NOV-002 suppresses tumor cell growth by modulating redox-sensitive cell signaling

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Abstract

Regulation of cell proliferation/survival is complex, impacted by multiple endogenous and exogenous stimuli capable of triggering overlapping and competing signaling pathways whose net effects can be quite cell dependent. Changes in redox status is one regulator of cell/biofuel decision under both physiologic and pathologic conditions. Here we report on the anti-proliferative effects of a pharmacologically generated oxidative stress in human tumor cells using NOV-002, a glutathione disulfide reductase. In advanced clinical trials for oncologic indications, NOV-002 has demonstrated significant activity against multiple cancers when combined with standard chemotherapeutic agents. In addition, treatment with NOV-002 mitigates chemotherapy-induced hematology toxicity. Pre-clinical data has linked the effect of NOV-002 to the generation of bone marrow progenitor cells subsequent to generation of an oxidative signal, intracellularly and at the cell surface of myeloid lineage cells, leading to activation of multiple kinases known to regulate cell proliferation (e.g. MAP kinase, JAK/STAT kinases). The data presented here extend redox modulation studies with NOV-002 to tumor cells. SKOV3 cells (a human ovarian tumor cell line) were exposed to NOV-002 (250 μM). Within 5 min after a single treatment, cellular levels of reactive oxygen species (ROS) were significantly elevated indicating the generation of an oxidative signal by NOV-002. This was not, however, sufficient to influence redox-sensitive cell signaling or tumor cell proliferation rate. In contrast, more prolonged exposure to NOV-002 (daily treatment for 3 days) resulted in a sustained elevation in ROS and dose-dependent activation of the proliferation-regulating stress kinases, JNK, AKT, and p38, as well as up-regulation of genes known to promote cell proliferation. These data suggest that the therapeutic effect was associated with a significantly decreased proliferation rate of the SKOV3 cells that persisted even after stopping treatment with NOV-002. Thus, oxidative stress generation and MAP kinase pathway activation by NOV-002 appears to result in cell-type dependent effects on proliferation/survival. In myeloid lineage bone marrow cells, chronic exposure to NOV-002 leads to increased proliferation while in tumor cells the result is a decrease in proliferation. These dichotomous effects may contribute to the unique clinical profile that NOV-002 has demonstrated to date—a demonstrated anti-tumor efficacy and survival combined with enhanced recovery from chemotherapy-induced hematology toxicity.

NOV-002 treatment leads to cell cycle alterations and enhanced apoptosis in SKOV3 cells

Effect of NOV-002 on cell cycle arrest. SKOV3 cells were treated with vehicle (■) or 250 μM NOV-002 (▲) daily for 4 days. Cell cycle analysis was performed in the flow cytometry facility at MUSC. The results are expressed as the mean ± S.E., N=3.

Conclusions

Repetitive treatment of SKOV3 tumor cells with NOV-002 leads to:

- Oxidative signaling as evidenced by formation of ROS, increased protein S-glutathionylation and up-regulation of ROS-induced genes
- Concurrent activation of MAP kinase signaling pathways
- Apoptosis and diminished tumor cell growth rate
- Enhancement of cisplatin-induced tumor cell cytotoxicity

These data support the hypothesis that the improved efficacy seen in cancer patients treated with combinations of NOV-002 and chemotherapy may be due at least in part to direct anti-tumor effects of NOV-002.