 30 amino acids. The PPAR-γ2 isoform is expressed almost exclusively in adipose tissue, whereas PPAR-γ1 is widely expressed. No difference in the abilities of the two isoforms to participate in ligand-induced initiation of transcription of target genes or in ligand-induced adipocyte differentiation was demonstrated (Werman et al., 1997). Insulin potentiated PPAR-γ activation of transcription is ligand-independent. The γ2 isoform is much more active at doing so than is the γ1 isoform, suggesting a possible distinct role for PPAR-γ2 in obesity, insulin resistance, and diabetes.

It was found that the Pro12Ala PPAR-γ2 variant was associated with higher body mass index in two independent Caucasian populations, thus it may influence susceptibility to obesity in humans (Beamer et al., 1998). The missense mutation, Pro115Gln, in the gene for PPAR-γ2 is also associated with marked obesity (Ristow et al., 1998).

Although obesity is usually connected with insulin resistance in proportion to the excess in body weight, one might predict that mutations of PPAR-γ2 would be related to insulin resistance.

3.5. LDL receptor and familial hypercholesterolemia

Our understanding of the molecular mechanism of atherosclerosis has changed during the past 20 years. A large variety of different risk factors such as smoking, shear stress, hypertension, hypercholesterolemia, diabetes mellitus, and obesity lead to endothelial activation and/or dysfunction, which can elicit a series of cellular interactions that culminate in the lesions of atherosclerosis. To date, there have been a great number of studies investigating how hypercholesterolemia, particularly hyper-low density lipoproteinemia affects endothelial cells and forms atherosclerotic lesions.

Clinically, heterozygous familial hypercholesterolemia is characterized by a markedly elevated plasma cholesterol level ($> 7{,}5$ mmol/l) accompanied by the presence of tendon xanthoma, and by the occurrence of raised plasma cholesterol, tendon xanthoma or premature coronary heart disease in first-degree relatives (Goldstein and Brown, 1989). Fortunately homozygous familial hypercholesterolemic patients are rarely seen, but are unmistakable at an early age because of their massive increase in plasma cholesterol that frequently leads to fatal coronary disease before the age of maturity unless stringent cholesterol-lowering interventions are taken.

The increase in plasma cholesterol is entirely due to an increased concentration of low-density lipoproteins caused by abnormal catabolism of low-density lipoprotein and

very low-density lipoprotein. Studies by Brown and Goldstein and their colleagues have shown that familial hypercholesterolemia is due to an inherited defect in the low-density lipoprotein receptor, a cell-surface glycoprotein that mediates the specific uptake and degradation of low-density lipoprotein and other apolipoprotein B-containing lipoproteins.

Analysis of the sequence of the normal human low-density lipoprotein receptor gene and its intron–exon structure has revealed that the protein consists of five distinct structural domains. It has also been shown that several of the domains share a remarkable sequence homology with other apparently unrelated proteins, giving support to the hypothesis that the genes for many multifunctional proteins have evolved by the shuffling of exons derived from other genes (Sudhof et al., 1985). The low-density lipoprotein receptor itself is a member of a gene family. One close relative is the low-density lipoprotein receptor related protein, which consists of several tandem repeats of the extracellular domains of the low-density lipoprotein receptor together with a membrane-spanning domain and cytoplasmic tail.

Site-directed mutagenesis studies and transfection of the mutant gene into heterologous cells confirmed that a mutation identified in a familial hypercholesterolemia patient is indeed responsible for the LDL receptor phenotype.

To date, more than 500 mutations have already been reported.

Identification of the mutation on the low-density lipoprotein receptor gene of an individual familial hypercholesterolemic patient is of value for several reasons. Not only can an unequivocal diagnosis be made, but also affected relatives can be identified by a simple DNA-based test at an early age, when a clear-cut diagnosis based on clinical criteria alone is not possible. Although treatments for familial hypercholesterolemia and other inherited disorders such as familial defective apoB-100 are similar at present, it will become important to make a definite diagnosis if gene therapy for familial hypercholesterolemia becomes available.

3.6. Antidiuretic hormone and diabetes insipidus

Antidiuretic hormone or arginine vasopressin is a nonpeptide hormone secreted by the posterior pituitary in response to low urine osmolality or reduced blood pressure. In the collecting duct of the kidney it promotes water reabsorption and concentration of the urine by binding to the vasopressin 2 receptor, a member of the G protein-coupled receptor superfamily. Upon binding to arginine vasopressin, the receptor activates cAMP production, protein kinase A function, and the recruitment of aquaporin-2 water channels to the apical membrane of the principal cell (Knoers and Monnens, 1999). It is a final step in the antidiuresis-signaling pathway that leads to increased water permeability.

More than 150 mutations within the coding sequence of the vasopressin 2 gene have been identified to cause nephrogenic diabetes insipidus. In most cases only one mutant gene per family can be detected, but some families have two or three mutations in the same gene (Szalai et al., 1998). The mutations are scattered within the coding region, and usually confined to a single amino acid change that significantly reduces the number of receptors present on the plasma membrane (Birnbaumer, 1999). Rarely, mutations do not affect protein synthesis but significantly reduce coupling efficiency between the receptor and G protein.

3.7. Vitamin D receptor, immundiseases and malignancies

Vitamin D3 is involved deeply in immunregulatory processes, it activates monocytes and macrophages but suppresses lymphocyte proliferation and immunoglobulin production. It inhibits the action of the proinflammatory transcription factor, NF-[κ]β, and the production of a variety of different cytokines, including interleukin-2, interleukin-12, and interferon.

$1,25(OH)_2D3$ binds to a nuclear receptor termed vitamin D3 receptor and when bound to the receptor associates with specific recognition sequences called vitamin D-responsive elements, which are present in the promoter region of target genes and are involved in regulating their own transcription.

The linked commonly occurring single nucleotide polymorphisms at the 3′ end of vitamin D3 receptors are restriction fragment length polymorphism (RFLP) of *Bsm*I, *Apa*I, and *Taq*I (Morrison et al., 1994) and the exon 2 splice site *Fok* polymorphism (Gross et al., 1996).

*Bsm*I and *Apa*I polymorphisms are located in introns 7 and 8 and no direct change in the coding sequences is expected. This region, which is especially long in the vitamin D3 receptor gene has been reported to affect gene expression or mRNA stability. The *Taq*I polymorphism is an A-to-C base substitution at codon 352 of exon 8 of vitamin D3 receptor but this does not produce an amino acid coding change (both isoleucine). It has been shown, using a vitamin D3 receptor-luciferase reporter gene construct, that the “t” allele may be associated with increased levels of mRNA production in vitro (Morrison et al., 1994).

In 1994, Morrison et al. reported a strong association between polymorphisms in the vitamin D receptor and bone mineral density. Some studies published since have supported this relationship while others could not confirm it (Melhus et al., 1994).

Overall, vitamin D3 receptor polymorphisms have a slight effect (2–3%) on bone mineral density. The average rate of bone loss among postmenopausal women is approx-

imately 1% per year (Jones et al., 1994) so the effect of vitamin D3 receptor polymorphism is approximately equivalent to a 2- to 3-year difference in age.

The greatest difference between BB and bb alleles in bone mineral density measurements was seen in the "mixed" menopausal status groups (particularly at the spine) (Glinda and Umbach, 1996).

Associations have been identified between $1,25(OH)_2D3$ and susceptibility to and outcome of systemic malignancies such as breast, prostate, and colon. These include association with both serum $1,25(OH)_2D3$ levels as well as with polymorphisms in the vitamin D3 receptor gene.

Malignant melanoma is the most serious cutaneous malignancy and the prognosis of some forms is very poor (Boyle et al., 1995; Rivers, 1996). The vitamin D3 receptor gene may influence susceptibility and outcome in malignant melanoma. Data showing that melanocytes and malignant melanoma cells express the vitamin D3 receptor, and that $1,25(OH)_2D3$ has an antiproliferative effect in vitro support this view. Current literature remains controversial with regard to a causative association between ultraviolet exposure and the risk of developing the disease. Some studies, on the other hand, support the view of a possible protective effect of vitamin D3 (generated at least in part by ultraviolet).

In a recent study, homozygosity for the wild-type (F) allele at the *Fok*I restriction sites was associated with a reduced risk of malignant melanoma (Hutchinson et al., 2000). It seems to be a better determinant for outcome than for risk of development of the disease. The *Fok*I RFLP has been reported to be connected with breast cancer (Ingles et al., 1997a,b), where the FF genotype was associated with an approximately 50% decrease in risk in certain racial groups. The net effect of the ff and the fF polymorphisms can be envisaged as a reduction in the cellular effect of $1,25(OH)_2D3$ and therefore a growth advantage of the melanocytes. There is evidence of a blocking effect of $1,25(OH)_2D3$ at the transition from the G1 to the S phase of the cell cycle via several mechanisms, such as stimulation of the cyclin-dependent kinase inhibitory proteins, p21, which contains a vitamin D3 receptor response element, and p27, and inhibition of cyclin D. Furthermore, the low serum levels of vitamin D (Cornwell et al., 1992) detected imply a possible role of vitamin D deficiency in malignant melanoma pathogenesis. In addition, a protective effect of vitamin D (produced at least in part by sun exposure) might explain previous ambiguous results.

Another genetic variation, the poly (A) polymorphism (classified as long, L, or short, S) has been associated with an altered risk of breast (Ingles et al., 1997a,b) and prostate (Taylor et al., 1996) cancer. In breast cancer, the presence of LL and LS alleles was also associated with an approximately 50% reduction in risk (Ingles et al., 1997a,b). Conversely, in prostate cancer, the presence of L, either in the heterozygous (LS) or homozygous (LL) state, was associated with a 4- to 5-fold increased risk of prostate cancer (Taylor et al., 1996). *Taq*I polymorphism has also been associated with the risk of prostate cancer (Ingles et al., 1997a).

Breast cancer is the most common malignant tumor in women. A great effort has been made to identify factors of genetic background and susceptibility as well as the pathophysiology elements of the cellular proliferation processes. Vitamin D shows inhibitory effects on cell replication and induces differentiation of some breast (Frampton et al., 1982; Simpson and Arnold, 1986) and other cancer cell lines (Tanaka et al., 1982; Corder et al., 1993).

The studies regarding vitamin D metabolism in patients with breast cancer have revealed that $1,25(OH)_2D3$ receptor-negative patients relapsed significantly earlier than those who have a receptor-positive tumor, but receptor status did not correlate with age, menopausal status, T stage or lymph node involvement. Others observed that the *Taq*I genotype occurred with similar frequencies in women with breast cancer and in the control group (Lundin et al., 1999; Dunning et al., 1999), however patients without a *Taq*I site (TT genotype) showed a significantly increased risk for lymph node metastases (Lundin et al., 1999).

We studied the relationship between vitamin D3 receptor gene polymorphism (*Bsm*I RFLP) and tumor risk in 71 Caucasian women with breast cancer and 54 healthy controls. Bb genotype was found 33.8% in patients and 38.8% in controls. The occurrence of genotype bb was more frequent (36.6% in patients, 44.4% in the control group) than BB (29.5% in patients, 16.6% in the healthy group). The variances between the frequencies of genotypes and alleles in the two groups were not significant ($p = 0.24$). Similarly, no significant difference was found on comparison of BB and Bb + bb forms ($OR = 2.1/0.87–5.05/$). Vitamin D3 receptor genotypes did not significantly correlate in patients with bone metastases ($p = 0.72$) or with histological type of cancer (ductal carcinoma vs. other histology, $p = 0.99$). Our results, similarly to those of others, suggest that there is no relationship between vitamin D3 receptor gene polymorphism and breast cancer risk.

It has been reported that vitamin D3 can inhibit interferon-γ secretion by Th1 cells in a dose-dependent manner. Recent studies revealed that complex cytokine networks including both Th1- and Th2-type cytokines might be involved in the pathogenesis of systemic lupus erythematosus. The pathogenesis of systemic lupus erythematosus remains elusive, since there is no clear-cut explanation for the loss of self-tolerance. Serological studies have long suggested an association between the occurrence of certain human leukocyte antigens and systemic lupus erythematosus or autoantibody production. On the other hand, it is still controversial which cytokines play roles in the pathogenesis of systemic lupus erythematosus. There are, however, several reports supporting a Th1/Th2-cytokine imbalance in systemic lupus erythematosus. Recently, decreased production of interleukin-12 and Th1-type

cytokines (interferon-γ and tumor necrosis factor-α) in patients with early systemic lupus erythematosus were reported, suggesting that a displacement between interleukin-10 and interleukin-12 may play a central role in the Th1/Th2 cytokine shift.

Allelic variants of vitamin D3 receptor are involved in T-lymphocyte function, suggesting differences in the effect of $1,25(OH)_2$ D3 as an immunosuppressive agent.

The vitamin D3 receptor BB genotype was positively associated with systemic lupus erythematosus, proposing that the BB genotype may contribute to the Th1/Th2 cytokine imbalance through repression of interleukin-2 gene transcription and negative regulation of interleukin-12 production (Ozaki et al., 2000).

On the other hand, a correlation was found between vitamin D3 receptor allelic variation and lupus nephritis. Specifically, bb genotype was positively related to the development of the nephrotic syndrome (Ozaki et al., 2000).

Type 1 diabetes is a T-cell-dependent autoimmune disease characterized by infiltration and destruction of the pancreatic islets (Todd, 1990). The main genetic association in type 1 diabetes susceptibility is with the major histocompatibility complex on the short arm of chromosome 6. Several non-major histocompatibility complex chromosomal regions are also involved. Various approaches have been used to identify type 1 diabetes genetic susceptibility loci. Among these were case-control studies of candidate genes including the human leukocyte antigen gene, the regulatory region of the insulin gene and the interleukin-1 receptor type 1 gene (Nerup et al., 1974). Although the vitamin D receptor locus was not one of the genetic loci identified by the systemic genome searches, various pieces of evidence suggest that vitamin D3 and its receptor may play a role in the pathogenesis of type 1 diabetes mellitus. First, vitamin D3 has an important immunomodulatory property and may influence insulin secretion (Frankel et al., 1980). Furthermore, vitamin D3 administration prevents the development of type 1 diabetes as well as the associated autoimmune insulitis in non-obese diabetic mice. Recently, the vitamin D receptor *Bsm*I polymorphism was shown to be connected with type 1 diabetes in a Southern Indian population (McDermott et al., 1997). *Apa*I vitamin D receptor gene polymorphism was combined with risk for type 1 diabetes mellitus in the Taiwanese population also, and frequencies of B and A alleles were higher in type 1 diabetics than in normal controls, therefore *Bsm*I and *Apa*I polymorphism can influence vitamin D receptor expression. As stated, $1.25(OH)_2$D3 is a potent inhibitor of T-cell proliferation and of interleukin-2 and interferon-γ production. Vitamin D3 metabolites may also play a role in thymic maturation and T-lymphocyte differentiation. Vitamin D compounds indirectly inhibit immunoglobulin production due to vitamin D3-induced reductions in CD4 + T-helper cells (Todd, 1990). How vitamin D receptor gene polymorphisms influence immunoregulatory effects of vitamin D or susceptibility to type 1 diabetes deserves further exploration.

There is now good familial and molecular genetic evidence that predisposition to inflammatory bowel disease has a strong genetic component. Genome screen by microsatellite marker allele sharing in affected relative pairs has demonstrated a linkage to chromosomes 3, 7, 12, and 16 (Satsangi et al., 1996). Linkage to the region on chromosome 12 has been emphasized in a number of studies in various populations (Curran et al., 1998; Duerr et al., 1998). A strong candidate for an inflammatory bowel disease susceptibility gene is the vitamin D receptor gene. The different polymorphism in the vitamin D receptor gene may be associated with the immunosuppressive capacity of $1,25(OH)_2$ vitamin D3. The pathogenesis of inflammatory bowel disease is unknown but may be related to aberrant regulation of the mucosal immune response. According to recent observations more homozygotes for the *Taq*I polymorphism at codon 352 of exon 8 (genotype "tt") were observed among patients with Crohn's disease (frequency 0.22) than in patients with ulcerative colitis (0.12) or controls (0.12) (Simmons et al., 2000).

The mechanism by which the *Taq*I "tt" genotype might influence development of Crohn's disease is not clear. Evidence regarding the true functional significance of the "tt" genotype is scarce and contradictory. It is possible that the "t" allele can be related to an abundance of mRNA or might serve as a marker for a linked, but as yet unidentified, functional polymorphism elsewhere in the vitamin D receptor gene or in another neighboring gene. A stronger cell-mediated immune response or increased monocyte activation might predispose to the development of Crohn's disease. An alternative explanation for these results may be the inhibitory effect of $1,25(OH)_2$ vitamin D3 on the production of interleukin-12 and interleukin-10. These play a central role in the immune activation seen in Crohn's lesions. Of great interest are the recent studies of African and Indian populations, which have demonstrated associations between the "tt" genotype and infectious disease, providing further biological evidence for the importance of this polymorphism in immune regulation. One remarkable idea is that subjects with Crohn's disease may have been positively selected through having resistance to infectious diseases. This could be excellent support for the conclusion that polymorphic genes, that have only a relatively modest effect on their own, together with environmental factors, play an important role in the pathogenesis of certain diseases.

Based on the associations found between allelic polymorphisms of the vitamin D receptor gene and different immune-mediated diseases, we have selected primary biliary cirrhosis for analysis. Several studies demonstrated a relationship between certain human leukocyte antigen and complement alleles and primary biliary cirrhosis, suggesting a genetic predilection, and the disease itself is under strong hormonal influence, an assumption which is sup-

ported by the overwhelming female predominance of this disease.

Primary biliary cirrhosis is a rare, chronic, usually progressive disease of unknown etiology. It is widely believed that primary biliary cirrhosis is of autoimmune origin and is associated with the development of severe bone disease, which is in essence very similar to osteoporosis; however, its etiology is poorly understood and its treatment is not established. Because of the recently recognized role of vitamin D derivatives in the immune system we decided to search for a relation between the frequency of different vitamin D receptor genotypes and primary biliary cirrhosis and also to investigate the influence of vitamin D receptor gene polymorphisms on the bone disease in patients with primary biliary cirrhosis.

We found a significantly higher frequency of the B allele (*Bms*I polymorphism) in a group of Hungarian patients with primary biliary cirrhosis as compared with healthy age-matched female controls, based on the overrepresentation of the BB genotype (Halmos et al., 2000). An apparent trend to lower bone mass was observed in patients carrying at least one B allele, which is consistent with the findings of a recent meta-analysis showing that the B allele is associated with lower bone mineral density. The finding that there is an association between the vitamin D endocrine system and genetic predilection for primary biliary cirrhosis has never been described. These polymorphisms could have a direct influence on immune regulation by affecting cytokine (such as TNF-α) production, the expression of co-stimulatory molecules, etc., in immune cells. It could also be in linkage disequilibrium with another nearby gene that alters the risk of primary biliary cirrhosis.

4. Hemostasis

4.1. Glycoprotein IIb / IIIa and coronariasclerosis

Most acute ischemic coronary syndromes result from the formation of a platelet-rich thrombus at the site of a ruptured atherosclerotic plaque. Platelet aggregation is mediated through the binding of fibrinogen or von Willebrand factor to the activated form of the platelet glycoprotein IIb/IIIa (integrin$^{\alpha}_{IIb}\beta_3$) receptor. Platelet membrane adhesive receptors are polymorphic, and recent reports of associations between the platelet $(Pl)^{A2}$ polymorphism of glycoprotein IIIa and ischemic coronary syndromes (Weiss et al., 1996; Pastinen et al., 1998) raise the question of whether this genetic variation may contribute to platelet hyperreactivity. The molecular basis of this polymorphism is that persons positive for Pl^{A1} have a leucine at position 33 of mature glycoprotein IIIa; persons positive for Pl^{A2} have a proline at this position, which is the result of the substitution of cytosine for thymidine at position 1565 in exon 2 of the glycoprotein IIIa gene (Newman et al., 1989).

Data from various worldwide studies provide estimates of different phenotypic or genotypic frequency of the Pl^{A2}, ranging from 0.5% in Koreans and 3.7% in Japanese, to 15% in central Europe, and 26.5% in northern Europe (von dem Borne and Decary, 1990; Kim et al., 1995). Pl^{A2}-positive platelets, compared to Pl^{A1A1} platelets, have a lower threshold for platelet activation, granule release, glycoprotein IIb/IIIa activation, and fibrinogen binding. This "hyperreactive" state suggests that in vivo Pl^{A2}-positive platelets may have a greater thrombotic tendency than Pl^{A1A1} platelets.

According to the recent findings in coronary syndrome patients, there is a significant, more than 7-year difference in the age at onset of disease between Pl^{A2}-positive and Pl^{A2}-negative patients (51.8 vs. 59.2 years, $p = 0.02$).

Another study confirmed a significantly higher prevalence of Pl^{A2} polymorphism of the glycoprotein IIIa gene in patients with coronary syndrome and documented coronary stenosis than in a control group matched for sex and age (Garcia-Ribes et al., 1998). As previously mentioned, the prevalence of Pl^{A2} was higher among younger patients (60 years or less).

The relationship of the Pl^{A1A2} glycoprotein IIIa gene polymorphism and coronary artery disease has been studied only in cohorts with relatively small sample size but not in a large population of individuals whose coronary anatomy was defined by coronary angiography. Only Carter et al. (1997), but not other investigators, detected an association of the Pl^{A1A2} gene polymorphism with coronary artery disease. In one study, the Pl^{A2} allele was found to occur with similar frequency in single, and triple vessel disease.

With the focus on low risk patients, after exclusion of individuals with high body mass index (26.9 kg/m^2) and/or low apolipoprotein AI level (1.43 g/l), Pl^{A2A2} carriers had clearly higher coronary heart disease scores than Pl^{A1A1} genotype whereas Pl^{A1A2} heterozygotes had intermediate values. In the same low risk groups, an association of the Pl^{A2} allele with severe coronary artery disease was also found when the study population was divided into one group of individuals without any angiographic signs of coronary artery disease (score = 0) and another group of patients with severe coronary artery disease (score > 120) (Gardemann et al., 1998).

A greater sensitivity to therapeutic concentrations of aspirin and abciximab in Pl^{A1A2} platelets was also observed. This difference in sensitivity to antiplatelet agents may have potential clinical implications as individual antiplatelet therapy can be designed according to a patient's Pl^{A} genotype (Michelson et al., 2000).

It has also been suggested that Pl^{A2}-positive patients with unstable coronary syndromes would receive extra benefit from direct therapy with anti-glycoprotein IIb/IIIa, because recent studies indicate that treatment with specific inhibitors of the fibrinogen receptor leads to better outcomes than does aspirin therapy.

4.2. Thromboxane A2 receptor and bronchial asthma

Bronchial asthma, one of the most common chronic inflammatory diseases in human populations, is considered to result from a combination of detrimental factors both environmental and genetic. Several genome-wide linkage analyses and association studies suggested the involvement of IgE Fc ε receptor 1 β variant (Hijazi et al., 1998), β2 adrenoreceptor (Hopes et al., 1998), or interleukin-4 (Noguichi et al., 1999). Other susceptibility genes may be related to inflammation or apoptosis, such as those encoding proteins related to cell–cell interactions (cytokines and their receptors), and those involved in the arachidonic acid cascade. Thromboxane A2, a compound that causes constriction of vascular and respiratory smooth muscles has been implicated as a mediator of several diseases, including bronchial asthma. Any alteration of quality or quantity of the receptor of thromboxane A2 is likely to have some effect on the airway constriction stimulated by inflammation and may influence susceptibility to bronchial asthma. A very extensive analysis showed that among 29 candidate genes, only in the thromboxane A2 receptor gene was there a significant association between the T924C single nucleotide polymorphism and the disease (Unoki et al., 2000). However, since the related polymorphism is a synonymous substitution, it could possibly affect the efficiency of the transcription or translation of the receptor.

4.3. Thrombin receptor (protease-activated receptor-1) and venous thrombosis

Thrombin is a serine-protease that plays a central role in hemostasis and thrombosis at molecular levels (by activating several coagulation factors to form fibrin clots) and at cellular levels (by activating platelets and vascular endothelial cells). Thrombin-induced cellular effects are mediated by a G-protein-coupled receptor activated by proteolysis of the amino-terminal exodomain. Thrombin activates platelets to aggregate and secrete granules, which is the primary step to ensure hemostasis. Endothelial cell activation by thrombin leads to various responses, such as release of von Willebrand factor and prostacyclin, synthesis of nitric oxide, and cellular proliferation. Endothelium-derived nitric oxide and prostaglandin I_2 act synergistically to inhibit platelet adhesion, aggregation, and secretion (Bahou et al., 1993). Some known genetic risk factors contribute to the increase in thrombosis and some of them involve receptor mechanisms. As thrombin activates endothelial cells and platelets through the thrombin receptor, protease-activated receptor-1 might be a real candidate for this. The protease-activated receptor-1 gene comprises 2 exons separated by a large intron (22 kb) and is located on chromosome 5q11.2 to q13.3 (Bahou et al., 1993). The first sequence analysis of the regulatory region reveals the lack of evident TATA and CAAT sequences in the appropriate locations, a frequent feature of G-protein-coupled receptor genes and the presence of several putative regulatory motifs (SP1, Ets, transcriptional enhancer factor-1, and GATA). Promoter functional analysis showed that two clusters, SP1 and enhancer factor 1, are important for basal activity. Three polymorphisms were identified in the regulatory regions of the protease-activated receptor-1, i.e. in the promoter and in the exon/intron boundaries that could influence gene expression, or the response to different stimuli. One polymorphism was found in the 3′ end of the large intron near a putative acceptor site (14 A/T). Two others were a C-to-T transition at position −1426 and a 13-bp insertion corresponding to a repeat of the preceding 5′-CGGCC-GCGGGAAG-3′ sequence at position −506 in the promoter. This results in the duplication of the binding site for Ets.

The role of these polymorphisms in venous thromboembolism was studied. In 250 patients with venous thromboembolism similar frequencies were observed, suggesting no overall association (Arnaud et al., 2000). However, comparison of cases with controls showed a strong gender heterogeneity for the distribution of the −506 insertion/deletion polymorphism. Men carrying one or two −506 insertion alleles had a reduced risk of developing thrombosis with an odds ratio at 0.52 (95% CI 0.32–0.82, $p < 0.01$), meaning that the insertion allele might protect men from venous thromboembolism. The absence of a protective effect in women might be related to an influence of female hormones on protease-activated receptor-1 expression. It will be important to determine whether the insertion/deletion polymorphism influences the density of protease-activated receptor-1 on both platelets and endothelial cells, and to evaluate the putative consequences for each cellular response.

5. Conclusions

The multiple pathogenetic mechanism of diseases involves the influence of a number of genes and of several environmental factors. The role of the receptors provided communicating structure for the cellular reaction seems to be crucial. A set of receptor variations a (prevalence greater than 1%) considered by this review could potentially have important impact on the health of populations.

To improve the efficacy of investigation of genetic polymorphism some inconsistencies should be excluded. A better selection of patients and controls may offer a more homogeneous profile of subjects studied differing only in a few factors.

Furthermore, more attention has to be paid to decrease the environmental contribution for the better understanding the role of specific genes. The number of analyzing clinical endpoints and factors could be reduced. It is also required to delineate that genetic polymorphism may differ within racial groups.

For estimation of the functional and clinical consequences of certain polymorphism, the genetic variant must

be related to the quantitative trait of heritability to the phenotype, which—in this context—concerns the density of expression of receptors.

It is conceivable that our genetic approach will expend our understanding the mechanisms of diseases and will give new therapies for prevention and treatment.

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