

A12 Protein oxidation, proteolysis and atherogenesis

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Protein oxidation creates reactive intermediates, both free radicals and long-lived reductants (e.g. DOPA) and oxidants (e.g. hydroperoxides) on polypeptides. Whether altered proteins accumulate *in vivo* depends on their relative rates of formation and removal by degradation. This then determines the likelihood that the reactive moieties damage other molecules. In cataractogenesis and atherogenesis, proteins accumulate a variety of oxidised amino acids. The spectra of products suggest the involvement of Fenton/hydroxyl chemistry, without or with a contribution from hypochlorite reactions, respectively. We have found that accumulation of some oxidised protein-bound amino acids in atherogenesis is detectable prior to that of sterol and oxidised lipid. It is not yet known whether this accumulation is perturbed when lipid oxidation is inhibited experimentally.

In a new approach allowing incorporation of oxidised amino acids by protein synthesis, we have demonstrated that increasing substitution of native amino acids in cellular proteins by oxidised amino acids leads to a biphasic response. Modest levels of substitution accelerate degradation, while more extensive incorporation retards. Lysosomes and proteasomes participate in the degradation of these substrates, and substrate molecules may pass from proteasomes to lysosomes. This approach may allow elucidation of the relative importance of *in situ* protein oxidation vs biosynthetic incorporation of oxidized amino acids.