Sorafenib induces apoptosis in hepatocellular carcinoma cells by inhibiting c-Myc and prothymosin-alpha

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The anti-apoptotic protein prothymosin alpha (PTMA) is overexpressed in various cancers, including hepatocellular carcinoma (HCC). Earlier studies have shown that PTMA blocks apoptosis in cancer cells by inhibiting caspase-9 activation and apoptosome formation. Our recent study shows that silencing of PTMA potentiates the mitochondria-dependent apoptosis pathway in sorafenib-treated HCC cells, leading to Bax translocation, pBad dephosphorylation, and cytochrome c release. Our findings also indicate that the pERK/c-Myc/Max/PTMA axis represents a newly identified target of sorafenib in chemotherapy against HCC.

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positions in vitro \[20\]. This observation may partly explain tolerance to ischemic injury \[21, \, 22\] which involves repression of necrosis by selective activation of the TRIF pathway (for TLR4/MD-2/Toll/IL-1 receptor-domain-containing adaptor inducing IFN-β), instead of the MAL pathway (pro-inflammatory myeloid differentiation protein -88 (MyD88)/MyD88-adaptor-like protein).

In cancer cells, PTMA plays an important role in inhibiting apoptosis \[18, \, 23\], and is highly expressed in various cancers, including HCC \[24-28\]. Early studies showed that PTMA may represent a cancer biomarker as a positive correlation has been observed between high PTMA gene expression and poor prognosis in human HCC patients \[29, \, 30\].

PTMA prevents apoptosis in cancer cells by interacting with Apaf-1 and blocking apoptosome formation, suggesting that PTMA may represent a potential target for cancer therapy \[23, \, 31\]. In our study, we found that PTMA inhibits Bax expression and translocation to mitochondria, pBad dephosphorylation, and cytochrome c release into the cytosol, therefore inhibiting the mitochondrial-dependent apoptosis pathway in sorafenib-treated HCC cells \[32\].

Although PTMA is known to be an anti-apoptotic protein, its detailed mechanism of action remained unclear. Earlier studies showed that c-Myc regulates PTMA expression in various cancer cells. c-Myc binds to the proximal promoter and the first intron of the PTMA gene to upregulate PTMA transcription; on the other hand, one study showed that c-Myc did not regulate PTMA transcription \[33-36\]. In our study, we found that c-Myc/Max interacts with both the proximal promoter and first intron of the PTMA gene in HCC cells, but only the proximal promoter could be regulated through ERK kinase and sorafenib \[32\]. The different results reported in these studies suggest that the effects of PTMA may be dependent on cell type. We also found that sorafenib enhances the degradation rate of PTMA mRNA, but produces no effect on PTMA protein degradation. This observation may be due to down-regulation of the human antigen R (HuR), a known translation regulator of PTMA, in response to sorafenib \[32, \, 37\].

Together, our observations indicate that PTMA activity is highly relevant to cancer progression and drug resistance in HCC cells. Based on the observation that sorafenib induces mitochondria-dependent apoptosis via inhibition of the pERK/c-Myc/Max/PTMA pathway in HCC cells, we conclude that PTMA represents a newly identified target of sorafenib therapy against HCC.

Conflicting interests

The authors declare no conflict of interest.

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Abbreviations

ERK: extracellular regulated protein kinase; HCC:
hepatocellular carcinoma; HURP: hepatoma upregulated protein; JNK: c-Jun N-terminal kinases; PTMA: prothymosin alpha.

References


