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NCL1, a highly selective lysine-specific demethylase 1 inhibitor, suppresses prostate cancer without adverse effect

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Abstract

Prostate cancer is one of the most frequently diagnosed cancers in the Western world. There are many therapeutic options against localized prostate cancer. However, in advanced cancers, most tumors ultimately relapse after a period of initial response to

therapy and progress to metastatic cancer, for which effective therapeutic procedures are extremely limited. Herein, we investigated therapeutic potential of a novel histone lysine demethylase 1 (LSD1) inhibitor, NCL1, in prostate cancer. Hormone-sensitive prostate cancer cells, (LNCaP) and castration resistant cancer cells (PC3 and PCai1) were treated with NCL1, and LSD1 expression and cell viability were assessed. Prostate cancer cells showed strong LSD1 expression, and cell viability was decreased by NCL1. ChIP analysis showed that NCL1 induced H3K9me2 accumulation at the promoters of androgen-responsive genes. NCL1 also induced cell cycle arrest and apoptosis. In addition, autophagosomes were induced by NCL1 treatment in LNCaP. Furthermore, LC3-II expression was significantly increased by NCL1 and chloroquine. In mice injected subcutaneously with PCai1 and intraperitoneally with NCL1, tumor volume was reduced with no adverse effects in NCL1-treated mice. Finally, LSD1 expression in human cancer specimens was significantly higher than that in normal prostate glands. In conclusion, NCL1 effectively suppressed prostate cancer growth without adverse event.