Quinoline Derivative 10E Induces Cytoplasmic Vacuolization in Hepatocellular Carcinoma via NUR77

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Abstract

Background: Some quinoline derivatives induce excessive vacuolation of the cytoplasm in hepatocellular carcinoma (HCC) cells, leading to cell death. The mechanism underlying cytoplasmic vacuolation is complex and involves cellular senescence, autophagy, endoplasmic reticulum stress, and more. If the mechanism of vacuolation in hepatocellular carcinoma cells can be elucidated and key targets identified, it could play a positive role in addressing the current lack of effective treatment drugs for advanced HCC. *Objective*: This study aims to elucidate the molecular biological mechanisms by which a Nur77 agonists, quinoline derivative 10E, induces cytoplasmic vacuolization in HCC. *Method*: This study established a cell line-derived xenograft tumor (CDX) model expressing luciferase. The inhibitory effect of 10E on HCC cells in vivo was assessed by HE staining. The effects of 10E on the autophagy signaling pathway and autophagic flux were analyzed using immunofluorescence, Western blot (WB), and lysosomal pH probe. *Result*: 10E was able to inhibit the growth of HCC tumors in the CDX model and induced cytoplasmic vacuolation in HCC cells both in vitro and in vivo (Figure 1. A-E). Transmission electron microscopy observations and fluorescent fusion protein tracing results indicated that cytoplasmic vacuoles originated from autolysosomes (Figure 1. F, G). Additionally, 10E not only increased the expression of autophagy-related proteins but also prevented the degradation of p62 protein (Figure 1. H). Lysosomal pH probe detected that 10E leads to the inability of autolysosomes to acidify, showing its ability to block autophagic flux (Figure 1. I). After knocking down Nur77, the presence of distinct red autophagic puncta in cells expressing mRFP-eGFP-LC3B indicates that the blockage of autophagy flux has been reversed, and the inhibitory effect of 10E on hepatocytes has decreased (Figure 1. J, K). *Conclusion*: This study demonstrated the anti-hepatoma effects of the quinoline derivative 10E both in vitro and in vivo, and its ability to cause the persistent accumulation of autolysosomes and blockage of autophagic flux in HCC cells via Nur77. Therefore, this study confirmed that vacuolar-like cell death induced by 10E is an autophagy-mediated cell death, which holds promise for providing a new strategy for the treatment of advanced HCC.

Keywords

Quinoline Derivative, Hepatoma, Vacuolization, Autophagic-Flux, NUR77