Accepted Manuscript

New Compound ChlA-F Induces Autophagy-dependent Anti-cancer Effect *via* Upregulating Sestrin-2 in Human Bladder Cancer

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PII: S0304-3835(18)30525-1

DOI: 10.1016/j.canlet.2018.08.013

Reference: CAN 14027

To appear in: *Cancer Letters*

Received Date: 1 May 2018

Revised Date: 16 July 2018

Accepted Date: 9 August 2018

Please cite this article as: X. Hua, J. Xu, X. Deng, J. Xu, J. Li, D.Q. Zhu, J. Zhu, H. Jin, Z. Tian, H. Huang, Q.-s. Zhao, C. Huang, New Compound ChlA-F Induces Autophagy-dependent Anti-cancer Effect *via* Upregulating Sestrin-2 in Human Bladder Cancer, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.08.013.

Abstract

ChlA-F is a novel conformation-derivative of Cheliensisin A, styryl-lactone isolates that show potent anti-tumor potential *in vivo* and *vitro*. However, the anti-cancer activity and its potential mechanisms underlying ChlA-F action have never been explored. In the present study, we evaluated the potency of ChlA-F on autophagy-mediated anchorage-independent growth inhibition in human high-grade invasive bladder cancer (BC) cells. We found that ChlA-F treatment significantly inhibited anchorage-independent growth of human BC cells by inducing autophagy in a Sestrin-2 (SESN2)-dependent fashion. Our results revealed that ChlA-F treatment specifically induced SESN2 expression via increasing its transcription and mRNA stability. On one hand, ChlA-F treatment markedly attenuated Dicer protein abundance, in turn abolishing miR-27a maturation and further relieving miR-27a binding directly to SESN2 mRNA 3'UTR, thereby promoting SESN2 mRNA stabilization. On the other hand, ChlA-F treatment promoted Sp1 abundance and consequently mediated SESN2 transcription. These results demonstrate that its activation of the autophagic pathway through specifically promoting SESN2 expression mediates the anti-cancer effect of ChlA-F, which offers insights into the novel anti-cancer effect of ChlA-F on BC, as well as providing therapeutic alternatives against human BC.