Abstract

Most non-small cell lung cancer (NSCLC) patients are treated with platinum-based compounds like cisplatin, yielding highly heterogeneous therapeutic responses. Here, I will report a genome-wide siRNA-based screening that identified proteins affecting the response of NSCLC cells to cisplatin. Functional and pharmacological experiments coupled to combinatorial analyses led to the validation of multiple cisplatin response modifiers including one major metabolic pathway. This phylogenetically conserved pathway involves pyridoxal kinase (PDXK), which generates the bioactive form of vitamin B6 and is required for optimal cisplatin responses. Vitamin B6 accrued intracellular cisplatin accumulation and exacerbated cisplatin-mediated DNA damage, in vitro, thus sensitizing NSCLC cells to apoptosis, in vitro and in vivo. Moreover, low PDXK expression levels turned out to be associated with poor disease outcome in NSCLC and ovarian carcinoma patients. These results point to vitamin B6 metabolism as a promising biomarker and target for the development of personalized anticancer regimens.