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Caffeine-mediated inhibition of calcium release channel inositol 1,4,5-trisphosphate receptor subtype 3 blocks glioblastoma invasion and extends survival.

Kang SS, Han KS, Ku BM, Lee YK, Hong J, Shin HY, Almonte AG, Woo DH, Brat DJ, Hwang EM, Yoo SH, Chung CK, Park SH, Paek SH, Roh EJ, Lee SJ, Park JY, Traynelis SF, Lee CJ.

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Calcium signaling is important in many signaling processes in cancer cell proliferation and motility including in deadly glioblastomas of the brain that aggressively invade neighboring tissue. We hypothesized that disturbing Ca(2+) signaling pathways might decrease the invasive behavior of glioblastoma, extending survival. Evaluating a panel of small-molecule modulators of Ca(2+) signaling, we identified caffeine as an inhibitor of glioblastoma cell motility. Caffeine, which is known to activate ryanodine receptors, paradoxically inhibits Ca(2+) increase by inositol 1,4,5-trisphosphate receptor subtype 3 (IP(3)R3), the expression of which is increased in glioblastoma cells. Consequently, by inhibiting IP(3)R3-mediated Ca(2+) release, caffeine inhibited migration of glioblastoma cells in various in vitro assays. Consistent with these effects, caffeine greatly increased mean survival in a mouse xenograft model of glioblastoma. These findings suggest IP(3)R3 as a novel therapeutic target and identify caffeine as a possible adjunct therapy to slow invasive growth of glioblastoma.

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