

Letter to the Editor

## Serum $\gamma$ -glutamyltransferase: linking together environmental pollution, redox equilibria and progression of atherosclerosis?

**Alfonso Pompella<sup>1,\*</sup>, Michele Emdin<sup>2</sup>, Maria Franzini<sup>3</sup> and Aldo Paolicchi<sup>1</sup>**

<sup>1</sup> Department of Experimental Pathology, University of Pisa Medical School, Pisa, Italy

<sup>2</sup> Fondazione Gabriele Monasterio CNR-Regione Toscana, Pisa, Italy

<sup>3</sup> Scuola Superiore S. Anna, Pisa, Italy

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Evidence has accumulated that serum activities of the enzyme  $\gamma$ -glutamyltransferase (GGT), routinely used as an index of hepatobiliary dysfunction and alcohol abuse, may be related to the progression and complications of atherosclerosis. Epidemiological investigations on large unselected populations, including the Framingham Heart Study, suggest that serum GGT has independent value in the prognostic assessment of atherosclerosis-related cardiovascular diseases (1, 2). Several observations support the involvement of GGT enzyme activity in the disease process itself. Active GGT is in fact accumulated in atherosclerotic lesions, and biochemical data indicate that such deposits likely originate from protein complexes circulating in blood (3).

In a recent paper published in CCLM (4), that also referred to earlier research from the same group (5), Lee and Jacobs provided further convincing evidence in support of a role for serum GGT activities on exposure of individuals to various persistent and short-lived environmental pollutants. GGT activity is primarily involved with the cellular metabolism of glutathione, a major antioxidant. The authors propose that exposure to xenobiotics may induce the enzyme in tissues as a defensive mechanism. Thus, increased serum GGT might hold value as a sensitive biomarker of exposure to environmental pollution. These observations are of interest, and might actually extend even further. Due to its established roles in the regulation of redox equilibria at the cellular and extracellular level, GGT activity can modulate a variety of (redox-sensitive) molecular targets, such as receptors and

transcription factors (6, 7). The function of these targets has been implicated at various levels in the progression of atherosclerosis. Several studies have shown that GGT can in fact exert pro-oxidant effects on redox-sensitive molecular targets in the extracellular space. This is due to interactions of its product, cysteinyl-glycine, with transition metal ions (6). Availability of the latter is a pre-requisite for considering these processes pathophysiologically relevant, and indeed, two lines of evidence strongly suggest that suitable conditions may occur in vivo. First, diseased tissues, such as atherosclerotic intima do contain significant concentrations of redox-active iron (8). Second, it has been shown that GGT itself can promote the reductive release of free iron from ferritin and transferrin (9). GGT-dependent generation of pro-oxidants, such as superoxide and hydrogen peroxide has been described repeatedly, with a variety of modulatory effects on targets, such as nuclear factor  $\kappa$ B (NF- $\kappa$ B), activator protein-1 (AP-1), iron uptake, protein kinase/phosphatase balance and protein S-glutathiolation (10). All of these targets have been implicated in cellular pathophysiology. Finally, a direct role for GGT in the metabolism of the vasoactive mediator NO can also be envisaged (11).

An unexpected sequence of events can thus be hypothesized, with all too obvious implications for the understanding of recent epidemiological trends in industrialized countries. Environmental pollutants induce GGT in the tissues of exposed subjects, in turn inducing a slight but significant increase in serum GGT activity. Thus, in addition to being a sensitive biomarker, GGT might also participate directly in the progression of pathological processes, thus establishing a connection between environmental pollution and progression of atherosclerosis. Recent characterization of at least four distinct macromolecular complexes formed by GGT in serum, and detected occasionally in atherosclerotic plaques (12), will probably help elucidate these intriguing aspects and allow us to establish the primary source(s) of circulating GGT.

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\*Corresponding author: Alfonso Pompella, MD, PhD, Department of Experimental Pathology, University of Pisa Medical School, Pisa, Italy  
Phone: +39050 2218 537, Fax: +39050 2218 557,  
E-mail: apompella@biomed.unipi.it

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