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Quinuclidinone derivatives induced apoptosis in human breast cancer cells via sphingomyelinase and JNK signaling

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Novel quinuclidinone derivatives have been previously reported by our laboratory. In this study, we investigated the impact of two novel quinuclidinone derivatives 4 and 6 on apoptotic signaling in breast cancer cells (MCF-7) and their normal counterparts (MCF-12a). Our data revealed that derivatives 4 and 6 reduced proliferation and induced apoptosis in breast cancer cells. However, derivative 6 was less cytotoxic to normal breast epithelial cells than breast cancer cells; therefore, we focused on derivative 6 for further investigation. Flow cytometric analysis showed that quinuclidinone derivative 6 reduced the percent of MCF-7 cells in G_2/M which is confirmed by increased expression levels of cyclin B while it arrests MCF12a in G1 phase judging from increased p21. Quinuclidinone derivative 6 increased expression level of p53 and bax at both protein and mRNA levels and reduced expression level of Mdm2,Bcl2, Akt and Bcl-XL It also increased mitochondrial apoptotic pathways by activating release of cytochrome c which is consistent with activation of caspase-9 as confirmed by caspase-9 inhibitor LEHD-CHO. Finally, it increased sphingomyelinase signaling and ceramide formation as well as its downstream targets ERK1/2, p38 and JNK. Inhibition of ERK1/2 with PD98059 exerted little effect on the derivative 6-induced apoptosis and p38 inhibition with SB203580 slightly lessened apoptosis whereas, inhibition of JNK with SP600125 markedly suppressed derivative 6-induced apoptosis. These results indicate that derivative-6 induced the activation of sphingomyelinase signaling and that JNK played a pivotal role in induction of apoptosis in human breast cancer cells. In vivo studies and molecular docking experiments are now in progress for further anticancer investigations.

Biography

Ahmed M Malki has completed his Ph.D in Molecular Oncology at the age of 30 years from Edison Institute of Biotechnology, Ohio University in USA and He completed postdoctoral studies from University of California Berkeley, USA. He is the director of Molecular therapeutics laboratory, City of Research and Technology applications. He is currently an associate professor of Molecular Biology in Alexandria University; he has published more than 15 papers in reputed journals and serving as an editorial board member of Journal of Genetic Syndromes and Gene Therapy, African Journal of Biochemistry Research and Biotechnology and Molecular Biology Reviews. He also received Best Research Award, Global Breast Cancer conference,2011, Seoul, South Korea.

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