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Review

Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease

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ABSTRACT

Gamma-glutamyl transferase (GGT) is a ubiquitous cell surface enzyme that cleaves extracellular glutathione (G-SH) or other gamma-glutamyl compounds. GGT serves to increase the availability of amino acids, primarily cysteine, for intracellular G-SH synthesis and plays a crucial role in maintaining G-SH homeostasis and defense against oxidative stress in organisms. Measurement of circulating GGT activity is widely used for the diagnosis of liver and obstructive biliary diseases and as an indicator of alcohol consumption. Epidemiological studies suggest an association between elevated GGT activity level and a risk of incident coronary heart disease (CHD) or CHD-related mortality. Elevated GGT activity level is associated with a plethora of cardio-metabolic risk factors, including traditional cardiovascular risk factors, metabolic syndrome, systemic inflammation, oxidative stress burden and various comorbidities that incur a negative impact on patient risk profile and prognosis. Experimental studies and studies of human atherosclerotic plaques have revealed not only the presence of catalytically active GGT in atherosclerotic plaques, but also a correlation between GGT activity and indices of plaque instability, suggesting direct involvement in the pathophysiology of atherosclerosis and related clinical events via promotion of pro-oxidant reactions by the enzyme. However, it remains unknown whether GGT plays a direct role in the pathophysiology of atherosclerosis and CHD or is merely a correlate of coexisting cardiovascular risk factors. The exact molecular mechanisms of GGT participation in atherosclerosis or CHD and assessment of GGT-lowering therapies, as well as their impact on clinical outcomes, remain to be investigated in longitudinal studies.

1. Introduction

Gamma-glutamyl transferase (GGT; Enzyme Commission number [EC] 2.3.2.2.) is a ubiquitous enzyme that plays a crucial role in the metabolism of glutathione (G-SH) - the most important cellular antioxidant in humans. While the current nomenclature recommends the use of the name gamma-glutamyl transferase, some authors continue to use the older name gamma-glutamyl transpeptidase. Although cleavage of G-SH by extracts obtained from rat kidney was initially described > 80 years ago [1,2], subsequent studies by Hanes et al. [3] in sheep kidney extracts are credited with the characterization of the transpeptidase reaction and nomenclature of the enzyme. The measurement of circulating GGT activity is widely used for the diagnosis of liver and obstructive biliary diseases and as a marker of alcohol consumption. Aside from its diagnostic uses, GGT has attracted interest mainly for its association with diabetes and metabolic syndrome, cancer, atherosclerosis, and cardiovascular disease. The primary focus of this review is to summarize the current status of knowledge regarding the association of GGT with atherosclerosis and coronary heart disease (CHD) risk. The association between GGT and other cardiovascular diseases such as congestive heart failure, arterial hypertension, embolic disease, stroke, arrhythmias or sudden cardiac death and diabetes has been recently reviewed [4–7] and is therefore not addressed in the current review. After a brief description of the structure and metabolic role of GGT, the review will focus on epidemiological evidence linking GGT with CHD as well as the pathophysiological mechanisms of GGT involvement in atherosclerosis or CHD.

2. GGT structure and function

GGT is a cell surface N-terminal nucleophile hydrolase that cleaves extracellular G-SH and gamma-glutamyl compounds (glutathione-conjugates or other gamma-glutamyl substrates) from various sources. In fact, GGT has wide specificity and cleaves the gamma-glutamyl bond in all substrates in which the glutamate moiety is unfettered. GGT cleaves G-SH by transfer of the gamma-glutamyl moiety from G-SH to various

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acceptors, including amino acids, peptides or water releasing gamma-glutamyl products (or free glutamate) and dipeptide cysteinyl-glycine, the latter of which is further hydrolyzed by dipeptidase into free cysteine and glycine. Apart from reduced G-SH, the other known substrates of GGT are oxidized G-SH (G-S-S-G), glutathione-S-drug compounds, leukotriene C4, glutathione-S-nitric oxide and gamma-glutamyl-taurine [8].

Physiological functions of GGT are only partially known. The most important metabolic action of the enzyme is cleavage of G-SH. The high expression of the enzyme on the apical surface of tissues with transport function – tubular structures such as the proximal tubules of the nephron or the hepatocyte microtubular system – has led to the hypothesis that GGT is involved in the transport of amino acids across cell membranes [9]. However, this hypothesis is weakened by documentation of normal amino acid transport in humans and animals with GGT deficiency. According to current knowledge, GGT is important because it increases the availability of amino acids such as cysteine [10], a rate limiting substrate for intracellular G-SH synthesis (glutamate and glycine are readily supplied in the cell by products of glycolysis). The high activity of GGT on the surface of cells lining the proximal kidney tubules enables cleavage of G-SH present in glomerular filtrate, preventing its elimination from the organism, thereby conserving amino acids - particularly cysteine – for its intracellular synthesis [10]. High G-SH concentrations in the plasma and urine of patients with GGT deficiency [11] – a very rare autosomal recessive disease [12] – and GGT gene knockout mice [13] have been reported. In addition, GGT is involved in the metabolism of leukotrienes (namely conversion of leukotriene C_4 into leukotriene D_4), xenobiotics, neurotransmitters (conversion of gamma-glutamyl-taurine into taurine) and modulation of nitric oxide signaling [14–16]. In various pathological conditions, GGT may be mislocalized and may act on substrates in locations such as serum or interstitial fluids where involvement of the enzyme in pathological processes like ischemia-reperfusion injury, airway hyper-reactivity in asthma, drug nephrotoxicity (through conversion of drug-conjugates to nephrotoxins) or resistance to antitumor drugs has been suggested [10,17]. GGT expression in atherosclerotic plaques is covered in detail later in this review.

Mammalian GGT is a heterodimeric glycoprotein anchored to the outer surface of the plasma membranes of all cells through a small N-terminal transmembrane domain. Human GGT is synthetized as a single 569 amino acid residue polypeptide which is enzymatically inactive. The activation process consists of a post-translational autocleavage reaction catalysed by threonine 381 residue. Mature GGT has a molecular weight of 68 kDa and consists of 2 subunits: a large subunit weighing 46 kDa, responsible for enzyme anchorage on cellular membranes through a hydrophobic transmembrane domain, and a small subunit weighing 22 kDa that carries the catalytic center. The mature enzyme has 7 glucan moieties linked by N-glycosylation bonds localized on the external surface of the protein which are important for proper protein folding and activation proces, in addition to 4 cysteine residues, which stabilize the structure through formation of disulfide bonds [18–20]. The degree of glycosylation differs between molecules, with resulting variations in molecular weight, tissue specificity or disease-related molecular variants of the enzyme. Details of structural organization of GGT are described elsewhere [18,20,21]].

Human GGT is encoded by a multigene family consisting of 7 different genes or pseudogenes located on chromosome 22q11 [22]. The best characterized is the GGT 1 gene, which encodes a single polypeptide that undergoes post-translational changes to form a mature enzyme [12]. GGT 1 gene transcription is controlled by multiple tandemly positioned promoters [23,24]. These promoters and alternative splicing contribute to diversity of molecular forms and tissue specificity of GGT. The GGT 2 gene represents a duplication of GGT 1 gene with 97% nucleotide analogy between both genes and 94% amino acid analogy between their polypeptide products [10]. Some studies have shown that polypeptide products of the GGT 2 gene fail to auto-activate and anchor on plasma membranes, resulting in rapid degradation by cytoplasmic proteases [25]. The only other GGT gene that produces a polypeptide with enzymatic activity is GGT 5 gene (formerly known as γ-glutamyl leukotrienase due to its ability to cleave glutathione-S-conjugate leukotriene C4 to leukotriene D4). The GGT 5 gene polypeptide product has 40% amino acid analogy with the GGT 1 gene product but only 4% enzymatic activity [16,26]. A detailed analysis of genetic variants of the GGT gene family can be found in a review by Heisterkamp et al. [12].

Regulation of GGT expression is complex, poorly understood and outside the scope of this review. However, there is ample evidence that GGT gene expression in animals and humans is controlled by redox mechanisms and signal pathways activated in response to oxidative stress [17,27]. Alcohol is a known inducer of GGT gene expression, possibly through increased oxidative stress caused by its consumption [28]. GGT deficiency is an extremely rare condition, being described in fewer than 10 patients worldwide; however, so far, no mutations in GGT gene 1 have been reported [12]. All described patients with GGT deficiency have had glutathionuria. Study of three patients with GGT deficiency showed complete absence of leukotriene D4 synthesis in monocytes [29]. Experimental studies have shown an up 2500-fold increase in urine G-SH and a 5-fold reduction in plasma cysteine concentration in GGT knockout mice compared with their wild-type counterparts [13]. These data clearly illustrate the central role of GGT in G-SH and cysteine homeostasis.

In healthy humans, measurable GGT activity tends to be low (< 60 U/L). Although the source of circulating GGT is unclear and there is no evidence to support a correlation between circulating and tissue enzyme levels, it is thought to originate predominantly from the liver. The possibility that a portion of GGT may originate from atherosclerotic plaques has also been suggested [30]. Earlier investigations have identified both amphiphilic (either associated with plasma lipoproteins or in the form of multi-enzyme complexes) and hydrophilic forms of the enzyme [31]. It is now known that GGT circulates in multiple forms, differing mainly in the degree of glycosylation. It is estimated that 60–80% of serum GGT from patients with hepatobiliary diseases circulates bound to plasma lipoproteins. GGT activity shows a great degree of variability and is influenced by both genetic and environmental factors [30,32]. Pathological processes, particularly in organs with the highest activity of the enzyme, may lead to elevated GGT levels in the circulation. Circulating GGT levels are markedly increased in patients with liver disease. It has been suggested that the origin of circulating GGT in the presence of cholestatic disorders is of biliary rather than hepatic origin [33]. Franzini et al. [34] and more recently, Fornaciari et al. [35] have identified 4 GGT fractions with different molecular weights: big GGT (with a molecular weight of 2000 kDa), medium GGT (with a molecular weight of 1000 kDa), small GGT (with a molecular weight of 200 kDa) and free GGT fraction (with a molecular weight of 70 kDa). Big GGT consists of membrane microvesicles (microparticles or exosomes) and may be a precursor for smaller fractions (medium and small variants), whereas free GGT represents a free soluble form of the enzyme. It has been shown that at least part of GGT does not need a carrier such as plasma lipoproteins or albumin. It has been proposed that GGT fractions may differ in their diagnostic specificity and may, therefore, help to differentiate between various disease processes despite similar total values [35]. However, this requires further study.

3. Epidemiological evidence

Epidemiological studies suggest an association between elevated GGT activity and almost all aspects of cardiovascular disease. The most extensively investigated aspect is the association of GGT with atherosclerosis and the risk of developing CHD.

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