Targeting mitochondrial protein NIX mediates resistance to sorafenib in hepatocellular carcinoma through autophagy

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Aims: Although sorafenib benefits patients with advanced hepatocellular carcinoma (HCC), its clinical efficacy is restricted by drug resistance. The pathogenesis of multisystem tumors is closely related to mitochondrial function, and anticancer drug research has also made significant progress in autophagy, but the regulatory role of mitochondria in the etiology and pharmacology of liver cancer remains unclear. To this end, we focused on the mitochondrial protein Nix (aka BNIP3L, BCL2/adenovirus E1B interacting protein 3-like), hypothesizing that induction of Nix-activated autophagy might represent a mechanism of sorafenib resistance.

Methods: We constructed two sorafenib-resistant HCC cell models (HepG2-SR, Huh7-SR) using the concentration-ascending method. Short hairpin RNA was used to knock down the expression of Nix in drug-resistant strains, and the consequences of autophagy signals and drug-resistant cells were observed. The correlation between Nix, autophagy and sorafenib resistance was mainly verified by western blot, IHC, qRT-PCR, CCK8 assay, and flow cytometry.

Results: Nix is overexpressed in liver cancer tissues and HCC lines resistant to sorafenib. In addition, the expression level of Nix was dose-dependent and positively correlated with Sorafenib resistance. Inhibiting the expression of Nix in drug-resistant strains can enhance its sensitivity to sorafenib. Furthermore, we showed that autophagy was activated in association with Nix-associated sorafenib resistance and was stopped by Nix knockdown and autophagy inhibitor.

Conclusion: Mitochondrial protein Nix regulated sorafenib resistance through autophagy in HCC, proving that autophagy is a cytoprotective mechanism mediating tumor drug resistance. The connection between Nix, autophagy and sorafenib resistance is first described in this study. These findings are significant as they suggest that the combination of targeting NIX therapy and autophagy provides new insights and strategies for the treatment of HCC.

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