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Increasing intracellular bio available copper selectively targets Prostate cancer cells

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The therapeutic efficacy of two bis-(thiosemicarbazonato) copper complexes, glyoxalbis[N4-methylthiosemicarbazonato] CuII [CuII(gtsm)] and diacetylbis-[N4-methylthiosemicarbazonato]CuII [CuII(atsm)], for the treatment of prostate cancer was assessed in cell culture and animal models. Distinctively, copper dissociates intracellularly from CuII(gtsm) but is retained by CuII(atsm). We further demonstrated that intracellular H2gtsm [reduced CuII(gtsm)] continues to redistribute copper into a bioavailable (exchangeable) pool. Both CuII(gtsm) and CuII(atsm) selectively kill transformed (hyperplastic and carcinoma) prostate cell lines but, importantly, do not affect the viability of primary prostate epithelial cells. Increasing extracellular copper concentrations enhanced the therapeutic capacity of both CuII(gtsm) and CuII(atsm), and their ligands (H2gtsm and H2atsm) were toxic only toward cancerous prostate cells when combined with copper. Treatment of the transgenic adenocarcinoma of mouse prostate (TRAMP) model with CuII(gtsm) (2.5 mg/kg) significantly reduced prostate cancer burden (70%) and severity (grade), while treatment with CuII(atsm) (30 mg/kg) was ineffective at the given dose. However, CuII(gtsm) caused mild kidney toxicity in the mice, associated primarily with interstitial nephritis and luminal distention. Mechanistically, we demonstrated that CuII(gtsm) inhibits proteasomal chymotrypsin-like activity, a feature further established as being common to copper-ionophores that increase intracellular bioavailable copper. We have demonstrated that increasing intracellular bioavailable copper can selectively kill cancerous prostate cells in vitro and in vivo and have revealed the potential for bis(thiosemicarbazone) copper complexes to be developed as therapeutics for prostate cancer.

Association between *RASSF1A* promoter methylation and ovarian cancer: A meta-analysis

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Background: The RAS association domain family protein 1a gene (*RASSF1A*) is one of the tumor suppressor genes (TSG). Inactivation of *RASSF1A* is critical to the pathogenesis of cancer. Aberrant TSG methylation was considered an important epigenetic silencing mechanism in the progression of ovarian cancer. A number of studies have discussed the association between *RASSF1A* promoter methylation and ovarian cancer. However, they were based mostly on a small number of samples, and the results are inconclusive. Therefore, we conducted a meta-analysis to better identify the association between *RASSF1A* promoter methylation and ovarian cancer.

Methods: Eligible studies were identified by searching the PubMed, EMBASE, Web of Science, and CNKI databases using a systematic searching strategy. We pooled the odds ratio (ORs) from individual studies using a fixed-effects model. We performed heterogeneity and publication bias analysis simultaneously.

Results: Thirteen studies, with 763 ovarian cancer patients and 438 controls were included in the meta-analysis. The frequencies of *RASSF1A* methylation ranged from 30% to 58% (median is 48%) in the cancer group and 0 to 21% (median is 0) in the control group. The frequencies of *RASSF1A* methylation in the cancer group were significantly higher than those in the control group. The pooled odds ratio was 11.17 (95%CI=7.51-16.61) in the cancer group versus the corresponding control group under the fixed-effects model.

Conclusion: The results suggested that *RASSF1A* promoter methylation had a strong association with ovarian cancer, which indicated that *RASSF1A* promoter methylation may be a potentially useful biomarker in the process of ovarian carcinogenesis. The result also requires confirmation through large prospective studies.

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