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Mechanistic studies on the anti-tumor effects of indirubin-3'-oxime on human neuroblastoma cells

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Neuroblastoma is the most common extracranial solid tumor found in infancy and childhood and accounts for ~15% of all childhood cancer-related deaths. Naturally occurring compounds that can inhibit neuroblastoma cell proliferation or trigger them to undergo apoptosis have attracted increasing interest as an alternative therapy for human neuroblatoma. Indirubin-3'-oxime (I3M), an indigo alkaloid was found to exhibit potent anti-tumor activities on various types of cancer cells. However, its modulatory effects on human neuroblastoma and the underlying mechanisms remain poorly understood. Our results showed that I3M inhibited the growth of the human neuroblastoma LA-N-1, SH-SY5Y and SK-N-DZ cells in a concentration- and time-dependent manner with minimal cytotoxicity on normal cells. Mechanistic studies showed that I3M specifically decreased the expression of mitochondrial regulators ERRα and PGC-1β and resulted in decreased mitochondrial mass and mitochondrial membrane potential in LA-N-1 cells. I3M also increased the level of CDK inhibitor p27Kip1 and reduced the levels of CDK2 and cyclin E in LA-N-1 cells leading to cell cycle arrest at the G0/G1 phase. Studies on the anti-angiogenic activities showed that I3M inhibited the *in vitro* proliferation, migration and tube formation of the human microvascular endothelial HMEC-1 cells in a concentration-dependent manner and significantly suppressed the in vivo angiogenesis in Matrigel plugs in mice. Moreover, I3M also down-regulated the expression of Ang-1 and MMP2 genes and up-regulated the expression of Ang-2 gene in HMEC-1 cells. Collectively, our results indicate that I3M might exert its anti-tumor activity by causing mitochondrial dysfunction which led to cell cycle arrest in LA-N-1 cells or through expression of its anti-angiogenic activities. Therefore, I3M might be exploited as a potential therapeutic candidate for the treatment of some forms of human neuroblastomas.

Biography

K.N. Leung graduated with a B.Sc. Degree in Biochemistry (First Class Honors) from The Chinese University of Hong Kong (CUHK) and obtained a Ph.D. Degree in Microbiology and Immunology from the John Curtin School of Medical Research, Australian National University. After two years of postdoctoral work at the Pathology Department of the University of Cambridge, he returned to the CUHK as a Lecturer in the Department of Biochemistry in 1983. K.N. Leung is now a Professor in the School of Life Sciences, CUHK and was appointed as Assistant Dean of the Faculty of Science in 2007, and then Associate Dean (Education) of the Faculty of Science in 2014. He was the chairman of the Hong Kong Society for Immunology from 2000-2002. He has served the Editorial Boards of several international journals and as a peer reviewer for 15 journals. He has over 30 years of experience in teaching and research in Immunology and Cancer Biochemistry. His main research interests include immunopharmacological studies of food components, natural products and Chinese medicinal herbs, cancer immunotherapy, and molecular studies of leukemic cell proliferation, differentiation and apoptosis.

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