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INSOLUBLE NICKEL COMPOUNDS CAUSE GENE AMPLIFICATION AND GENE SILENCING, DISRUPTING 15 SIGNAL TRANSDUCTION PATHWAYS, LEADING TO DIFFERENTIAL EXPRESSION OF 144 GENES AND MORPHOLOGICAL, A. I., AND NEOPLASTIC TRANSFORMATION OF C3H/10T1/2 MOUSE EMBRYO CELLS

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Abstract: Workers who inhaled Ni sulfidic ore dusts and smoked cigarettes in Ni refineries had an increased incidence of nasal/lung cancers. Inhalation of nickel subsulfide (Ni_2S_3)/green NiO induced respiratory cancer in rats. Ni_2S_3 and green/black NiOs were phagocytosed into and induced chromosome aberrations and morphological, A. I., and neoplastic transformation in C3H/10T1/2 (10T1/2) cells. mRNA differential display showed 144 genes were differentially expressed between non-transformed vs. Ni^{+2} ion-transformed (Tx) and 3-methylcholanthrene (MCA)-Tx 10T1/2 cell lines. In Ni/MCA-Tx cell lines, 6 driver genes were over-expressed, causing over-expression of 52 more genes. Nine tumor suppressor-like genes were under-expressed/not expressed in Ni-/MCA-Tx cell lines, causing under-expression/no expression of an additional 77 genes. This caused disruption of 15 signal transduction pathways. Among the differentially expressed genes/disrupted pathways, Ni^{+2} Tx/MCA-Tx cell lines had 1) Ect-2 gene amplification, higher steady-state levels of ect-2 mRNA and protein, and consequently higher levels/aggregation of microtubules (MTs) and altered cell shapes. 2) β-centaurin-2 mRNA was detected in 10T1/2 cells but not in Ni^{+2} or MCA-Tx 10T1/2 cell lines. While microfilaments (MFs) were expressed in 10T1/2 cells, there were higher levels of/aggregation of MFs in Ni-/MCA-Tx cell lines, also altering shapes of Tx cells. Tx cells also had 3) higher levels of calnexin mRNA/protein. Non-Tx cells had Vitamin D interacting protein (DRIP80) gene mRNA; 4) Tx cell lines had none detectable. Events #3 and #4 altered distributions of Ca^{+2} ions in Tx cell lines. In non-Tx cells at low density, there was a high concentrations of nuclear Ca^{+2} ions, lower amounts of cytoplasmic Ca^{+2} ions (State I). In non-Tx cells at high density, there were less nuclear Ca^{+2} ions, most cytoplasmic (State II). In 6 NiO- or MCA-Tx cell lines, Ca^{+2} ions were pre-dominantly cytoplasmic (State II). We conclude Ni^{+2} ions and MCA induced mutations or amplifications in 6 primary target driver genes, leading to over-expression of 52 additional genes, and silenced 9 other target genes, leading to down-regulation of expression of 77 additional genes. Together, the resultant disruption of 15 signal transduction pathways led to over-expression of 52 genes and down-regulation of expression of 77 genes, resulting in differential expression of 144 genes between non-Tx and Ni/MCA-Tx cell lines. In addition, Ni^{+2} ions amplified the ect-2 gene, leading to higher steady-state levels of MTs, and silenced the β-centaurin-2 gene, leading to higher steady levels of MFs, changing cell shape/gene expression. Ni^{+2} ions increased expression of the calnexin gene and silenced the DRIP80 gene in Tx cell lines, altering distributions of Ca^{+2} ions Tx 10T1/2 cell lines. These Ni ion-induced events caused disruption of 15 signal transduction pathways and differential expression of 144 genes, leading to induction/maintenance of Tx phenotypes in Ni^{+2} ion-Tx/MCA-Tx cell lines.

Key Words: Carc. nickel compounds, 10T1/2 cells, differential display, ect2, calnexin, DRIP80.

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