SIRT1-regulated REST gene expression in medulloblastoma cells

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In the nervous system, several key steps in cellular complexity and development are regulated by the repressor element-1 silencing 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, via two repressor domains located at the N- and C-terminus ends of the protein. These respectively enrol mSin3A, which may recruit histone deacetylases (HDACs), and CoREST, which recruits HDACs; furthermore, REST may influence histone demethylase activity.

Highlighting its importance, 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.

Medulloblastoma (MB) is a malignant pediatric brain tumor, which originates in the cerebellum, presumably due to the alterations of some neurogenetic elements. Despite the improved combination of surgery, radiation and chemotherapy, 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 REST, indicating that the REST repressor function is important in tumorigenesis. In contrast, 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.

Sirtuins are found in all organisms and act as the critical regulators at the crossroads between cancer and aging. Sirtuin 1 (SIRT1), as a deacetylase, regulates cell growth, differentiation and apoptosis. A body of evidence has revealed that SIRT1 plays multifaceted roles in carcinogenesis as a tumor promoter or a tumor suppressor, meaning that SIRT1 functions in a cell- or tissue-related fashion.

Moving from these observations, the current study investigated the role of SIRT1 in REST regulation in MB cells. Changes in REST expression (both mRNA and protein) and apoptosis levels were investigated. Treatment with resveratrol (resv), an activator of SIRT1 and a natural compound known to prolong lifespan and prevent cancer formation, did not change REST expression which is increased by nicotinamide, a SIRT1 inhibitor. Increased nuclear levels of REST exerted an antiapoptotic effect related to the reduced histone acetylation. Moreover, nicotinamide, elevating REST, counteracted apoptosis of MB cells induced by antibody anti-Fas and PD98059. Our results show that REST expression could be mediated by SIRT1. In previous studies we have found that transcription factor FoxO3a up-regulates REST expression in MB cells. We proved that SIRT1 may influence REST expression by modulating FoxO3a acetylation since mutant form of FoxO3a no more acetylable did not increase REST levels.

Dissection of the role of REST may shed light upon gene trascription processes regulating apoptosis.