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expression of CD95/CD95L and caspase-8 activity was abolished by L-NAME or p53 siRNA. The tail vein infusion of AFP-NOS- 3/RSV-Luciferase adenovirus increased cell death markers, and reduced cell proliferation of established tumors in fibrotic livers. The increase of oxidative/nitrosative stress induced by NOS-3 overexpression induced DNA damage, p53, CD95/CD95L expression and cell death in hepatocellular carcinoma cells. The effectiveness of the gene therapy has been demonstrated *in vitro* and *in vivo*.

http://dx.doi.org/10.1016/j.redox.2015.09.032

Young Investigation Session
Selected Oral Communications

NOSH-Aspirin Inhibits Colon Cancer Cell Growth: Effects Of Positional Isomerism

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Background: NOSH-aspirin, a novel hybrid that releases nitric oxide (NO) and hydrogen sulfide (H_2S) was designed to overcome the potential side effects of aspirin.
Aim: We compared the cell growth inhibitory properties of ortho-, meta-, and para-NOSH-aspirins. Effects of electron donating/withdrawing groups on the stability and biological activity of these novel compounds were also evaluated.
Methods: Cell line: HT-29 (Cyclooxygenase, COX-1 & -2 expressing) and HCT 15 (COX null) human colon adenocarcimoa; Cell growth: MTT; Cell cycle phase distribution: Flow cytometry; Apoptosis: subdiploid (sub-G_0/G_1) peak in DNA content histograms; Proliferation: PCNA; ROS: measured hydrogen peroxide and super oxide by flow cytometry using DCFDA and DHE dyes.
Results: The IC_{50}s for growth inhibition in μM at 24 h were, HT-29: ortho-NOSH-ASA (0.04±0.011), meta-NOSH-ASA (0.24±0.11), para-NOSH-ASA (0.46±0.17); significance between the groups were: o *vs* m $P>0.05$, o *vs* p $P<0.05$, m *vs* p $P>0.05$; HCT 15: ortho-NOSH-ASA (0.062±0.006), meta-NOSH-ASA (0.092±0.004), para-NOSH-ASA (0.37 ±0.04); significance between the groups were: o *vs* m $P<0.01$, o *vs* p $P<0.001$, m *vs* p $P<0.001$. Electron donating/withdrawing groups significantly affected these IC_{50}s. All positional isomers qualitatively had similar effects on proliferation, apoptosis, and caused G_0/G_1 cell cycle arrest in both colon cancer cell lines. The underlying mechanism for these observations appeared to be mediated through ROS, as pretreatment of the cells with N-acetylcysteine, partially blocked these effects.
Conclusions: Positional isomerism affects the potency of NOSH-aspirin. The effects appear to be COX independent.

http://dx.doi.org/10.1016/j.redox.2015.09.033

Keynote Session
Moderator: Professor José López Barneo

Nitric Oxide And Oxygen: Actions And Interactions In Health And Disease

Professor Sir Salvador Moncada

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Nitric oxide (NO) inhibits cell respiration reversibly and in competition with O_2 through the inhibition of the mitochondrial cytochrome c oxidase (Complex IV). At concentrations lower than those required to inhibit respiration, endogenous NO enhances the reduction of the electron transport chain, thus enabling cells to maintain their O_2 consumption. This however facilitates the release of superoxide anion, which initiates the transcriptional activation of NF-*k*B as an early signal of a stress response. Through free radical formation, long-term inhibition of mitochondrial respiration by NO leads to persistent inhibition of Complex I. This is dependent on the S-nitrosylation of a specific thiol in the active form of this protein. S-nitrosylation of Complex I might indicate the early stages of a pathological process.

Inhibition of mitochondrial respiration by low concentrations of NO at critical O2 concentrations also leads to prevention of the stabilization of hypoxia-inducible factor-1α (HIF-1α) due to the redistribution of O_2 towards non-respiratory O_2-dependent targets. This prevents the cell from registering a state of hypoxia at low O_2 concentrations. On the other hand, at higher concentrations such as those generated in certain forms of cancer, NO increases the expression of HIF-1α by an action most probably involving a free radical mechanism.

It is likely that the interactions between oxygen and NO, either at the mitochondria or in the cell in general, play a role in the initiation and development of neoplastic transformation and spreading. The ways in which these interactions operate remain unclear and are likely to vary from cancer to cancer.

http://dx.doi.org/10.1016/j.redox.2015.09.034