**Abstract**

Proline oxidase (POX) is a redox enzyme localized in the mitochondrial inner membrane. We and others have shown that POX is a *p53*-induced gene that can mediate apoptosis through generation of reactive oxygen species (ROS). The peroxisome proliferator-activated receptor gamma (PPARgamma) ligand troglitazone was found to activate the POX promoter in colon cancer cells. PPARgamma ligands have been reported to induce apoptosis in a variety of cancer cells. In HCT116 cells expressing a wild-type PPARgamma, troglitazone enhanced the binding of PPARgamma to PPAR-responsive element in the POX promoter and increased endogenous POX expression. Blocking of PPARgamma activation either by antagonist GW9662 or deletion of PPAR-responsive element in the POX promoter only partially decreased the POX promoter activation in response to troglitazone, indicating also the involvement of PPARgamma-independent mechanisms. Furthermore, troglitazone also induced p53 protein expression in HCT116 cells, which may be the possible mechanism for PPARgamma-independent POX activation, since POX has been shown to be a downstream mediator in p53-induced apoptosis. In HCT15 cells, with both mutant p53 and mutant PPARgamma, there was no effect of troglitazone on POX activation, whereas in HT29 cells, with a mutant p53 and wild type PPARgamma, increased activation was observed by ligand stimulation, indicating that both PPARgamma-dependent and -independent mechanisms are involved in the troglitazone-induced POX expression. A time- and dose-dependent increase in POX catalytic activity was observed in HCT116 cells treated with troglitazone with a concomitant increase in the production of intracellular ROS. Our results suggest that the induction of apoptosis by troglitazone may, at least in part, be mediated by targeting POX gene expression for generation of ROS by POX both by PPARgamma-dependent and -independent mechanisms.

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**The metabolism of proline, a stress substrate, modulates carcinogenic pathways.**


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**Abstract**

The resurgence of interest in tumor metabolism has led investigators to emphasize the metabolism of proline as a "stress substrate" and to suggest this pathway as a potential anti-tumor target. Proline oxidase, a.k.a. proline dehydrogenase (POX/PRODH), catalyzes the first step in proline degradation and uses proline to generate ATP for survival or reactive oxygen species for programmed cell death. POX/PRODH is induced by p53 under genotoxic stress and initiates apoptosis by both mitochondrial and death receptor pathways. Furthermore, POX/PRODH is induced by PPARgamma and its pharmacologic ligands, the thiazolidinediones. The anti-tumor effects of PPARgamma may be critically dependent on POX/PRODH. In addition, it is upregulated by nutrient stress through the mTOR pathway to maintain ATP levels. We propose that proline is made available as a stress substrate by the degradation of collagen in the microenvironmental extracellular matrix by matrix metalloproteinases. In a manner analogous to autophagy, this proline-dependent process for bioenergetics from collagen in extracellular matrix can be designated "ecophagy".

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**The metabolism of proline as microenvironmental stress substrate.**


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**Abstract**

Proline, a unique proteogenic secondary amino acid, has its own metabolic system with special features. Recent findings defining the regulation of this system led us to propose that proline is a stress substrate in the microenvironment of inflammation and tumorigenesis. The criteria for proline as a stress substrate are: 1) the enzymes utilizing proline respond to stress signaling; 2) there is a large, mobilizable pool of proline; and 3) the metabolism of proline serves special stress functions. Studies show that the proline-utilizing enzyme, proline oxidase (POX)/proline dehydrogenase (PRODH), responds to genotoxic, inflammatory, and nutrient stress. Proline as substrate is stored as collagen in extracellular matrix, connective tissue, and bone and it is rapidly released from this reservoir by the sequential action of matrix metalloproteinases, peptidases, and prolylase. Special functions include the use of proline by POX/PRODH to generate superoxide radicals that initiate apoptosis by intrinsic and extrinsic pathways. Under conditions of nutrient stress, proline is an energy source. It provides carbons for the tricarboxylic acid cycle and also participates in the proline cycle. The metabolism of proline, a stress substrate, modulates carcinogenic pathways.

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