EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 12
526-529
Year: 2018

INTERLEUKIN-6 GENE POLYMORPHISMS AND CORONARY ARTERY DISEASE- A REVIEW

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Article Received on 03/10/2018 **Article Revised on 24/10/2018** **Article Accepted on 14/11/2018**

ABSTRACT
Coronary artery disease (CAD) is a common and fatal chronic disease with high mortality. It is estimated that there have been 17.5 million deaths every year worldwide, with most of the cardiovascular events having occurred below the age of 75 years. Previous studies have shown that CAD is caused by various factors, such as inflammation, gender, age, smoking, soy food intake, hypertension, and diabetes, as well as hereditary factors. The underlying pathological mechanism of CAD is atheroma plaque instability, which is characterized by chronic inflammation caused by oxidized lipids adherent on the inner layer of the arterial wall. Recent studies have shown that inflammation-related genes might be correlated with CAD risk. Interleukin-6 (IL-6) is a proinflammatory and immunoregulatory cytokine found in diverse tissues, including fibroblasts, monocytes, adipocytes, and endothelial cells. IL-6 has a role in the genesis and maintenance of the inflammatory response. The polymorphisms of the IL-6 gene are associated with different levels of secreted protein according to the genotype. Two functional variants in the IL-6 gene, -174 G>C (rs1800795) and -572 C>G (rs1800796), have been widely investigated with relation to their association with risk of various disease. These two gene polymorphisms may influence CAD susceptibility by altering gene regulation and protein expression. Several studies show that IL-6 gene polymorphisms are associated with risk for CAD, but different studies have reported conflicting results.

KEYWORD: CAD, IL-6 gene, Polymorphims.

INTRODUCTION
One of the major health problems severely threatening public health is coronary artery disease (CAD). The pathogenesis of CAD is associated with different factors, including hypertension, family history of atherosclerosis, obesity, diabetes mellitus, hyperlipemia, and smoking habits. Recently published studies have revealed that many inflammatory molecules play a very important role in the development of CAD. Among them, inflammatory-associated cytokines are deeply involved in the development of CAD.[1]

Interleukin (IL)-6, as a proinflammatory cytokine, plays an important role in the pathogenesis of cardiovascular disease. Current data have revealed that genetic variations in the IL-6 gene and its receptor gene (IL-6R) induced different immune responses and susceptibility to CAD. In this direction, numerous studies have examined different single nucleotide polymorphisms (SNPs) in the IL-6/IL-6R genes in relation to the susceptibility to different cardiovascular pathologies. Recent study has shown that people with developed CAD expressed different profiles of cytokines, indicating that genetic factors are important determinants of the susceptibility to

CAD. An in vitro study has shown that SNPs (rs1800795 and rs1800796) in the promoter region of the IL-6 gene are functionally very important in the susceptibility to CAD. However, recent genetic population studies are inconclusive regarding associations between the SNPs and circulating IL-6 levels. The reason for the discrepancies among different studies is unclear.[2]

IL6 is a pleiotropic cytokine which bridges the innate and adaptive immune systems. Perturbations or dysfunction in the transition from innate to adaptive immunity have long term consequences for inflammation and autoimmunity. The acute response to IL6, which is largely protective, to chronic, long term signaling leading to pathogenic inflammation and autoimmunity is an example of the varying faces of IL6.[2,3]

IL6 has a wide array of biological functions and is produced by many cells of the body. Originally identified as a B-cell differentiation factor, IL6 is now recognized as a cytokine that regulates many processes such as the acute-phase response, inflammation and hematopoiesis. IL6 can be made by most tissues as well as virtually all cells of the immune system. IL6 can signal either through membrane-bound receptors or, uniquely within the IL-6 family of cytokines, can signal in trans, with a soluble form of its receptor. IL6 has been shown to participate in neurogenesis, wound healing and hepatic regeneration. Acutely, IL6 responds to almost all perturbations of homeostasis. However, when IL6 remains elevated chronically, the protective roles IL6 have maintaining tissue integrity and signaling the immune response, are no longer required and constant signaling becomes associated with fibrosis and chronic inflammation.[4]

IL6 biological functions and signalling[5-7]

IL6 is a member of the IL6 family of cytokines that also includes cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), cilliary neurotrophic factor (CNTF) leukemia inhibitory factor (LIF), neuropoietin (NPN), and oncostatin M.

As a multi-functional cytokine, IL6 acts on the immune system as well as other local tissues. Within the immune system, IL6 can direct the development and activation status of both innate and adaptive immune cells. IL6 signaling up-regulates anti-apoptotic molecules in T cells. In addition, IL6 is required for Th17-lineage differentiation through STAT3 dependent mechanisms. This is particularly important because the Th17 lineage has been implicated as a contributor to pathogenesis in many autoimmune diseases. IL6 also has functions in the innate immune system, where it induces the differentiation of monocytes to macrophages rather than dendritic cells. IL6 may also influence DC activity as it can suppress DC CCR7 expression and IL6 secretion by DCs can affect the immunosuppressive activity of Tregs, thus bridging the innate and adaptive immune responses. And importantly for the initiation of many inflammatory responses, in the tissue IL6 suppresses neutrophil infiltration while promoting the infiltration and activation of mononuclear leukocytes. Together, these studies show how IL6 can direct a proinflammatory immune response that can trigger an auto-aggressive response through the Th17 lineage if not properly controlled.

The IL6 cytokine family signals through a cytokine-specific receptor complexed with at least one subunit of the signal-transducing protein gp130. IL6 specifically signals through a complex of the IL6R (also known as IL6R-alpha) and the IL6-family common receptor gp130. GP130 signaling mediates a variety of cellular processes including cell survival, apoptosis, growth, proliferation, differentiation and survival. GP130 is part of the receptor complex for CNTF in the brain, LIF, oncostatin M, NPN, cardiotrophin (CT-1) in the heart, IL11, IL27 and IL31. Importantly, gp130 is expressed on nearly all cells in the body. Therefore what gives IL-6 family cytokines tissue-specificity is the cellular expression of the co-receptor for each family member cytokine.

The IL6R is mainly expressed on hepatocytes and immune cells. However, IL6 is unique in the IL6-family because it has a soluble form of its receptor. Therefore, cells lacking the IL6R can still respond to IL6 because the naturally occurring soluble form of the IL6R exists and can create a complex with IL6. IL6 first binds to the IL6R and this complex of IL6 and IL6R then binds with gp130.The soluble IL6R (sIL6R) is generated either by cleavage of the membrane-associated receptor or, independently, by translation of an alternatively spliced mRNA. This signaling of the sIL6R and the membrane bound gp130 is referred to as IL6 trans-signaling. Trans-signaling has been shown to be active in many systems where cells only become responsive to IL6 in the presence of the sIL6R, such as in hematopoietic progenitor cells, T cells, and endothelial cells.

Downstream signaling of the IL6R combined with gp130, whether soluble or membrane bound, signals through either JAK-STAT, Ras-MAPK, or PI3K, pathways. Within the JAK-STAT pathway, IL6 specifically signals through STAT3, which dimerizes and then translocates to the nucleus. Regulation and termination of downstream IL6 signaling is mediated through suppressor of cytokine signaling (SOCS) proteins. The negative regulator of IL6-STAT3 activation, SOCS3, may in part regulate the protective versus pathogenic affects of IL6.

Genome-Based Prediction of CVDs[8,9]

Genetic association studies investigate a correlation between disease status and a genetic alteration(s) (e.g., SNPs, VNTRs, and CNVs) to identify risk or protective alleles that play a part in the development of a specific disease. An increased frequency of a risk allele or genotype in the individuals affected with a disease can result in the conclusion that the variant of interest

increases the risk of a specific disease. According to our results, association studies still represent an important tool in identifying genes contributing susceptibility to several complex CVDs. Association studies (and meta-analyses) have reconfirmed that many different genetic variants affect disease risk, but each variant has only a relatively small effect. Single markers identified are unlikely to be considered for clinical use unless they yield a high effect size (characterized by odds ratio/beta coefficient).

Meta-analyses that combine the results of single-gene association studies provide an opportunity to obtain more robust effect sizes. In the last decade, meta-analyses were related to atrial fibrillation, MRI-defined brain infarct, ischemic stroke, and susceptibility to any type of atherosclerotic CVD, such as coronary artery disease, acute coronary syndrome, or ischemic heart diseases. It is worth mentioning that meta-analyses may be biased: publication bias, population stratification, control selection bias, and lack of genotype blinding exist, thus results should be interpreted with caution.

Genome-Wide Association Studies[10]

Genome-wide association studies use high-throughput genotyping technologies to assay thousands of SNPs and correlate them to clinical conditions or measurable traits. GWA studies are very useful in discovering genetic variants related to different diseases but also have important limitations (summarized by Pearson and Manolio), "including false-positive and false-negative results and biases related to selection of study participants, and genotyping errors." But most of the variants identified by GWA studies still have very modest effects on disease risk and explain only a small fraction of population risk or total estimated heritability.

It is important to point out that a variant with even small odds ratios can improve the indicative power of the predictive models, such as the 9p21 locus. Despite several studies that show consistent associations of 9p21 locus with CVD traits, the biological role of the locus is still not well understood. In a study by Visel et al., the results provide direct evidence that the coronary artery disease risk interval has a crucial role in regulation of cardiac Cdkn2a/b expression (a mouse ortholog of the 9p21 locus) and suggest that this region has an effect on the progression of coronary artery disease by modifying the dynamics of vascular cell proliferation. If it is confirmed this would represent a new mechanism for myocardial infarction that is unrelated to traditional risk factors.

Genetic Testing to Improve Diagnostic Accuracy[8,11]

Besides the several studies mentioned earlier on coronary heart disease, a study on risk models that predict a person's risk for developing venous thrombosis was published by de Haan et al. GRS based on 31 venous thrombosis-associated SNPs was developed for subjects of a large case–control study (2,712 patients and 4,634 controls). GRS computed from all the 31 SNPs or from the 5 most strongly associated SNPs performed very similarly (AUCs of 0.70 and 0.69, respectively). The AUC of a risk model based on known non-genetic risk factors was 0.77 (95% CI: 0.76–0.78). After combining the non-genetic and genetic risk models, the AUC improved to 0.82 (95% CI: 0.81–0.83), which indicates better diagnostic accuracy.

Genome-Based Prediction of Treatment Response[12,13]

In addition to genetic testing that can improve the treatment by increasing drug efficacy and safety, a genetic test can be used to select patients for therapies that target-specific genes/gene products. An area where genome-based prediction of treatment response is important is the use of genetic testing for evaluating the antiplatelet effects of the antiplatelet drug clopidogrel. Several recent studies suggest that therapeutic responses to clopidogrel might depend on the genotype at the *CYP2C19* gene; however, some findings are contradictory. It was shown that clopidogrel-treated patients who had an allele of *CYP2C19* with reduced function [most commonly the *CYP2C19*2* or *CYP2C19*3* allele, roughly 30% of patients have loss-of-function (LOF) alleles] had less platelet inhibition, and consequently, a significantly higher risk of cardiovascular events than those who had a normally functioning CYP2C19 enzyme. Furthermore, it was shown that the CYP2C19*17 variant is the gain-of-function (GOF) allele (prevalence is between 3 and 21%) and is an independent factor in increased bleeding risk. Recently, Shen et al. demonstrated the explicit clinical benefit of CYP2C19 genetic testing for guiding the antiplatelet therapy on a sample of 628 patients; clinical outcomes were analyzed at 1, 6, and 12 months after discharge. Individual antiplatelet therapy guided by CYP2C19 genetic testing significantly improved the prognosis of patients after percutaneous coronary intervention. The morbidity rates of "major adverse cardiovascular events" in the intervention group were decreased by 4.3, 4.6, and 5.2% compared with the routine group (conventionally treated with 75 mg daily of clopidogrel without CYP2C19 genetic testing) at 1, 6, and 12 months, respectively.

According to a review by Chan et al., there is a good evidence of analytical validity for testing LOF polymorphisms in managing clopidogrel therapy. They highlighted that LOF polymorphisms are associated with reduced levels of the active clopidogrel metabolite and with reduced on-treatment inhibition of ADP-induced platelet activation. In percutaneous coronary intervention populations, there is consistent evidence for an association between LOF polymorphisms and adverse clinical outcomes (stent thrombosis and major adverse cardiovascular events). Evidence for clinical utility of CYP2C19 genotyping as a predictive biomarker is limited to subgroups with indecisive findings.

In a single-center study of 535 ischemic stroke patients who received clopidogrel, Yi et al. found that for patients carrying the reduced function *LOF* polymorphisms the inhibition of platelet aggregation was significantly lower in patients treated with proton-pump inhibitors.

CONCLUSION

Classically IL6 is considered to be a proinflammatory cytokine. When homeostasis is disturbed within a host IL6 is elevated and induces protective responses determined by the nature of the insult. IL6 can activate immune cells, direct immune cell trafficking, signal protective responses in local tissue, initiate the acute phase response or contribute to wound healing. In the acute response, these are all vital functions. However, beyond this temporally limited role, the proinflammatory nature of IL6 can become pathogenic. In the short term, what are protective responses, increased cell infiltration, increased wound repair, can turn deleterious in the long term leading to inflammatory and fibrotic disorders. The heart is a tissue where this duality is very apparent. Studies from MI show how short-term IL6 signaling can protect and preserve the heart tissue in response to acute damage, where long term IL6 signaling or an over-production of IL6R protein plays a causal role in cardiovascular disease.

The identification of the unique nature of IL6 signaling, which occurs through both classical, membrane-bound signaling and through signaling in trans, with a soluble form of the IL6R, has created the opportunity for therapeutic intervention. Blocking all IL6 signaling has severe consequences as IL6 serves many vital functions, although is only currently used for severe cases of RA. Having a method to only block the particularly pathogenic signals of IL6 is an exciting avenue of research. The current use of the available IL6R antibody, which targets both classical and trans signaling, is limited as tocilizumab is given monthly by intravenous (IV) infusion. However, many animal studies are aimed to design more specific inhibitors, through the use of a soluble gp130 decoy, sgp130Fc, which inhibits only trans-signaling.

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