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REVIEW

Potential to inhibit growth of atherosclerotic plaque development through modulation of macrophage neopterin/7,8-dihydroneopterin synthesis

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The rise in plasma neopterin observed with increasing severity of vascular disease is a strong indicator of the inflammatory nature of atherosclerosis. Plasma neopterin originates as the oxidation product of 7,8-dihydroneopterin secreted by γ-interferon stimulated macrophages within atherosclerotic plaques. Neopterin is increasingly being used as a marker of inflammation during clinical management of patients with a range of disorders including atherosclerosis. Yet the role of 7,8-dihydroneopterin/neopterin synthesis during the inflammatory process and plaque formation remains poorly understood and controversial. This is partially due to the unresolved role oxidants play in atherosclerosis and the opposing roles of 7,8-dihydroneopterin/neopterin. Neopterin can act as pro-oxidant, enhancing oxidant damage and triggering apoptosis in a number of different cell types. Neopterin appears to have some cellular signalling properties as well as being able to chelate and enhance the reactivity of transition metal ions during Fenton reactions. In contrast, 7,8-dihydroneopterin is also a radical scavenger, reacting with and neutralizing a range of reactive oxygen species including hypochlorite, nitric oxide and peroxyl radicals, thus protecting lipoproteins and various cell types including macrophages. This has led to the suggestion that 7,8-dihydroneopterin is synthesized to protect macrophages from the oxidants released during inflammation. The oxidant/antioxidant activity observed *in vitro* appears to be determined both by the relative concentration of these compounds and the specific chemistry of the *in vitro* system under study. How these activities might influence or modulate the development of atherosclerotic plaque *in vivo* will be explored in this review.
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Abbreviations: AAPH, 2,2′-azobis(amidinopropane) dihydrochloride; GM-CSF, colony-stimulation factor; GTP, guanosine 5′-triphosphate; 3HAA, 3-hydroxyanthranilic acid; HMDM, human monocyte-derived macrophages; HPLC, high-performance liquid chromatography; IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; TNF-α, tumour necrosis factor-α