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Immunoexpression and localization of heme-oxygenase-1 and MIF in lung exposed to asbestos-like fibers: An *in vivo* study

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Fluoro-edenite (FE) fibers are similar to other amphibole asbestos fibers. These fibers stimulate aberrant host cell proliferation and induce the release of cytokines, growth factors, reactive oxygen and nitrite species, which result in DNA damage. Previous studies demonstrated that FE lead to chronic inflammation and carcinogenesis in lung tissue shown after its inhalation. However, the biological and molecular mechanisms that are linked to cancer development following mineral fibre exposure have not been fully investigated. Heme-oxygenase-1 (HO-1) protects lung tissue against oxidative stress and Macrophage migration Inhibitory Factor (MIF) is a potent upstream regulator of the immune system. In the present study, the immunoexpression of HO-1 and MIF was investigated in an *in vivo* sheep model, and lung tissue was exposed to asbestos-like fibers. HO-1 and MIF overexpression was detected in alveolar interstitium, notably in close proximity to FE fibers. The data suggest an involvement of HO-1 and MIF in the pathogenesis of the lung diseases induced by mineral fibres. The expression of HO-1 could be associated with oxidative lung injury caused by exposure to FE instead of MIF that could influence different molecular processes essential for the maintenance of cellular homeostasis. FE may influence the incidence and/or clinical manifestations of chronic lung diseases. In conclusion, the involvement of HO-1 and MIF in the mechanisms of cellular and molecular toxicity and of cellular response may be useful in order to identify possible preventive interventions in FE-associated pathogenesis.

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MMP-9 overexpression as a result of MMP-9 intragenic hypermethylation

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Inflammation is a physiological response of tissues to several stimuli, such as pathogens, irritants and/or damaged cells. Conversely, it is well documented that the inflammation compartment is critically involved in tumor development and progression. Cancer cells release several inflammation factors, such as matrix metalloproteinase-9 (MMP-9), which may modulate inflammation effectors as well as enhance their proliferation. MMP-9 is overexpressed in several cancer types by different mechanisms that led to the activation of Activator Protein-1/A Polyoma Enhancer Binding Protein-3 factor (AP-1/PEA3) and NF-κB. Genetic modification within the promoter region may increase MMP-9 expression. C-1562T polymorphism and di-nucleotide CA repeats in the AP-1 regulatory sequence were more frequent. Furthermore, the role of several miRNAs and promoter methylation was described in the modulation of MMP-9 expression. Most recently, it was demonstrated that the intragenic methylation is positively correlated with the expression of the same modulating different mechanisms, such as transcriptional elongation, intragenic activation (enhancer) and alternative splicing. To date, the role of intragenic methylation in the modulation of MMP-9 gene expression has not been yet fully clarified. In order to better understand the relationship between the DNA intragenic methylation of MMP-9 gene and its expression melanoma was used as a tumor model. Computational analysis performed in melanoma samples showed a positive correlation between the hypermethylation of an intragenic region of MMP-9 gene (CpG-2 hotspot) and higher MMP-9 transcript levels. *In vitro* experiments revealed that the A375 melanoma cell line with highest levels of MMP-9 expression indicated hypermethylation of the CpG-2 hotspot region, while lower methylation levels were observed in the A2058, M14 and MEWO cell lines that showed lower MMP-9 levels. These results may provide further insights on the mechanisms of MMP-9 overexpression in cancer and help to define new strategies to reverse the MMP-9-mediated inflammatory activation.

Key words: MMP-9, intragenic methylation, cancer, melanoma

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Immunotoxicity of pesticides: Potential health effects on exposed subjects

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The widespread use of pesticides has contributed to an increase in the agricultural production in the last decades. Along with these benefits, pesticides have further caused several disadvantages, such as toxicity issues. Occupational exposure to pesticides depends on a variety of variables namely, the worker's task, the correct use of personal protective equipment and the weather. Pesticides can also accumulate in the soil and contaminate groundwater and food thus making them partly responsible for environmental pollution. Evidence suggests the effects of pesticides on the immune system. Cytokines humoral levels can be altered by chronic exposure to these substances and this could, in turn, be a cause of detrimental health effects. Immune dysregulation is a characteristic of various diseases, and the understanding of the mechanisms underlying these alterations could clarify the role of pesticide exposure in the development of certain chronic diseases. One of the major issues in the epidemiological studies on pesticides is the assessment of exposure, which is often complicated by many variables and by the lack of reliable biomarkers. The use of tools such as job exposure matrices could aid the production of well-designed and accurate studies, which are indispensable for the achievement of reliable results.

Key words: pesticides, occupational exposure, chronic diseases, immunotoxicity

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Cytokine patterns following occupational exposure to wood dust

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Occupational exposure to wood dust has been shown to cause several respiratory disorders, such as allergic rhinitis, chronic bronchitis, asthma, sino-nasal adenocarcinoma and impairment of lung function. Wood dust has been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer. It is essential to identify better ways of prevention, early diagnosis and treatment of wood dust-related diseases in order to reduce the risk of cancer. However, the mechanisms underlying the inflammatory responses of the airways following wood dust exposure are poorly defined. The immunotoxicity of wood dust was assessed in 35 occupationally exposed joiners and 35 non-exposed controls by comparison of the serum levels of IL-1β, IL-2p70, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, TNF-β and INF-γ. Joiners were occupationally exposed mainly to hard wood dust. The exposure of each subject was assessed by environmental monitoring with personal samplers. Exposed workers indicated neither clinical signs of immunosuppression or alterations in total leukocytes nor leukocyte subpopulations. The airway mucosa showed no significant alteration. The subjects that were exposed to wood dust pro-inflammatory cytokines were significantly higher than the controls. The data highlighted that the exposure to wood dusts can influence the development of the inflammatory process in the airways by modulating the expression of macrophage-derived cytokines and chemokines.