Nipped-B homolog increases the sensitivity of cisplatin to ESCC cells through the histone deacetylation-dependent upregulation of PUMA.

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BACKGROUND: Cisplatin is a well-known chemotherapeutic drug used frequently for treatment of esophageal squamous cell carcinoma (ESCC). Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA, interfering DNA repair, causing DNA damage, and subsequently inducing apoptosis of cancer cells. However, few ESCC cells could escape from apoptosis and lead to drug resistance, recurrence and metastasis. Thus, searching for a new therapeutic target which could increase the sensitivity of ESCC cells to cisplatin will bring new insights to the treatment of ESCC. The cohesin complex is crucial for chromosome segregation during mitosis and has recently also been implicated in transcriptional regulation and chromatin architecture. The NIPBL protein is required for the loading of cohesin onto chromatin. However, the relevance of NIPBL to ESCC development remains unknown. In our previous studies, Kaplan-Meier analysis illustrated that low NIPBL expression predicted poor survival in ESCC patients. Overexpression of NIPBL could distinctly inhibit ESCC cells growth, however, NIPBL depletion could significantly promote ESCC cells growth, and erase the lethal effect of cisplatin to ESCC cells. PUMA (p53 upregulated modulator of apoptosis), a key tumor suppressor gene in mitochondrial apoptotic pathway, was dramatically downregulated by NIPBL depletion. Since NIPBL could recruit HDAC1 and 3 to regulate the expression of its target genes, and HDAC3 could bind to PUMA promoter directly to regulate its expression level, thus, we propose our hypothesis.

HEPOTHESIS: NIPBL increase the sensitivity of cisplatin to ESCC cells through the histone deacetylation-dependent upregulation of PUMA.

METHODS: More cisplatin resistant and non-resistant samples will be collected from Zhejiang Cancer Hosipital. Double immunofluorescence labeling method will be used to detect the expression of NIPBL and PUMA protein. NIPBL vector and PUMA siRNA or NIPBL siRNA and PUMA vector will be co-transfected into ESCC cells to elucidate whether PUMA could rescue the function of NIPBL in mediating the cisplatin sensitivity to ESCC cells. Chromatin immunoprecipitation and luciferase reporter assay will be used to clarify the transcriptional mechanism between NIPBL and PUMA.

RESULTS: Our finding will provide new insights that incombination with cisplatin treatment, targeting NIPBL will be a promising strategy to increase the sensitivity of cisplatin to ESCC cells.