Resveratrol exerts anti-proliferative and pro-apoptotic effects through transcription factor REST in human medulloblastoma cells

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Resveratrol is a polyphenol found in grapes, peanuts, a variety of berries and some other fruits. Resveratrol exerts anti-inflammatory and anticancer effects and reduces blood sugar. The beneficial effects of resveratrol against cancer have been shown in all the stages of carcinogenesis: initiation, promotion and progression.

Medulloblastoma (MB) is originated from primitive neural precursor cells in the external germinal layer of the developing cerebellum and accounts for more than 25% of cancer-related death among child patients. Despite improved therapies, the outcome of MBs remains poor due to limited knowledge about its molecular pathogenesis. Therefore, further exploration of molecular factors related to the formation and progression of MB would be of prognostic and therapeutic value. Poor differentiation, a hallmark of MBs, is associated with elevated expression levels of the transcription factor REST. Since its initial discovery, REST has emerged as a central hub in a complex network of transcriptional and epigenetic mechanisms that precisely regulate neuronal development. REST facilitates chromatin remodeling and inhibits gene expression through recruitment of multiple enzymatic co-repressor complexes that comprise histone deacetylases (HDACs). Additionally, REST has been implicated in a number of disorders, ranging from Down syndrome, X-linked mental retardation, and epilepsy syndromes to neurodegenerative disorders, such as Huntington's disease, and cancers.

Although REST represses neuronal genes, it appears to play a paradoxical role in cancer cells: it can exert tumor suppressor activity in some settings and oncogenic activity in others, making it a biological enigma. In fact, in MB REST repressor function seems to be important in tumorigenesis, while in breast, prostate, and small cell lung cancer REST has been demonstrated to act as a tumor suppressor that promotes cell transformation, proliferation, and migration.

The current study was performed to elucidate the molecular mechanisms of the anti-cancer activity of resveratrol through the regulation of REST in human MB cells (DAOY cell line).

Resveratrol was able to down-regulate REST in a concentration-dependent manner (100-200-400 μM), at both mRNA and protein levels (74% of reduction); as a consequence we observed an increase of histone H3 acetylation (81%). Moreover, resveratrol let to a reduction of cell growth of 43% and to an arrest in G0/G1 phase of cell cycle.

In a previous study, we demonstrated that silencing of REST increased apoptosis, whereas apoptosis induced by anti-Fas receptor antibody was reduced by REST overexpression in HeLa cells [Baiula et al., 2012]. This anti-apoptotic role played by REST confirmed previous data in MB cells: a recombinant form of REST named REST-VP16, built by replacing repressor domains of REST with the activating domain of a viral protein, was able to compete with the endogenous REST and to trigger apoptosis through the activation of caspases. Furthermore, REST-VP16 inhibited MB growth in nude mice [Lawinger et al., 2000].

Since several evidences showed that REST possesses an anti-apoptotic activity, we investigated how resveratrol-mediated REST regulation could affect apoptosis in DAOY cells with a multi-strategies approach. As expected, probably because of the reduction of REST levels, resveratrol strongly induced apoptosis in MB cells. In addition we proved that resveratrol may regulate REST through the transcription factor FoxO3a by SIRT1 deacetylase: overexpression of FoxO3a induced an increase of REST levels. In fact, resveratrol activates SIRT1 which may influence REST expression modulating FoxO3a acetylation since mutant forms of FoxO3a no more acetylable were not able to increase REST levels.

In conclusion we proved that REST is a gene target of resveratrol and REST decrement contributes to the anti-proliferative, pro-apoptotic and anti-cancer activity of resveratrol.