cellular target genes of EBV viral genes. Functional classification of these genes exhibited cell cycle, apoptosis, signal transduction pathways, and regulation of transcription. We verified the differential expression of STMN1, RAB27A, RAB9A, COX5A, BACH1 and BACH2 between LCLs and primary B-cells by quantitative RT-PCR. Interestingly, STMN1 was increased at both transcriptional and translational levels in LCLs, but not in primary B cells. We suggest that STMN1 is one of the putative cellular targets of EBV.

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THE NADPH OXIDASE HOMOLOGS NOX1 AND NOX4 ATTENUATE INTERLEUKIN-1β INDUCED NITRIC OXIDE SYNTHASE EXPRESSION IN VASCULAR SMOOTH MUSCLE CELLS

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Mounting evidence indicates that reactive oxygen species (ROS) produced in the vascular wall upon cytokine stimulation play an important regulatory function in cell signaling during vascular injury. In the present study, we tested the hypothesis that non-phagocytic NADPH oxidase (NOX)-derived H_2O_2 regulates the expression of inducible nitric oxide synthase (iNOS) in primary rat vascular smooth muscle cells (VSMC) by modulating the extracellular regulated kinases 1 and 2 (ERK). This is based on previous observations that IL-1β-mediated iNOS expression in VSMC is completely dependent upon ERK activation. Using confoncal microscopy, we found that IL-1β rapidly increased intracellular ROS production. Catalase loading inhibited ROS production and potentiated ERK activation and iNOS expression indicating that IL1β-derived H_2O_2 negatively regulates iNOS expression. We found that Nox4 mRNA was approximately 680 fold more abundant than Nox1 mRNA in quiescent VSMC. A 24 hour stimulation with IL-1β caused a 420% increase in Nox1 mRNA and an 85% decrease in Nox4 mRNA levels. Silencing of either Nox1 or Nox4 expression with adenoviral expression of siRNA hairpins prior to stimulation reduced IL-1β induced ROS production and increased iNOS expression. We then tested the role of p38MAPK since we found that the p38MAPK inhibitor SB203580 also potentiated both ERK activation and iNOS expression. However, the combination of catalase and SB203580 had synergistic effects on iNOS expression but not on ERK activation, indicating that p38MAPK inhibits iNOS expression through ERK –dependent and –independent pathways. All together, our results suggest that targeting intracellular oxidant producing enzymes in the injured vessel may increase the bioavailability of NO by increasing VSMC iNOS expression. (Supported by NIH CA89366, HL49426, and T32-HL-07194).

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THE ROLE OF p53 IN SILICA-INDUCED CARCINOGENICITY

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Although silica has been ranked by IARC as a human carcinogen in certain occupational settings since 1997, there is still some dispute as to its carcinogenicity. The association between silica and cancer has been the subject of studies since 1982, and the lack of an animal model for silica-induced carcinogenesis suggests to some that there is no causal relationship between silica exposure and cancer. Our hypothesis is that silica carcinogenicity follows the two-hit hypothesis in humans, so that only silica exposure in susceptible individuals, or those with a predisposing genetic alteration, would result in cancer formation. To determine this, we utilized three cell lines with variable expression of p53, a cell cycle control gene commonly mutated in human cancers. The goal of this study was to determine the effect of exposure to freshly fractured silica compared to aged silica using a normal human cell line (HBEAS), a human adenocarcinoma cell line (H460) with altered p53 expression, and a non-small cell lung cancer cell line (H1299) deficient in p53. Cell cycle parameters showed an increase in aneuploidy in the cancer cell lines following exposure to silica as compared to normal cells. Microarray analysis found variability in expression patterns of genes involved in apoptosis (BCL6) and cell cycle arrest (PCNA) as well as DNA damage repair genes (ERCC3, RAD23A). Gene expression analysis has highlighted differences related to p53 expression in the three cell lines following exposure to silica. These results suggest a potential role for p53 in silica-induced carcinogenicity. *The findings and conclusions in this abstract have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.*

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THE ROLE OF LOW-MOLECULAR-WEIGHT THIOLS IN T LYMPHOCYTE PROLIFERATION AND IL-2 SECRETION

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Glutathione (GSH) is an abundant intracellular tripeptide that has been implicated as an important regulator of T cell proliferation. The effect of pharmacological regulators of GSH and other thiols on murine T cell signaling, proliferation and intracellular thiol levels was examined. L-Buthionine-S,R-sulfoximine (BSO), an inhibitor of glutathione synthesis, markedly reduced GSH levels and blocked T cell proliferation without significant effect on cell viability. N-acetyl-cysteine (NAC) markedly enhanced T cell proliferation without affecting GSH levels. Co-treatment of T cells with NAC and BSO failed to restore GSH levels but completely restored the proliferative response. 2-mercaptoethanol (2-ME) and L-cysteine also reversed the BSO inhibition of T cell proliferation. Intracellular L-cysteine levels were reduced with BSO treatment and restored with co-treatment with NAC or L-cysteine. However, 2-ME completely reversed the BSO inhibition of proliferation without increasing intracellular cysteine levels. Therefore, neither GSH nor cysteine is singularly critical in limiting T cell proliferation. Reducing equivalents from free thiols were required since oxidation of the thiol moiety completely abolished the effect. Furthermore, BSO did not change the expression of surface activation markers, but effectively blocked IL-2 and IL-6 secretion. Importantly, exogenous IL-2 completely overcame BSO-induced block of T cell proliferation. These results demonstrate that T cell proliferation is regulated by thiol sensitive pathway involving IL-2.

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DECREASED PEROXIREDOXIN EXPRESSION IN MUTANT CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR (CFTR)-EXPRESSING AIRWAY EPITHELIAL CELLS

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Cystic fibrosis (CF) is caused by mutations in the gene encoding CFTR and results in loss of function of cAMP-regulated chloride channel conductance in epithelial cell plasma membranes. The most prevalent CFTR mutation, deltaF508, results in the