Differential antiproliferation effect of 2¢-benzoyloxycinnamaldehyde in K-ras-transformed cells via downregulation of thiol antioxidants

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Abstract:

2'-Benzoyloxycinnamaldehyde (BCA), one of the derivatives of 2'-hydroxycinnamaldehyde (HCA) isolated from the bark of Cinnamomum cassia, induces apoptosis in human cancer cells. We found that BCA induces stronger antiproliferative effects in K-ras-transformed cells (RK3E-ras) than in isogenic non-transformed cells (RK3E). Treatment of RK3E-ras with BCA resulted in increased ROS generation and depletion of intracellular glutathione, whereas BCA-treated RK3E showed no significant increase in the ROS level with concurrent increase in intracellular glutathione (GSH). Thiol antioxidants recovered cell proliferation inhibition caused by BCA in both cell lines, while non-thiol antioxidants failed to recover cell death. BCA decreased metallothionein (MT) expression in RK3E-ras, while inducing remarkable MT expression in RK3E. The increase of intracellular GSH in RK3E is partially caused by differential induction of ∥-glutamylcysteine synthetase (∥-GCS) due to BCA treatment. To evaluate the upstream pathway for differential expression of ∥-GCS and MT, we analyzed early DJ-1 (PARK7) and NF-E2 p45-related factor 2 (Nrf2) changes after BCA treatment. In RK3E, DJ-1 expression considerably increased for 3 h with concurrent induction of Nrf2, whereas in RK3E-ras cells BCA decreased these protein levels. Based on these findings, it seems that the therapeutic selectivity of BCA in RK3E-ras results from decreased thiol antioxidants via decreased DJ-1 and Nrf2 expression.

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