

**001****MOLECULAR BIOLOGY OF NICKEL CARCINOGENESIS****Max Costa, Ph.D., Konstantin Salnikow, Ph.D., Yong-Woo Lee, Ph.D., and Daoji Zhou, M.S., Department of Environmental Medicine and Kaplan Cancer Center, New York University Medical Center, New York, NY 10016, USA**

Certain carcinogenic particulate nickel compounds, such as crystalline nickel sulfide and nickel subsulfide display much higher activities than water-soluble nickel compounds because these particles are phagocytized by cells and produce very high concentrations of Ni(II) inside the cell in contrast to water-soluble nickel salts which do not readily enter cells. Carcinogenic nickel compounds are not highly mutagenic and do not induce a high degree of DNA damage. However, certain tumor suppressor and senescence genes are transcriptionally inactivated in nickel-transformed cells. Using a model system of transgenic cell lines to study the mechanism of transcriptional inactivation by nickel compounds, it was found that carcinogenic nickel compounds induce inactivation of transgenes placed near heterochromatin by a nickel-enhanced chromatin condensation which was subsequently fixed in an inherited state by DNA 5-cytosine hypermethylation. We will describe the mechanism by which nickel produces localized DNA hypermethylation addressing the question of whether carcinogenic nickel compounds induce only DNA hypermethylation near heterochromatic regions and whether they are also capable of inducing generalized cytosine hypo- or hypermethylation of genomic DNA. There are also examples of genes up-regulated during nickel-induced cell transformation, but the up-regulation of ATF transcription factor for example leads to the loss of thrombospondin expression (a tumor suppressor gene). ATF-1 transcription factor was found to be enhanced in both nickel-transformed cells and by acute nickel treatment but it negatively suppressed the expression of thrombospondin. A new gene specifically induced by water-soluble and insoluble nickel compounds will also be described. Although the function of this gene is unknown, its specificity to Ni(II) is remarkable.