How Macrophages are Converted to Foam Cells

We agree with Nicolaou et al. in their view about the conversion of macrophages to foam cells[1]. Foam cell formation cannot be caused by the uptake of oxidized low-density lipoprotein (LDL) via the scavenger receptor because, as they point out, neither inhibition of LDL oxidation nor inhibition of scavenger receptor uptake are able to prevent foam cell formation by bacteria. However, we have a different interpretation of the early accumulation of lipids in macrophages exposed to bacteria, in contrast to their suggestion that “increased lipid uptake and reduced cholesterol efflux” are responsible[1].

It is not widely known that lipoproteins are able to bind and inactivate microbes and their toxins effectively by complex formation, as documented by more than a dozen research groups[2, 3]. For instance, complex formation between all lipoprotein subclasses and both bacteria and viruses has been demonstrated by electron microscopy, enzyme-linked immunosorbent assay, and column chromatography[2]. It has also been demonstrated that human LDL inactivates up to 90% of Staphylococcus aureus alpha-toxin and even a larger fraction of bacterial lipopolysaccharide (LPS)[3].

The protective effect of lipoproteins has also been demonstrated in animal experiments. For instance, compared with normal rats, hypocholesterolemic rats injected with LPS have markedly increased mortality, which can be ameliorated by injecting purified human LDL[1]. In addition, compared with normal mice, hypercholesterolemic mice challenged with LPS or live bacteria have an eightfold increase of LD[2].

In the case of major microbial invasion, the complexes with LDL may aggregate, particularly in the presence of hyperhomocysteinemia, because of complex formation and aggregation through homocysteinylated LDL. Homocysteine thiolactone reacts to form a peptide bond with the free amino groups of apoB protein of LDL, causing aggregation and spontaneous precipitation, and homocysteinylated LDL is phagocytosed by cultured macrophages to produce foam cells[4]. Autoantibodies against oxidized and homocysteinylated LDL, aggregated LPS, lipoteichoic acid, and complexes between sphingolipids and bacterial toxins may further increase the size of the accumulated lipoprotein complexes[5].

A more likely explanation of the early accumulation of lipids in macrophages exposed to bacteria is therefore phagocytosis of lipoprotein complexes with pathogens. Accordingly, in vitro experiments have shown that LPS from Chlamydia pneumoniae and also from several periodontal pathogens is able to convert macrophages to foam cells in the presence of human LDL[5, 6]. The finding by Nicolaou et al.[1] that lipid body formation within macrophages in response to LPS is enhanced by adding LDL to the culture medium further supports this interpretation. Phagocytosis of pathogens bound to lipoproteins also explains why LDL becomes oxidized, since macrophages inactivate phagocytosed pathogens by producing oxygen radical species, promoting LDL oxidation[7].

As suggested by Nicolaou et al.[1], conversion of macrophages to foam cells by bacteria indicates that these pathogens contribute to the development of atherosclerosis. We have suggested that sufficiently large complexes between microorganisms and lipoproteins may occlude the vasa vasorum because of high extracapillary pressure and because of endothelial dysfunction induced by hyperhomocysteinemia[7], producing ischemia of the arterial wall and vulnerable plaques of the arteries[2, 8].

Both authors declare that we have no conflict of interest.

References
3) Han R: Plasma lipoproteins are important components of the immune system. Microbiol Immunol, 2010; 54: 246-253
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