The Association of Peroxiredoxin 4 with the Initiation and Progression of Hepatocellular Carcinoma

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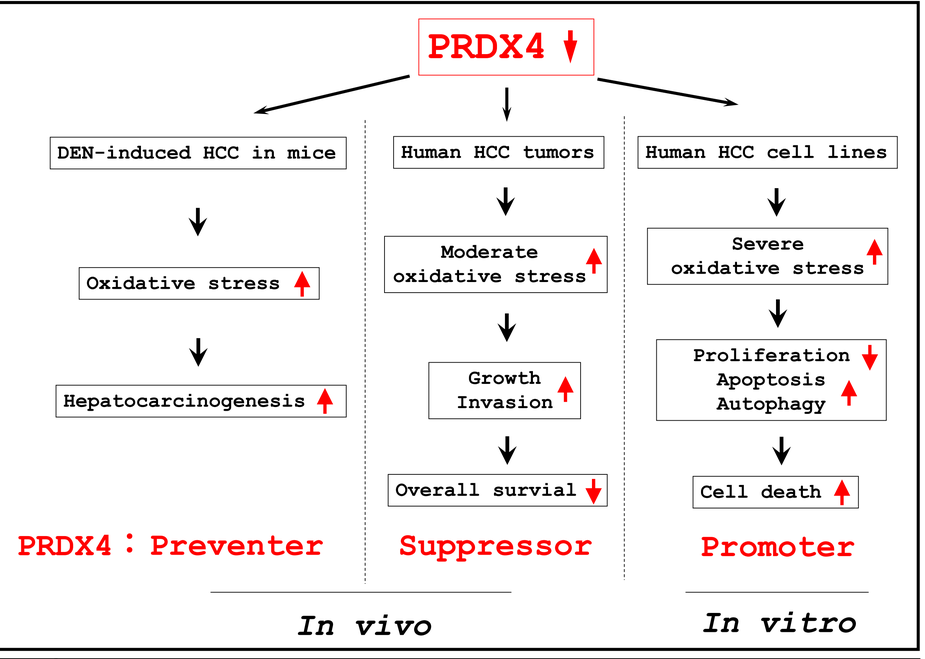
Abstract

Back: Peroxiredoxin 4 (PRDX4) is a member of the peroxiredoxin family of antioxidant enzymes. Previously, we reported that PRDX4 can restrain the initiation and progression of non-alcoholic steatohepatitis by reducing local and systemic reactive oxygen species (ROS) levels. Oxidative stress is recognized as a key factor in hepatocarcinogenesis, and a high ROS level has also been found in hepatocellular carcinoma (HCC).

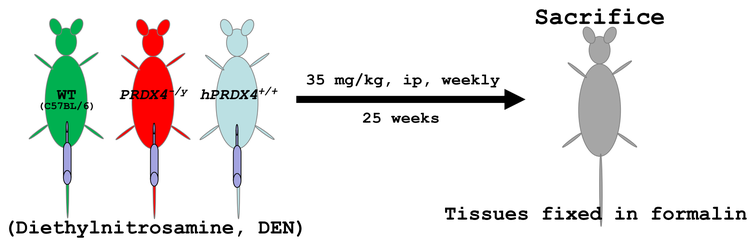
Results: In this study, for hepatocarcinogenesis, wild-type (WT), PRDX4 knockout (*PRDX4*$^{-/y}$) and human PRDX4 transgenic (*hPRDX4*$^{+/+}$) mice were given a weekly intraperitoneal injection of diethylnitrosamine (DEN) for 25 weeks. The HCC incidence was higher in *PRDX4*$^{-/y}$ mice than in WT or *hPRDX4*$^{+/+}$ mice. Intrahepatic and circulating oxidative stress and inflammatory cell infiltration in the liver were obviously decreased in *hPRDX4*$^{+/+}$ mice, compared to WT mice. Furthermore, in our cohort study, human HCC specimens with low expression of PRDX4 had higher ROS levels and a highly malignant phenotype, which was associated with a reduced overall survival, compared to those with high PRDX4 expression. However, in human HCC cell lines, PRDX4 knockdown led to a rapidly increased intracellular ROS level and suppressed cell proliferation, inducing cell death.

Conclusion: Our results clearly indicate that PRDX4 has an inhibitory effect in the initiation of HCC but a dual (inhibitory or promoting) role in the progression of HCC, suggesting the potential utility of PRDX4 activators or inhibitors as therapy for different stages and phenotypes of HCC.

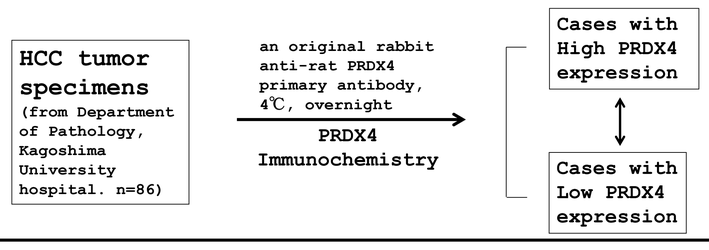


Aim: Here, our aim is to investigate roles of PRDX4 in the initiation and progression of HCC.

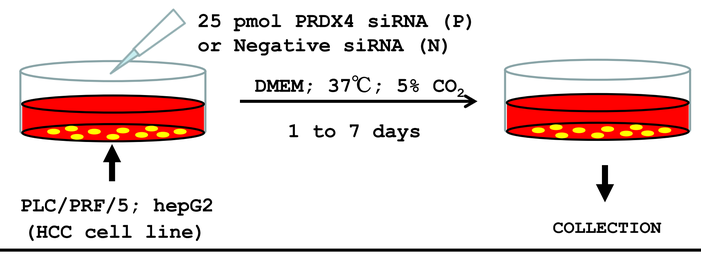
Methods ①



Methods ②



Methods ③



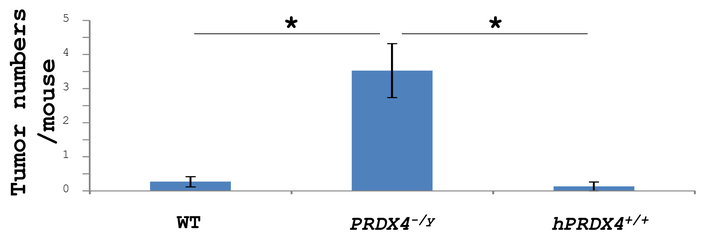
Results ①

HCC incidence

	With tumor Number (%)	Tumor-free Number (%)	*P*
WT	3(20)	12(80)	
PRDX4$^{-/y}$	12(80)	3(20)	0.0028
hPRDX4$^{+/+}$	1(7)	14(93)	0.598

A significant increase in the HCC incidence rate was observed in *PRDX4*$^{-/y}$ mice.

Tumor Numbers

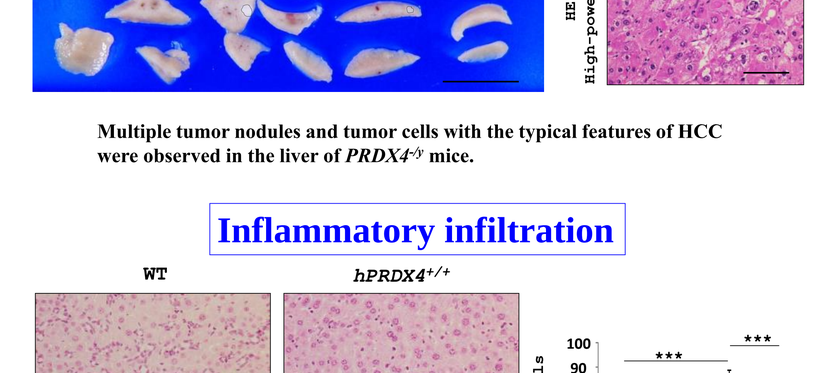


The number of tumors was also more in *PRDX4*$^{-/y}$ mice.

Multiple HCC

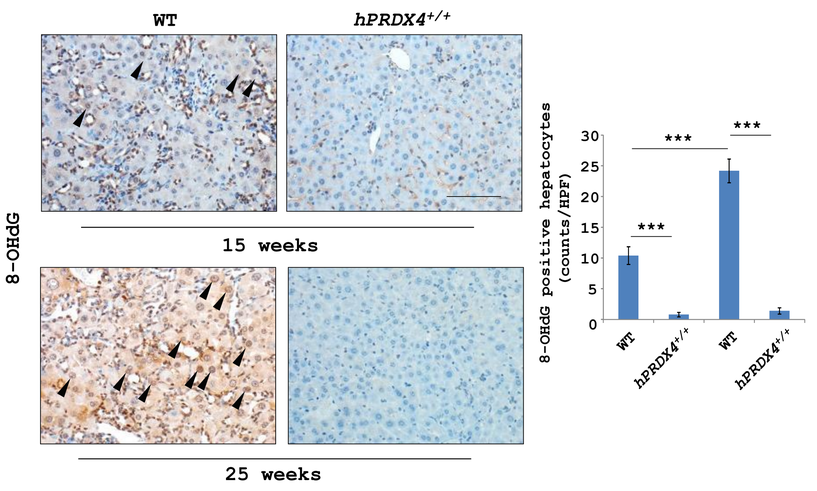
Multiple tumor nodules and tumor cells with the typical features of HCC were observed in the liver of *PRDX4*$^{-/y}$ mice.

Inflammatory infiltration



The number of infiltrated neutrophils was less in the liver of *hPRDX4*$^{+/+}$ mice

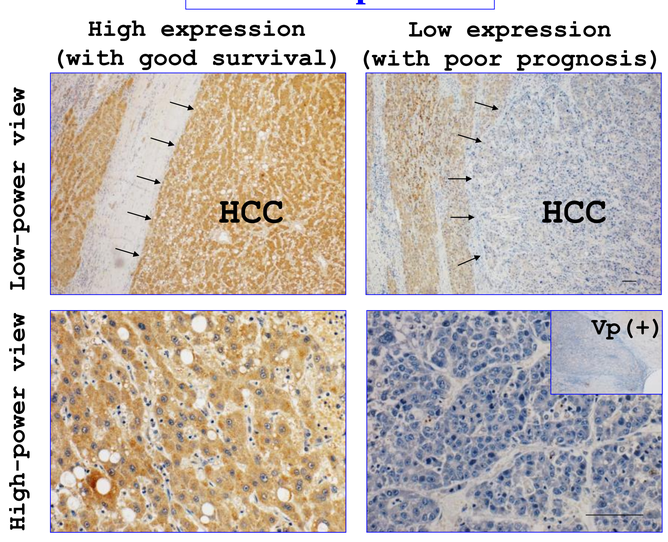
Oxidative Stress



The number of 8-OHdG positive hepatocytes in the liver was significantly lower in *hPRDX4*$^{+/+}$ mice.

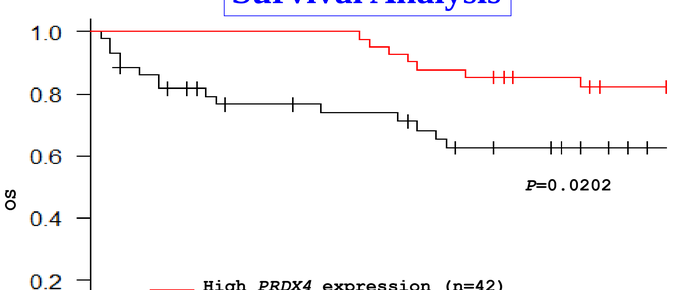
Results ②

PRDX4 expression



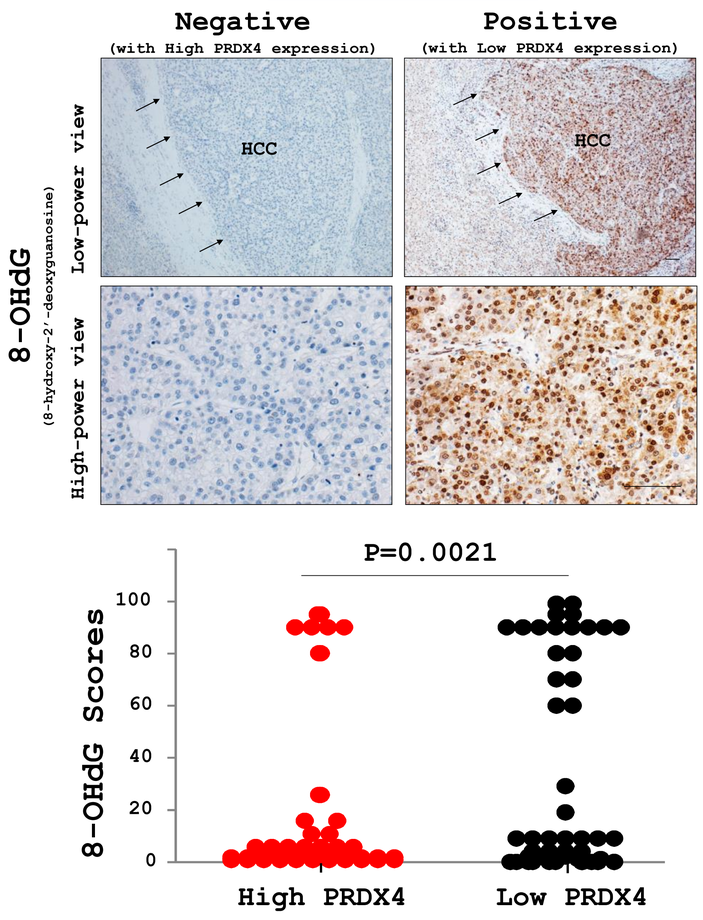
Based on the IHC staining scores cases were divided into two groups—low- and high-PRDX4 groups

Survival Analysis



The low-PRDX4 group had a significantly reduced overall survival.

Oxidative Stress



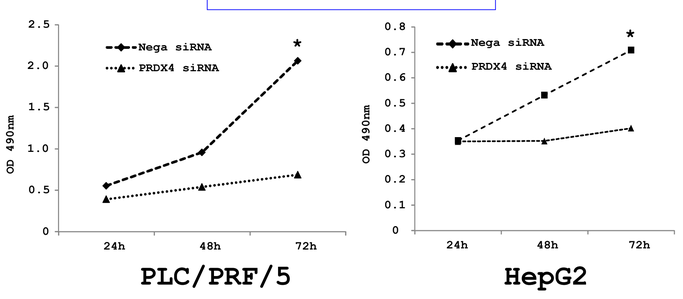
The 8-OHdG level in tumor tissues was higher in the low-PRDX4 group.

Results ③

PRDX4 expression

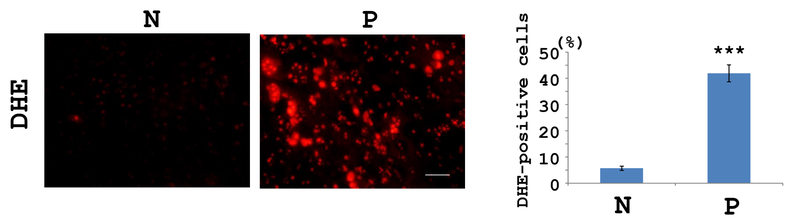
PRDX4 expression was gradually reduced in HCC cells after transfection with PRDX4 siRNA.

Cell Proliferation



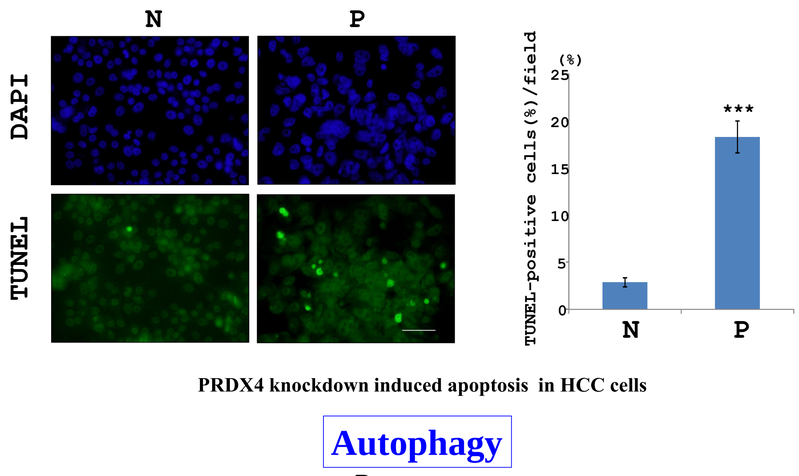
The proliferation of HCC cells was significantly suppressed after PRDX4 expression was down-regulated

Oxidative Stress



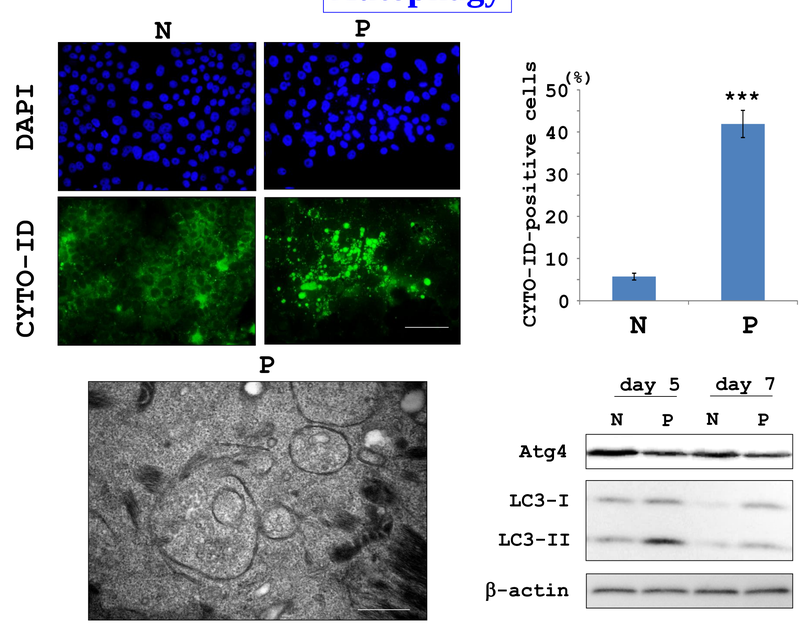
The number of dihydroethidium (DHE)-positive cells was much greater among HCC cells transfected with PRDX4 siRNAs

Apoptosis



PRDX4 knockdown induced apoptosis in HCC cells

Autophagy



PRDX4 knockdown increased autophagic activity of HCC cells

Discussion

1. PRDX4 may have an efficient effect in inhibiting ROS/inflammation-related hepatocarcinogenesis.
2. In human HCC tumors with low PRDX4 expression, a possible explanation is that an adaptable redox homeostasis may exist and enable cancer cells to tolerate a higher level of ROS that contribute for malignant progression.
3. At present, we cannot delineate that an increase in autophagy accelerated cell death or was only a protect response to oxidative stress.

Conclusion

our present data indicate that PRDX4 can restrain DEN-induced hepatocarcinogenesis in mice by reducing intrahepatic and circulating oxidative stress, as well as the inflammation response in the liver. However, due to the contradictory property of ROS, PRDX4 plays a dual role in the progression of HCC, promoting the survival of cancer cells but inhibiting the rapid growth and invasion of tumor.