Chlamydia pneumoniae and lipoprotein(a): the right combination for atherosclerosis?

See page 639 for the article to which this Editorial refers

In their provocative report, Glader and collaborators[1] demonstrated the presence of comparable amounts of circulating immunocomplexes with C. pneumoniae antibodies in 78 subjects who later suffered an acute myocardial infarction and in 156 matched controls. No significant difference in the C. pneumoniae antibodies (IgG or IgA) titres (soluble or circulating immunocomplex-associated) was detected between the two categories of subjects. However, C. pneumoniae circulating immunocomplexes were found to contain more lipoprotein(a) in cases than in controls, with a higher risk of cardiovascular disease when circulating immunocomplexes had $>13\text{ mg}\text{. l}^{-1}$ of the lipoprotein(a). Based on the synergistic interaction between high lipoprotein(a) and C. pneumoniae antibodies in circulating immunocomplexes, the authors hypothesized that C. pneumoniae antibodies could form immunocomplexes with some lipoprotein(a) epitopes cross-reactive with C. pneumoniae antigen.

Although some serological determinations used throughout this study are far from being standardized and no direct proof that lipoprotein(a) in cases than in controls, with a higher risk of cardiovascular disease when circulating immunocomplexes had $>13\text{ mg}\text{. l}^{-1}$ of the lipoprotein(a). Based on the synergistic interaction between high lipoprotein(a) and C. pneumoniae antibodies in circulating immunocomplexes, the authors hypothesized that C. pneumoniae antibodies could form immunocomplexes with some lipoprotein(a) epitopes cross-reactive with C. pneumoniae antigen. Nonetheless, the overall data lends some implicit support to the possibility that at least one component of atherosclerosis relies upon an autoimmune disorder, and that some circulating immunocomplexes of particular combination are involved in the initial endothelial damage.

The autoimmune theory of the atherosclerotic process is not new, nor is the idea novel that circulating immunocomplexes may play a role in this and other cardiovascular diseases. The novelty of the study by Glader et al. rather resides in the suggestion that at least some of the C. pneumoniae antibodies in circulating immunocomplexes would indeed interact with (recognize?) lipoprotein(a), thus assigning to this risk factor for myocardial infarction the possible role of a C. pneumoniae antigen mimic.

Antigenic mimicry is a widespread phenomenon whereby microbial epitopes are naturally endowed with, or acquire in vivo, a degree of similarity to host molecules sufficient to elicit Ab and/or T cell-response against the host target. Together with antigenic variation, antigenic mimicry is largely exploited by pathogenic microorganisms to evade, dilute or divert host immunity. Historically, the heart has been one of the early examples of an organ that may be severely affected by an antigen-mimicry primed, severe disorder, such as rheumatic fever, the Gram-positive bacterium Streptococcus pyogenes group A providing the host-deceiving mimotope. Molecular mimicry and circulating immunocomplexes have also been considered in the pathogenesis of some common forms of autoimmune disorders such as vasculitis. While the aetiology of these vasculopathies remains largely undefined, several data point to the production and deposition of circulating immunocomplexes as the critical pathogenetic mechanism of the vessel injury. Thus, deposited IgG target tissue macrophage accumulation through release, mediated by cross-linking of Fc gamma receptors, of the monocyte colony stimulating factor[2]. Organ injuries by circulating immunocomplexes are often driven by a self-reinforcing loop of lipid mediators, cytokines, chemokines, proteolytic enzymes and nitric oxide, all factors believed to foster the inflammatory response underlying the pathogenesis of atherosclerosis.

Atherogenesis has been associated with high titres of antibodies against the bacterial (chlamydial or non-chlamydial) hsp60 and cross-reactive with the human ortholog protein[3]. Lipoprotein(a) would therefore constitute an additional antigenic target of a C. pneumoniae antigen-primed immune reaction. If this target were an apoprotein epitope, identifying the priming chlamydia antigen could be more easily achieved now that the C. pneumonia genome has been sequenced and shown to code for at least 1000 proteins[4]. Less conventional, and more intriguing, would be another theoretical possibility, i.e. the antigenic determination of the lipid moiety of the lipoprotein(a). There is a potent antigenic recognition system based on CD1 molecules committed to present lipid to T lymphocytes. The circulating immunocomplexes could favour the capture of lipoprotein(a)
by macrophages, enhance its processing, and qualify parts of the lipid moiety for CD1-presentation. Remarkably, all four CD1 proteins have been found to be expressed in atherosclerotic plaques but not in normal arterial specimens\(^6\).

Among the many possible consequences of the formation of \textit{C. pneumoniae} antibodies and circulating immunocomplexes, two appear of particular relevance to the debated issue of the microbial component of atherogenesis. First, the detection of circulating immunocomplexes actually underline the production of \textit{C. pneumoniae} antigen and its shedding from the infected areas. They are an indicator of an infectious presence even when the infecting agent itself is not found, as often happens with \textit{C. pneumoniae} in atherosclerotic plaques. The second, and pathogenically more fruitful, feature is the natural tendency of circulating immunocomplexes to attract and bind complement fractions, initiating the inflammatory cascade. It would have been interesting to examine to what extent lipoprotein(a), \textit{C. pneumoniae} antibodies and circulating immunocomplexes were complement-positive and whether low complement levels accompanied the higher risk for myocardial infarction in subjects with high lipoprotein(a), \textit{C. pneumoniae} antibodies and circulating immunocomplexes.

The report by Glader \textit{et al}\(^1\) also deserves attention for its negative findings. In agreement with Ridker \textit{et al}\(^2\), seropositivity to \textit{C. pneumoniae} was not associated with a higher risk of myocardial infarction. Here the strong limitations of the current serological approaches to \textit{C. pneumoniae} infection should be recognized. Discrimination among the various stages (acute, chronic, recurrent) of this infection remains a critical, yet elusive, aspect of the relationship between \textit{C. pneumoniae} and its host. Among the plethora of antibodies and cellular responses that are elicited during such complex infection patterns, only a very few might be relevant to this relationship. Thus, the simple detection of unspecified ‘anti-chlamydial’ antibodies could be of no help in understanding the role of \textit{C. pneumoniae} in the pathogenesis of atherosclerosis. Importantly, the recent findings with apo E-deficient mice — which spontaneously develop atheromatous plaques without being fed hyperlipidaemic diets — showing accelerated atheromatous lesions upon infection by \textit{C. pneumoniae}\(^7\) and the limited, but significant, clinical benefit of roxithromycin treatment in patients with coronary syndromes\(^8\), indicate that the chlamydial involvement in cardiovascular disease no longer relies solely upon uncertain seroepidemiological or pathological associations.

Clearly, the microbial aetiology of atherosclerosis remains a mystery. Nonetheless, \textit{C. pneumoniae} would be highly revealing.

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(These comments partly reflect critical and passionate discussions on microbes and cardiovascular diseases with Attilio Maseri, MD from the Institute of Cardiology, Catholic University of Rome).

\section*{References}

\begin{itemize}
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