CORRELATION IS NOT CAUSATION: PROBABLE ROLE OF IMMUNIZATION WITH BACILLUS CALMETTE–GUERIN VACCINE IN ATHEROGENESIS

Peter I. Ghenev

Department of General and Clinical Pathology, Medical University, Varna, Bulgaria

When you light a candle, you also cast a shadow.

Ursula K. LeGuin, A Wizard of Earthsea,
Parnassus Press, 1968

In spite of the enormous volume of research in atherosclerosis, the etiological understanding of atherogenesis is still beyond compare. The Framingham Heart Study (started 1948) (1) identified the major risk factors and this concept has become an important part of the modern medical knowledge and has led to effective preventive strategies in clinical practice. But correlation is not causation. In an attempt to identify etiological factors and the immune mechanisms in atherogenesis, Georg Wick and his co-workers in a series of experiments obtained intriguing results, which confirm that atherosclerosis may be induced in rabbits by treatment with a variety of agents containing heat-shock protein of molecular weight 60 kD (HSP60) (2-7).

Following this data, we established positive immunohistochemical expression of HSP60 in all layers of human atherosclerotic arteries – endothelial cells in both the intima and *vasa vasorum*, also medial smooth muscle cells, and adventitial macrophages, fibroblasts and perivascular nerve bundles (8-11) (Fig.1).

Heat-shock proteins are highly conserved between species, and expressed during infection and inflammation. They

Figure 1. Immunohistochemical expression of HSP60 in the bottom part of a fibroatheroma and corresponding medial smooth muscle cells and adventitial nerve bundles in human coronary artery. Original magnification, x 100.

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Correspondence to Dr Peter I. Ghenev, Department of General and Clinical Pathology, Medical University, BG-9002 Varna, Bulgaria

Tel.: + 359 052 978604, E-mail: peterghenev@yahoo.com

are part of the antigenic content of infectious agents such as *Chlamydia pneumoniae*, *Helicobacter pylori*, *Mycobacterium tuberculosis* including bacillus Calmette-Guerin (BCG) strains (5,6). Infections may contribute to atherosclerosis through direct and/or cytokine-mediated actions on vascular cells (12). These latter authors reported that the aggregate burden (“infectious burden”) of these chronic infections, rather than the effects of a single organism, might contribute to atherosclerosis and its complications. Beyond the abovementioned infectious agents, a large number of infectious agents have been linked with the pathobiology of atherosclerosis; examples include *Porphyromonas gingivalis*, influenza A virus, herpes virus, hepatitis C virus, cytomegalovirus, human immunodeficiency virus (12-14) and fungi (15; also 16, 17 for fungalbionic hypothesis of gout and related diseases including atherosclerosis). These can mediate the T-cell sensitization required for the production of antibodies. Likewise, mycobacterial HSP appear to be among the best candidates for adjuvants in vaccine production (19).

Dancing round these data, we are tempted to suggest that immune products (antibodies following infection and/or immunization, including BCG vaccine) may be capable of inducing atherosclerotic lesions in humans, *via* HSP60 mechanism. We based this proposal on:

- (i) atherosclerosis is present even in children (six months after birth) (19),
- (ii) every newborn receives BCG and other approximately 15 compulsory applications of immune products during the first two years of life,
- (iii) all cell types involved in atherogenesis express constitutive and/or inducible HSP60 (8-11),
- (iv) HSP60 is a component of vaccines and adjuvants (4),
- (v) infections are the most common diseases of early childhood,
- (vi) HSP60 are existing in infectious agents (6,13,15),
- (vii) antibodies against HSP60 circulate in the blood of patients with atherosclerosis (5,20),
- (viii) experimental application of HSP60 triggers atherogenesis (3,21,22),
- (ix) BCG immunization induces atherosclerotic lesion in rabbits (22, 23)
- (x) Mycobacteria modulate proteins of host endothelial cells (24) and macrophages (25) to enter and persist within these cells

Altogether, we suggest that (i) in a manner similar to molecular Koch postulates, the atherogenic potential of HSP60/ BCG immunization should be thoroughly evaluated (see 26), and (ii) it is reasonable to try to invent immune products (vaccines) that will serve to prevent disease, without casting a shadow.

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