

Tyrosine nitration affects thymidylate synthase properties.

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Highly purified preparations of thymidylate synthase, isolated from calf thymus, and L1210 parental and FdUrd-resistant cells, were found to be nitrated, as indicated by a specific reaction with anti-nitro-tyrosine antibodies, suggesting this modification to appear endogenously in normal and tumor tissues. Each human, mouse and *Ceanorhabditis elegans* recombinant TS preparation, incubated in vitro in the presence of NaHCO_3 , NaNO_2 and H_2O_2 at pH 7.5, underwent tyrosine nitration, leading to a $V_{\text{max}}(\text{app})$ 2-fold lower following nitration of 1 (with human or *C. elegans* TS) or 2 (with mouse TS) tyrosine residues per monomer. Enzyme interactions with dUMP, meTHF or 5-fluoro-dUMP were not distinctly influenced. Nitration under the same conditions of model tripeptides of a general formula $\text{H}_2\text{N-Gly-X-Gly-COOH}$ ($\text{X} = \text{Phe, Tyr, Trp, Lys, Arg, His, Ser, Thr, Cys, Gly}$), monitored by NMR spectroscopy, showed formation of nitro-species only for H-Gly-Tyr-Gly-OH and H-Gly-Phe-Gly-OH peptides, the chemical shifts for nitrated H-Gly-Tyr-Gly-OH peptide being in a very good agreement with the strongest peak found in $(^{15}\text{N})\text{-(}^1\text{H)} \text{ HMBC}$ spectrum of nitrated protein. MS analysis of nitrated human and *C. elegans* proteins revealed several thymidylate synthase-derived peptides containing nitro-tyrosine (at positions 33, 65, 135, 213, 230, 258 and 301 in the human enzyme) and oxidized cysteine (human protein Cys(210), with catalytically critical Cys(195) remaining apparently unmodified) residues.

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