# Mitochondrial dysfunction in response to cytochrome c phosphorylation at position 48

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The regulation of mitochondrial activity allows cells to adapt to changing conditions and respond to oxidative stress. Mitochondrial dysfunction can lead to hypoxia-related pathologies. The phosphorylation of tyrosine-48 (Tyr-48) in cytochrome *c* is related to a wide range of human diseases due to the pleiotropic role of the latter in cell life and death. However, its analysis is difficult due to the low yield of purified phosphorylated cytochrome *c* obtained from cell extracts, as well as the lack of knowledge about the specific kinases involved. Therefore, the course taken involved the analysis of Tyr-48 in a phosphomimetic mutant, Y48*p*CMF C*c*, bearing a close resemblance to cytochrome *c*, and developed through the optimization of non-canonical amino acid *p*-carboxymethyl-L-phenylalanine (*p*CMF) synthesis[1].

It is noteworthy that the Y48*p*CMF mutation significantly destabilizes the Fe-Met bond in the ferric form of cytochrome *c*, thereby lowering the p$K_a$ value for the alkaline transition of the heme-protein to physiological pH. The NMR structure of the resulting mutant reveals significant conformational shifts and enhanced dynamics around *p*CMF that could explain changes observed in its functionality. The phosphomimetic mutation impairs cytochrome *c* diffusion between respiratory complexes, enhances hemeprotein peroxidase activity and hinders caspase-dependent apoptosis. Our findings provide a framework to further investigate the modulation of mitochondrial activity by phosphorylated cytochrome *c* and to develop novel therapeutic approaches based on its pro-survival effects[2].

References:

[1]Guerra-Castellano A, *et al.* *Chem. Eur. J.* (2015) 21: 15004-15012.

[2]Guerra-Castellano A, *et al. Proc. Natl. Acad. Sci. U.S.APlus*(2017) doi: 10.1073/pnas.1618008114.