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Protein oxidation is a frequent event as a result of the high abundance of proteins in biological samples and the multiple processes that generate oxidants. The reactions that occur are complex and poorly understood, but can generate major structural and functional changes on proteins. Current data indicate that pathophysiological processes and multiple human diseases are associated with the accumulation of damaged proteins. In this study we investigated the mechanisms and consequences of exposure of the key metabolic enzyme glucose-6-phosphate dehydrogenase (G6PDH) to peroxyl radicals (ROO•) and singlet oxygen (1O2), with particular emphasis on the role of Trp and Tyr residues in protein cross-linking and fragmentation. Cross-links and high molecular mass aggregates were detected by SDS-PAGE and Western blotting using specific antibodies. Amino acid analysis has provided evidence for Trp and Tyr consumption and formation of oxygenated products (diols, peroxides, N-formylkynurenine, kynurenine) from Trp, and di-tyrosine (from Tyr). Mass spectrometric data obtained after trypsin-digestion in the presence of H216O and H218O, has allowed the mapping of specific cross-linked residues and their locations. These data indicate that specific Tyr-Trp and di-Tyr cross-links are formed from residues that are proximal and surface-accessible, and that the extent of Trp oxidation varies markedly between sites. Limited modification at other residues is also detected. These data indicate that Trp and Tyr residues are readily modified by ROO• and 1O2 with this giving products that impact significantly on protein structure and function. The formation of such cross-links may help rationalize the accumulation of damaged proteins in vivo.
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