Klotho

Klotho, a single pass transmembrane protein associated with premature aging, acts as a tumor suppressor gene by inhibiting insulin/insulin-like growth factor-1 and fibroblast growth factor pathways. Downregulated Klotho expression is reported in melanoma, mesothelioma, bladder cancer, breast cancer, gastric cancer, cervix, lung cancer, and kidney cancers, and is associated with a poor prognosis. Klotho expression and Klotho promoter hypermethylation are predictive factors for patient prognosis. To investigate the potential role of Klotho in glioblastoma multiforme (Glioblastoma), 22 Glioblastoma samples were collected from the Sheba Tumor Bank and examined.

They found that increased Klotho mRNA expression predicted longer survival (p=0.03) of Glioblastoma patients. Methylation analysis was performed on bisulfite-treated DNA from the Glioblastoma patient samples using ionization time-of-flight mass spectrometry according to the Sequenom EpiTYPER protocols. Klotho promoter hypermethylation was detected in 65% of the Glioblastoma samples, and correlated significantly with improved survival (p<0.04).

Yeloz et al., found three major Klotho promotor hypermethylation sites located 585-579 bp, 540-533 bp, and 537-534 bp upstream of the transcription start site. Methylated DNA immunoprecipitation studies confirmed these results. Notably, the mRNA expression in these Glioblastoma samples revealed an unexpected linear correlation with methylation of these three hypermethylation sites identified in the Klotho promotor. Thus, Klotho expression and methylation could predict prognosis in patients with Glioblastoma. Epigenetic regulation in Glioblastoma appears to be very complicated. Specific CpG islands affect genes or micro RNAs that interact to control Klotho expression. The diverse effects of these islands may be due to unique factors of Glioblastoma [1].

The Klotho family consists of three single-pass transmembrane proteins—α-Klotho, βKlotho and γKlotho. Each of them combines with fibroblast growth factor (FGF) receptors (FGFRs) to form receptor complexes for various FGF’s.

1)
Yeloz NP, Ungar L, Wohl A, Jacoby E, Fisher T, Leitner M, Nass D, Rubinek T, Wolf I, Cohen ZR. Role of Klotho protein in tumorigenesis, cancer progression, and prognosis in patients with high-grade glioma. World Neurosurg. 2019 Jun 19. pii: S1878-8750(19)31634-1. doi: 10.1016/j.wneu.2019.06.082. [Epub ahead of print] PubMed PMID: 31228703.