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Curcumin: A Natural Multitarget Treatment for Pancreatic Cancer

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Dear Editor,

Curcumin is a naturally occurring polyphenolic compound and one of the most extensively studied natural products. Among its numerous health benefits,[1] curcumin has been particularly the focus of increasing research for its strong antitumor effects.[2] Several lines of preclinical evidence have shown the chemopreventive and antitumor effects of curcumin against different types of cancer.[1] With respect to pancreatic cancer (PC), in vitro studies have shown potent cytotoxic effects of curcumin on different PC cell lines including MiaPaCa-2, Panc-1, AsPC-1, BxPC-3, and Pan02.[2-6] Mechanistic evaluations have shown that the antiproliferative effects of curcumin are due to induction of apoptosis and inhibition of oxidative stress and angiogenesis.[1] At the molecular level, treatment of PC models with curcumin has been associated with reduced clonogenicity, spherical growth, invasiveness and migration of tumor cells, inhibition of cancer stem cell function, reversal of epithelial-mesenchymal transition, and suppression of NF-κB, miR-221, COX-2 and their effectors such as PTEN, p27, p57, and pro-inflammatory cytokines.[4-6] Curcumin can also block STAT1 and STAT3 phosphorylation and EGFR and Notch-1 signaling pathways, which are all essential for the growth of pancreatic tumors.[7] Notably, a novel curcumin analogue, namely, 3,4-difluorobenzylidene curcumin (CDF), has recently emerged as a potential drug for PC owing to its enhanced pharmacokinetic and cytotoxic properties compared with the parent compound. CDF has a preferential accumulation in pancreas, with a tissue concentration that is twice as much as that of curcumin.[8] CDF has been shown to enhance disintegration of pancreatospheres and possess greater cytotoxic effects on both resistant and nonresistant pancreatic tumor cell lines compared with curcumin. The low aqueous solubility of CDF is, however, still a limitation since it may necessitate dose escalation of the compound for intravenous injections and increase the risk of adverse reactions. To address this limitation, several nanosized delivery systems have been developed. These include hyaluronic acid[9] and styrene-maleic acid-engineered[10] nanomicelles, and hyaluronic acid (HA)-conjugated polyamidoamine dendrimers of CDF.[11] These systems have improved aqueous solubility, stability, release profile, and antitumor properties against PC cell lines compared with unformulated CDF. HA-containing formulations have an additional advantage of targeting CD44+ stem-like PC cells owing to the innate capacity of HA to recognize CD44.[12] Both curcumin and CDF have shown significant effects in reducing tumor growth in vivo using orthotopic and xenograft models of PC, though the antitumor effects have been reported to be greater with CDF.[13]

Although translation of the preclinical antitumor effects of curcumin into clinical practice is a necessary step, and has remained largely unknown, the multitarget action combined with pleiotropic effects,[14-21] unique safety,[22] and selective toxicity[23] of this dietary polyphenol for tumor cells holds a great promise for the use of this dietary polyphenol as an efficient adjuvant therapy for PC. Proof-of-concept clinical trials are also warranted to assess the safety and efficacy of CDF in PC, as this compound is a unique curcumin derivative in terms of its antitumor properties particularly on PC models, and there is promising evidence from direct comparative studies showing higher tissue accumulation and tumor growth–inhibiting effects of CDF versus native curcumin.

Declaration of Conflicting Interests

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