Arctigenin blocks the unfolded protein response and shows therapeutic antitumor activity.

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Source

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Abstract

Cancer cells in poorly vascularized solid tumors are constantly or intermittently exposed to stressful microenvironments, including glucose deprivation, hypoxia, and other forms of nutrient starvation. These tumor-specific conditions, especially glucose deprivation, activate a signaling pathway called the unfolded protein response (UPR), which enhances cell survival by induction of the stress proteins. We have established a screening method to discover anticancer agents that could preferentially inhibit tumor cell viability under glucose-deprived conditions. Here we identify arctigenin (ARC-G) as an active compound that shows selective cytotoxicity and inhibits the UPR during glucose deprivation. Indeed, ARC-G blocked expression of UPR target genes such as phosphorylated-PERK, ATF4, CHOP, and GRP78, which was accompanied by enhanced phosphorylation of eIF2 alpha during glucose deprivation. The UPR inhibition led to apoptosis involving a mitochondrial pathway by activation of caspase-9 and -3. Furthermore, ARC-G suppressed tumor growth of colon cancer HT-29 xenografts. Our results demonstrate that ARC-G can be served as a novel type of antitumor agent targeting the UPR in glucose-deprived solid tumors.

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