High zinc status in lung cells slows growth and induces DNA damage-induced gene expression

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Researchers at the University of Maryland at College Park have discovered that Normal Human Bronchial Epithelial (NHBE) cells cultured in medium with elevated zinc level, at the high end of plasma zinc attainable by oral supplementation, demonstrated inhibition of cell growth, up-regulation of growth arrest and DNA damage-induced gene (Gadd45) mRNA and protein expression, and blockage of G2/M cell cycle progression.

The research, published in the March 08 issue of the *Experimental Biology and Medicine*, demonstrated that the essential nutrient zinc, at elevated physiologic level, is capable of inducing stress responsive genes in the NHBE cells. NHBE cells function as a protective airway barrier and are representative of the cell population during lung tissue transformation and are considered to be progenitor cells for human bronchial cancer.

Gadd45 is ubiquitously expressed in response to genotoxic agents, and is involved in many biological processes related to the maintenance of genomic stability and apoptosis. Over expression of Gadd45 was found to induce G2/M cell cycle arrest. The importance of Gadd45 in G2/M regulation was further supported by findings of the inability of cells from Gadd45 knockout mice to arrest at the G2/M phase after exposure to UV radiation.

In addition, a functional association between stress-activated mitogen-activated protein kinase p38 pathway and Gadd45 in response to environmental stresses has been established in past studies. Moreover, the dependence of Gadd45 induction for the normal function of the tumor suppressor gene p53, which plays an important role in the maintenance of genomic fidelity by controlling cell cycle checkpoints and apoptotic processes following cell exposure to genotoxic stress, is well established. Furthermore, in response to DNA damage, Gadd45 was found to contribute to the stability of p53.

The research team, led by David K. Y. Lei, a professor of Nutrition, and Rita S. M. Shih, a recent doctoral graduate, designed the study to determine the influence of zinc status on Gadd45 expression and cell cycle progression in NHBE cells, and to decipher the molecular mechanism(s) exerted by the suppression of Gadd45 expression on cell growth and cell cycle progression in this normal human cell type.

“Inhibition of cell growth, up-regulation of Gadd45 mRNA and protein expression, and blockage of G2/M cell cycle progression were observed in NHBE cells cultured in high zinc medium - the zinc supplemented (ZS) cells ” said Lei. “ The siRNA-mediated knocking down of Gadd45 was found to relieve G2/M blockage in ZS cells, which indicated that the blockage was Gadd45 dependent. Moreover, the enhanced phosphorylation of p38 and p53 (ser15) observed in ZS cells was normalized after suppression of Gadd45 by siRNA, implicating that the enhanced phosphorylation of these proteins was Gadd45 dependent”. Thus, the researchers demonstrated for the first time that an elevated zinc status modulated the p53 and p38 signal transduction pathways to produce a delay at G2/M during cell cycle progression in NHBE cells.

Lei says “ the use of normal human cell types to evaluate the influence of nutrients and bioactive plant materials on the expression of stress responsive genes and cell cycle progression is a rapid and valuable

approach to identify potential targets and provide mechanistic data. However, the applicability of these in vitro mechanistic data would require confirmation by detailed in vivo studies”

Source: Society for Experimental Biology and Medicine