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Par-4-dependent p53 up-regulation plays a critical role in thymoquinone-induced cellular senescence in human malignant glioma cells

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Abstract

Thymoquinone (TQ), the predominant bioactive constituent present in black cumin (*Nigella sativa*), exerts tumor suppressive activity against a wide variety of cancer cells. Cellular senescence, characterized by stable and long term loss of proliferative capacity, acts as a potent tumor suppressive mechanism. Here, we provide evidence for the first time that TQ suppresses growth of glioma cells by potentially inducing the expression of prostate apoptosis response-4 (Par-4) tumor suppressor protein. In turn, TQ-induced Par-4 expression triggers cellular senescence, as evidenced by increasing cellular size, β-galactosidase staining, G1 phase arrest, and increased expression of senescence markers such as p53, p21, Rb, and decreased expression of lamin B1, cyclin E and cyclin depended kinase-2 (CDK-2). Further, overexpression of Par-4 significantly increases the expression of p53 and its downstream target p21, and increases β-galactosidase positive cells, while siRNA/shRNA mediated-knockdown of Par-4 reverses the TQ-induced effects. Altogether, we describe a novel mechanism of cross talk between Par-4 and p53, that plays a critical role in TQ-induced senescence in human malignant glioma cells.