Section A -Research paper

Role of Proteasome Subunit α Type 6 (PSMA 6) Gene Polymorphism in Pathogenesis of Coronary Artery Disease

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Abstract:

Coronary artery disease (CAD), including its most severe complication, myocardial infarction (MI), is the leading cause of death in the industrialized world. As the most serious clinical manifestation of CAD, MI is the condition of irreversible necrosis of the heart muscle that results from prolonged ischemia. Approximately 90 % of MI results from the formation of an acute thrombus that obstructs an atherosclerotic coronary artery. The proteasome system is a proteolytic pathway that regulates the expression of genes involved in inflammation. Recently, an association of a functional sequence variation, -8C/G, in the human proteasome subunit alpha type 6 gene (PSMA6) with the susceptibility to coronary artery disease (CAD) was reported. After that, several validation studies have been conducted among various ethnic populations, but the results have been inconsistent. G allele of PSMA6-8C/G polymorphism is a risk factor associated with increased CAD susceptibility, but these associations vary in different ethnic populations.

Keywords: CAD, PSMA 6**,** Atherosclerosis.

Introduction:

Coronary artery disease (CAD) is a manifestation of complex events including gene-gene and gene-environment interactions, partly triggered through inflammatory processes. Various pathways as well as candidate genes and loci identified thus far for susceptibility to CAD through case-control association studies or linkage analysis appear to be involved in the regulation of inflammatory mechanisms. Several of these genes have also been associated with myocardial infarction (MI), an event that underlies such inflammatory processes and is a critical component in the pathogenesis of CAD **(1)**.

The ubiquitin-proteasome system is one such pathway that regulates the inflammatory processes and presumably plays an important role in mechanisms leading to MI. This proteasome is a large multi catalytic proteinase that functions as a

central switch within the cell by selectively degrading a multitude of proteins, including metabolic enzymes, transcription factors, and cell cycle regulators **(2)**.

Not surprisingly therefore, the proteasomal alpha subunit type 6 gene (*PSMA6*), a component of the ubiquitin-proteasome system has been associated with MI, type 2 diabetes mellitus (DM2), greater intima-media thickness, and possibly atherosclerosis. On the other hand, its role in conferring risk for cardiovascular-related events in general has been called into question recently by a number of studies pointing to a lack of association with these disorders in some ethnic groups **(3)**.

The *PSMA6* gene is located on chromosome 14q13.2, a region containing microsatellites that have also been implicated in various diseases, including DM2, Grave's disease and familial schizophrenia **(4)**.

Atherosclerosis is a chronic inflammatory condition. It is the main pathologic basis of cardiovascular diseases. Plaque rupture and thrombosis may induce acute clinical events such as acute coronary syndrome. Wingless/beta catenin (Wnt/β-Catenin) is involved in the progression of vascular lesions, associated with endothelial dysfunction, macrophage activation, proliferation, and vascular smooth muscle cell migration **(5)**

Structure:

Protein expression:

The gene PMSA6 encodes a member of the peptidase T1A family, that is a 20S core alpha subunit. A pseudogene has been identified on the Y chromosome. The gene has 8 exons and locates at chromosome band 14q13. The human protein proteasome subunit alpha type-6 is also known as 20S proteasome subunit alpha-1 (based on systematic nomenclature). The protein is 27 kDa in size and composed of 246 amino acids. The calculated theoretical pI (isoelectric point) of this protein is 6.35 ***(6).***

Complex assembly:

The proteasome is a multicatalytic proteinase complex with a highly ordered 20S core structure. This barrel-shaped core structure is composed of 4 axially stacked rings of 28 non-identical subunits: the two end rings are each formed by 7 alpha subunits, and the two central rings are each formed by 7 beta subunits. Three beta subunits (beta1, beta2, and beta5) each contains a proteolytic active site and has distinct substrate preferences. Proteasomes are distributed throughout eukaryotic cells at a high concentration and cleave peptides in an ATP/ubiquitin-dependent process in a non-lysosomal pathway ***(7).***

Function:

Crystal structures of isolated 20S proteasome complex demonstrate that the two rings of beta subunits form a proteolytic chamber and maintain all their active sites of proteolysis within the chamber. Concomitantly, the rings of alpha subunits form the entrance for substrates entering the proteolytic chamber. In an inactivated 20S proteasome complex, the gate into the internal proteolytic chamber is guarded by the N-terminal tails of specific alpha-subunit***(8).***

The proteolytic capacity of 20S core particle (CP) can be activated when CP associates with one or two regulatory particles (RP) on one or both side of alpha rings. These regulatory particles include 19S proteasome complexes, 11S proteasome complex, etc. Following the CP-RP association, the confirmation of certain alpha subunits will change and consequently cause the opening of substrate entrance gate. Besides RPs, the 20S proteasomes can also be effectively activated by other mild chemical treatments, such as exposure to low levels of sodium dodecylsulfate (SDS) or NP-14. As a component of alpha ring, proteasome subunit alpha type-6 contributes to the formation of heptameric alpha rings and substrate entrance gate ***(8).***

The eukaryotic proteasome recognized degradable proteins, including damaged proteins for protein quality control purpose or key regulatory protein components for dynamic biological processes. An essential function of a modified proteasome, the immunoproteasome, is the processing of class I MHC peptides ***(7).***

Clinical significance:

The proteasome and its subunits are of clinical significance for at least two reasons: (1) a compromised complex assembly or a dysfunctional proteasome can be associated with the underlying pathophysiology of specific diseases, and (2) they can be exploited as drug targets for therapeutic interventions ***(6).***

More recently, more effort has been made to consider the proteasome for the development of novel diagnostic markers and strategies. An improved and comprehensive understanding of the pathophysiology of the proteasome should lead to clinical applications in the future. The proteasomes form a pivotal component for the ubiquitin–proteasome system (UPS) and corresponding cellular Protein Quality Control (PQC) ***(7).***

Protein ubiquitination and subsequent proteolysis and degradation by the proteasome are important mechanisms in the regulation of the cell cycle, cell growth and differentiation, gene transcription, signal transduction and apoptosis. Subsequently, a compromised proteasome complex assembly and function lead to reduced proteolytic activities and the accumulation of damaged or misfolded protein species ***(9).***

Such protein accumulation may contribute to the pathogenesis and phenotypic characteristics in neurodegenerative diseases, cardiovascular diseases, inflammatory responses and autoimmune diseases, and systemic DNA damage responses leading to malignancies. Several experimental and clinical studies have indicated that aberrations and deregulations of the UPS contribute to the pathogenesis of several neurodegenerative and myodegenerative disorders, including Alzheimer's disease, Parkinson's disease and Pick's disease, Amyotrophic lateral sclerosis (ALS), Huntington's disease, Creutzfeldt–Jakob disease, and motor neuron diseases, polyglutamine (PolyQ) diseases, Muscular dystrophies and several rare forms of

neurodegenerative diseases associated with dementia ***(10, 11).***

As part of the ubiquitin–proteasome system (UPS), the proteasome maintains cardiac protein homeostasis and thus plays a significant role in cardiac ischemic injury, ventricular hypertrophy, and heart failure. Additionally, evidence is accumulating that the UPS plays an essential role in malignant transformation. UPS proteolysis plays a major role in responses of cancer cells to stimulatory signals that are critical for the development of cancer ***(8).***

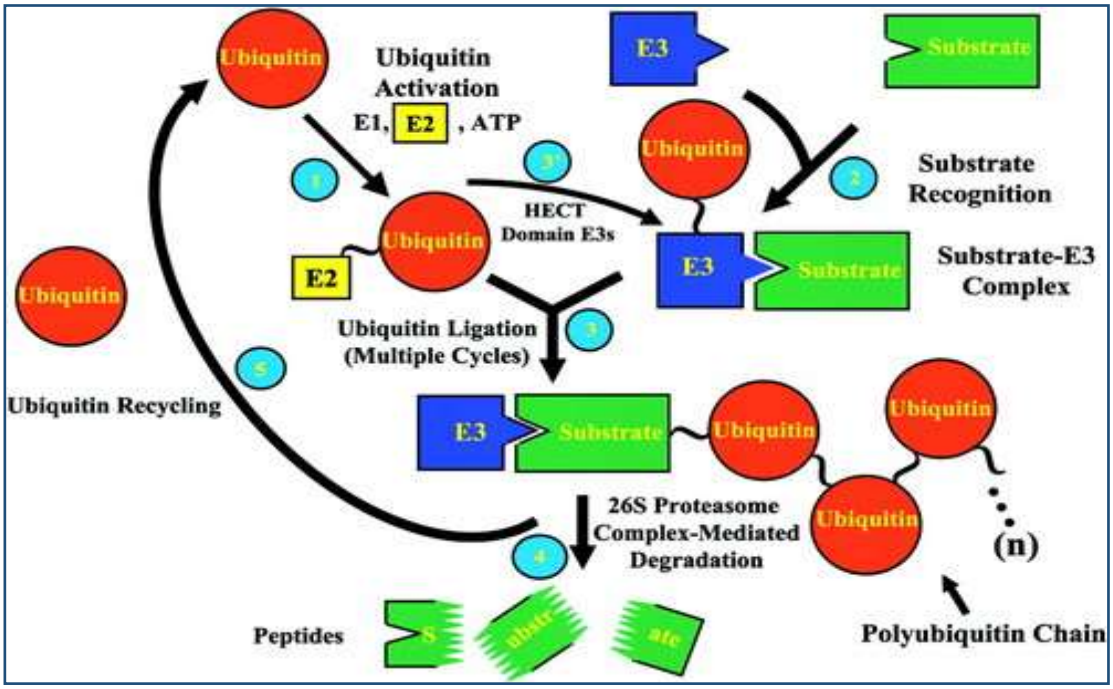

Figure (1): The ubiquitin–proteasome system ***(33).***

Accordingly, gene expression by degradation of transcription factors, such as p53, c-jun, c-Fos, NF-κB, c-Myc, HIF-1α, MATα2, STAT3, sterol-regulated element-binding proteins and androgen receptors are all controlled by the UPS and thus involved in the development of various malignancies***(7).***

Moreover, the UPS regulates the degradation of tumor suppressor gene products such as adenomatous polyposis coli (APC) in colorectal cancer, retinoblastoma (Rb) and von Hippel–Lindau tumor suppressor (VHL), as well as a number of proto-oncogenes (Raf, Myc, Myb, Rel, Src, Mos, ABL) ***(10).***

The UPS is also involved in the regulation of inflammatory responses. This activity is usually attributed to the role of proteasomes in the activation of NF-κB which further regulates the expression of pro inflammatory cytokines such as TNF-α, IL-β, IL-8, adhesion molecules (ICAM-1, VCAM-1, P-selectin) and prostaglandins and nitric oxide (NO) ***(11).***

Additionally, the UPS also plays a role in inflammatory responses as regulators of leukocyte proliferation, mainly through proteolysis of cyclines and the degradation of CDK inhibitors. Lastly, autoimmune disease patients with SLE, Sjögren syndrome and rheumatoid arthritis (RA) predominantly exhibit circulating proteasomes which can be applied as clinical biomarkers ***(6).***

PSMA6 has been implicated to be involved in the pathogenesis of ankylosing spondylitis (AS) and may therefore be a potential biomarker in this autoimmune disease. RPL17, MRPL22, PSMA4 in addition to PSMA6 are involved in the pathogenesis of AS and may be potential biomarkers for clinical application as well***(8).***

PSMA6 gene polymorphisms and CAD:

Coronary artery disease (CAD) is a manifestation of complex events including gene-gene and gene-environment interactions, partly triggered through inflammatory processes. Various pathways as well as candidate genes and loci identified thus far for susceptibility to CAD through case-control association studies or linkage analysis appear to be involved in the regulation of inflammatory mechanisms***(12).***

Several of these genes have also been associated with myocardial infarction (MI), an event which underlies such inflammatory processes and is a critical component in the pathogenesis of CAD. The ubiquitin-proteasome system is one such pathway that regulates the inflammatory processes and presumably plays an important role in mechanisms leading to MI ***(13).***

This proteasome is a large multicatalytic proteinase that functions as a central switch within the cell by selectively degrading a multitude of proteins, including metabolic enzymes, transcription factors and cell cycle regulators. Not surprisingly therefore, the proteasomal alpha subunit type 6 gene (PSMA6), a component of the ubiquitin-proteasome system has been associated with MI, type 2 diabetes mellitus (DM2), greater intima-media thickness, and possibly atherosclerosis ***(14).***

On the other hand, its role in conferring risk for cardiovascular-related events in general has been called into question recently by a number of studies pointing to lack of association with these disorders in some ethnic groups. The PSMA6 gene is located on chromosome 14q13.2, a region containing microsatellites that have also been implicated in various diseases, including DM2, Grave's disease and familial schizophrenia. These disorders have been associated partly with mutations in the KIAA0391 gene, which also resides in this chromosomal region. Among the familiar single nucleotide polymorphisms (SNPs) recently associated with various cardiovascular disorders in this region are the rs8008319, rs7157492, rs1048990, rs12878391 and rs4981283, which partly reside on either of the two genes ***(15).***

However, to date, it is still not known whether the KIAA0391 polymorphisms can influence the pathways to CAD or MI. Furthermore, while the PSMA6 gene codes for a characterized protein, the KIAA0391 gene is thought to encode a hypothetical protein (LOC9692) ***(12).***

The fact that the two genes form an evolutionarily conserved cluster on this locus, and the fact that both genes have been cited with respect to predisposing individuals to coronary vascular disorders points to a potential linkage of this chromosomal region with manifestation of CAD***(14).***

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