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 carcinomas (HCC).

Results: In this study, for hepatocarcinogenesis, wild-type (WT), PRDX4 knockout (PRDX4−/−) 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−/− 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.

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 rate homeostasis may exist and enable cancer cells to tolerate a higher level of ROS that contributes to 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.

Discussion

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.

Methods

1. Methods

2. Results

3. Conclusion

Figure 1: PRDX4 expression in the initiation and progression of HCC.

Figure 2: PRDX4 expression in the initiation and progression of HCC.

Figure 3: PRDX4 expression in the initiation and progression of HCC.

Figure 4: PRDX4 expression in the initiation and progression of HCC.

Figure 5: PRDX4 expression in the initiation and progression of HCC.