

Klotho: a tumor suppressor and a modulator of the IGF-1 and FGF pathways in human breast cancer

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Klotho is an anti-aging gene, which has been shown to inhibit the insulin and insulin-like growth factor 1 (IGF-1) pathways in mice hepatocytes and myocytes. As IGF-1 and insulin regulate proliferation, survival and metastasis of breast cancer, we studied klotho expression and activities in human breast cancer. Immunohistochemistry analysis of klotho expression in breast tissue arrays revealed high klotho expression in normal breast samples, but very low expression in breast cancer. In cancer samples, high klotho expression was associated with smaller tumor size and reduced KI67 staining. Forced expression of klotho reduced proliferation of MCF-7 and MDA-MB-231 breast cancer cells, whereas klotho silencing in MCF-7 cells, which normally express klotho, enhanced proliferation. Moreover, forced expression of klotho in these cells, or treatment with soluble klotho, inhibited the activation of IGF-1 and insulin pathways, and induced upregulation of the transcription factor CCAAT/enhancer-binding protein b, a breast cancer growth inhibitor that is negatively regulated by the IGF-1-AKT axis. Co immunoprecipitation revealed an interaction between klotho and the IGF-1 receptor. Klotho is also a known modulator of the fibroblast growth factor (FGF) pathway, a pathway that inhibits proliferation of breast cancer cells. Studies in breast cancer cells revealed increased activation of the FGF pathway by basic FGF following klotho overexpression. Klotho did not affect activation of the epidermal growth factor pathway in breast cancer cells. These data suggest klotho as a potential tumor suppressor and identify it as an inhibitor of the IGF-1 pathway and activator of the FGF pathway in human breast cancer.