Heteronemin, a cytotoxic marine sesterterpenoid-type natural product: A new weapon in the toolbox against LNcap and PC3 prostate cancer cell- Mohamed El-Shazly- The German University in Cairo, Egypt

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Abstract

Marine environment is the richest form of life on earth. It provided humanity with food, jewelry, and medicine. Marine sponges represent a rich source of potent therapeutics with thousands of biologically active compounds isolated from these magnificent creatures. One interesting example of the isolated class of secondary metabolites is heteronemin, which was isolated from the marine sponge Hyrtios sp. It is a marine sesterterpenoid-type natural product that exhibited potent cytotoxic activity against several cancer cell lines including prostate cancer cell lines. The importance of finding new therapeutic entities against prostate cancer encouraged us to evaluate the cytotoxic activity of heteronemin and its mechanism of action. Heteronemin exhibited potent cytotoxic effect against LNcap and PC3 prostate cancer cells with IC50 1.4 and 2.7 µM after 24 h, respectively. In the xenograft animal model, the tumor size was significantly suppressed to about 51.9% in the heteronemin-treated group in comparison with the control group with no significant difference in the mice body weights. Heteronemin inhibited topoisomerase II (topo II) as demonstrated by the cell-free system assay. Heteronemin induced apoptosis by 20.1–68.3%, disrupted mitochondrial membrane potential (MMP) by 66.9–99.1% and promoted calcium release by 1.8-, 2.0-, and 2.1-fold compared with the control group in a dose-dependent manner, as demonstrated by annexin-V/PI, rhodamine 123 and Fluo-3 staining assays, respectively. The pretreatment of LNcap cells with an inhibitor of protein tyrosine phosphatase (PTPi) diminished growth inhibition, oxidative and Endoplasmic Reticulum (ER) stress, as well as activation of Chop/Hsp70 induced by heteronemin, indicating that PTP activation played a crucial rule in the cytotoxic activity of heteronemin. Using molecular docking analysis, heteronemin exhibited more binding affinity to the N-terminal ATP-binding pocket of Hsp90 protein than 17-AAG, a standard Hsp90 inhibitor. It promoted autophagy and apoptosis through the inhibition of Hsp 90 and topo II as well as PTP activation in prostate cancer cells. These multiple targets render heteronemin as an interesting candidate which can be further developed into an antiprostatic agent.

A marine polycyclic quinone-type metabolite, halenaquinone (HQ), was found to inhibit the proliferation of Molt 4, K562, MDA-MB-231 and DLD-1 cancer cell lines, with IC50 of 0.48, 0.18, 8.0 and 6.76 µg/mL, respectively. It exhibited the most potent activity against leukemia Molt 4 cells. Accumulating evidence showed that HQ may act as a potent protein kinase inhibitor in cancer therapy. To fully understand the mechanism of HQ, we further explored the precise molecular targets in leukemia Molt 4 cells. We found that the use of HQ increased apoptosis by 26.23%-70.27% and caused disruption of mitochondrial membrane potential (MMP) by 17.15%-53.25% in a dose-dependent manner, as demonstrated by Annexin-V/PI and JC-1 staining assays, respectively. Moreover, our findings indicated that the pretreatment of Molt 4 cells with N-acetyl-l-cysteine (NAC), a reactive oxygen species (ROS) scavenger, diminished MMP disruption and apoptosis induced by HQ, suggesting that ROS overproduction plays a crucial rule in the cytotoxic activity of HQ.

The results of a cell-free system assay indicated that HQ could act as an HDAC and topoisomerase catalytic inhibitor through the inhibition of pan-HDAC and topoisomerase IIα expression, respectively. On the protein level, the expression of the anti-apoptotic proteins p-Akt, NFκB, HDAC and Bcl-2, as well as hexokinase II was inhibited by the use of HQ. On the other hand, the expression of the pro-apoptotic protein Bax, PARP cleavage, caspase activation and cytochrome c release were increased after HQ treatment. Taken together, our results suggested that the antileukemic effect of HQ is ROS-mediated mitochondrial apoptosis combined with the inhibitory effect on HDAC and topoisomerase activities. A marine fur Medical Toxicology: Current research anoterpenoid derivative, 10-acetylirciformonin B (10AB), was found to inhibit the proliferation of leukemia, hepatoma, and colon cancer cell lines, with selective and significant potency against leukemia cells. It induced DNA damage and apoptosis in leukemia HL 60 cells. To fully understand the mechanism behind the 10AB apoptotic induction against HL 60 cells, we extended our previous findings and further explored the precise molecular targets of 10AB.

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