CANCER RESEARCH

Tumor Biology

Abstract 3366: NCL targeting impairs the progression of pancreatic ductal adenocarcinoma and promotes tumor vessel normalization through Ang-2 inhibition

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive tumor, mostly resistant to the standard treatments. NCL is overexpressed in cancers and its inhibition impairs tumor growth. Herein we described, that NCL was overexpressed in human specimens of PDAC, and low NCL staining patients had increased overall survival. Previously, we described a family of multivalent pseudopeptides binding to NCL and inhibiting tumour growth. Here, NCL antagonist N6L, strongly impaired tumor growth, liver metastasis formation and angiogenesis in an orthothopic mouse model of PDAC. N6L inhibited both human and mouse tumor cell proliferation and invasion. Proteome analysis of endothelial cell secreted proteins showed that NCL inhibition decreased Ang-2 levels and switched a pro-angiogenic signature. Importantly, Ang-2 levels were decreased in plasma of N6L-treated PDAC mice. The analysis of tumor vasculature revealed a strong increase of pericyte coverage and vessel perfusion in parallel to an inhibition of tumor hypoxia. As consequence of N6L-induced tumor vessel normalization, pre-treatment with N6L efficiently improved chemotherapeutic drug delivery and increased the anti-tumor properties of gemcitabine in PDAC mice.

In conclusion, NCL inhibition is a new anti-tumor therapeutic strategy that dually blocks tumor progression and normalizes tumor vessels improving the delivery and efficacy of chemotherapeutic drugs in PDAC cancers. Moreover, we identified Ang-2 as a potential target and suitable response biomarker for N6L treatment in PDAC.

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