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**Green tea polyphenols reverses TIMP-3 expression in prostate cancer by inhibiting histone modifying enzymes**

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Green tea polyphenols (GTP) and its major constituent, epigallocatechin-3-gallate (EGCG) have been reported to demonstrate many interesting biological activities, including induction of epigenetic changes and cancer prevention. Recent studies in prostate cancer provide strong evidence that epigenetic mechanisms are major players in the regulation of the MMP-2 and MMP-9 and their binding partners Tissue Inhibitor of Matrix metalloproteinases viz. TIMP-2 and TIMP-3 involved in prostate cancer progression. In the present study, we demonstrate that GTP and EGCG mediate epigenetic reactivation of TIMP-3 levels and play a key role in suppressing invasiveness and gelatinolytic activity of MMP-2 and MMP-9 in prostate cancer cells. Treatment of human prostate cancer DU-Pro and LNCaP cells with 20 µM EGCG and 10 µg/mL GTP for 72 h significantly induces TIMP-3 mRNA and protein levels. Interestingly, investigations into the molecular mechanism revealed that TIMP-3 repression in prostate cancer cells is mediated by epigenetic silencing mechanism(s) involving increased activity of the enhancer of zeste homolog 2 (EZH2) and class I histone deacetylases (HDACs), independent of promoter DNA hypermethylation. Treatment of cancer cells with GTP and EGCG significantly reduced EZH2 and class I HDAC protein levels. Furthermore, transcriptional activation of TIMP-3 was found to be associated with decreased EZH2 localization and H3K27 trimethylation enrichment at the TIMP-3 promoter with a concomitant increase in histone H3K9/18 acetylation. Furthermore, clinical trial performed at the University Hospitals on patients undergoing radical surgery consuming 800 mg EGCG (Polyphenon E) up to 8 weeks and the grade-matched controls demonstrate increase in plasma TIMP3 levels, compared to controls. A marked decrease in HDAC activity; decrease in the protein expression of class I HDACs and EZH2; trimethylation of H3K27 were noted in the prostate tissue from GTP supplemented group. Our findings highlight TIMP-3 induction as a key epigenetic event modulated by green tea in restoring the MMP: TIMP balance to suppress prostate cancer progression.