NICLOSAMIDE DERIVATIVES INHIBIT CIP2A AND REACTIVATE TUMOR SUPPRESSOR PROTEIN PHOSPHATASE 2A IN NON-SMALL CELL LUNG CANCER CELLS

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Protein phosphatase 2A (PP2A) is a critical tumor suppressor complex responsible for the inactivation of various oncogenes. Recently, PP2A reactivation has emerged as an anticancer strategy. Cancerous inhibitor of protein phosphatase 2A (CIP2A), an endogenous inhibitor of PP2A, is upregulated in many cancer cells, including non-small cell lung cancer (NSCLC) cells. We demonstrated that the antihelminthic drug niclosamide inhibited the expression of CIP2A and reactivated the tumor suppressor PP2A in NSCLC cells. We performed a drug-repurposing screen and identified niclosamide as a CIP2A suppressor in NSCLC cells. Niclosamide inhibited cell proliferation, colony formation, and tumor sphere formation, and induced mitochondrial dysfunction through increased mitochondrial ROS production in NSCLC cells; however, these effects were rescued by CIP2A overexpression, which indicated that the antitumor activity of niclosamide was dependent on CIP2A. We found that niclosamide increased PP2A activity through CIP2A inhibition, which reduced the phosphorylation of several oncogenic proteins. Moreover, we found that a niclosamide analog inhibited CIP2A expression and increased PP2A activity in several types of NSCLC cells. Finally, we showed that other well-known PP2A activators, including forskolin and FTY720, did not inhibit CIP2A and that their activities were not dependent on CIP2A. Collectively, our data suggested that niclosamide effectively suppressed CIP2A expression and subsequently activated PP2A in NSCLC cells. This provided strong evidence for the potential use of niclosamide as a PP2A-activating drug in the clinical treatment of NSCLC.