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Session 1: Nitric Oxide, Mutagenesis, Carcinogenesis, Tumor Promotion and Tumor Growth Moderator: Professor Salvador Moncada INVITED SPEAKERS

Deciphering The Complex Biological Interactions Of Nitric Oxide In Cancer

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NO[•] is a free radical and is involved in a number of critical physiological processes including vasodilation, neurotransmission, immune regulation and inflammation. There are convincing evidence suggesting a role of NO[•] in the development and progression of different cancer types. However, the role of NO[•] in tumorigenesis is highly complex and both pro- and anti-neoplastic functions have been reported, which largely depends on the amount of NO[•], cell types, cellular microenvironment, its interaction with other reactive species and presence of metals. An interesting interaction occurs between NO[•] and p53 tumor suppressor, in which NO[•]-induced DNA damage causes the stabilization and accumulation of p53, which in turn, transrepresses inducible nitric oxide synthase (NOS2) in a negative feedback loop. In chronic inflammatory diseases, for example ulcerative colitis, NO[•] induces p53 stabilization and the initiation of DNA-damage response pathway, and also generation of p53 mutation and subsequent clonal selection of p53 mutant cells. Genetic deletion of NOS2 in p53-deficient mice can either suppress or enhance lymphomagenesis depending on the inflammatory microenvironment. These findings highlight the importance of understanding the complex biological interaction of NO[•] in the context of the molecular makeup of each individual cancer to design NO[•]-targeted treatment strategies.

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The Oncogenic Properties Of The Redox Inflammatory Protein Inducible Nitric Oxide Synthase In ER(-) Breast Cancer

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Inflammation generates reactive chemical species that induce conditions of oxidative nitrosative stress as emerged as factor in poor outcome of many cancers. Our recent findings show that in the inflammatory protein inducible nitric oxide synthase (iNOS) is a strong predictor of poor outcome in ER(-) patients (Glynn et al. JCI 2010). Furthermore 46 genes, of which 23 were associated with basal like breast cancer, were elevated when iNOS high. In vitro studies using ER(-) cell lines showed that fluxes of nitric oxide (NO) delivered by NO donors surprising mimic this relationship in the patient cohort. Using this model, we show that NO at different specific concentrations stimulate pro-oncogenic mechanisms such as AKT, ERK, NFκB, AP-1, and HIF-1α that lead to increase of metastatic and cancer stem cells proteins. In addition, we show that tumor suppressor gene BRCA1 and PP2A are inhibited by these NO levels. Similarly other studies show that these concentrations of NO increase immunosuppressive proteins TGF-β and IL-10 in leukocytes to decrease efficacy of some anticancer therapies further contributing to pro-tumorigenic environment. Using this model we have identified several new compounds that have efficacy in xenographic models. These finding have provided a model that shows how NO can affect numerous mechanism that leads to a more aggressive phenotype.

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