OCCUPATIONAL AND LIVING ENVIRONMENT AND THE IMMUNE SYSTEM

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SUPPRESSIVE EFFECT OF ASBESTOS ON CYTOTOXICITY OF HUMAN NK CELLS

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Asbestos, a naturally occurring fibrous mineral, causes malignant mesothelioma (MM). However, it takes a very long time to develop MM, which suggests that effects other than tumorigenicity of asbestos might contribute to the development of MM, and one of the possible targets is anti-tumor immunity. Therefore, we examined the effect of asbestos exposure on human natural killer (NK) cells using the cell line of YT-A1, peripheral blood mononuclear cells (PBMCs) cultures and specimens from patients with MM. In particular, we focused on expression of NK cell-activating receptors, including NKG2D, 2B4 and NKp46. Analysis of the YT-CB5 subline of YT-A1, cultured with CB for over 5 months, showed a decrease in cytotoxicity with low expressions of NKG2D and 2B4, although there were no decreases after about one month. YT-CB5 showed decreases in phosphorylation of extracellular signal-regulated kinase (ERK) and degranulation stimulated by antibodies to NKG2D. Peripheral blood (PB-) NK cells from MM patients also showed decreased cytotoxicity compared with healthy volunteers (HV), and was accompanied with low expression of NKp46 unlike YT-CB5. PBMCs cultured with CB resulted in decreased expression of NKp46 on NK cells, although this did not occur when using glass wool, an asbestos substitute. These results indicate that asbestos has the potential to suppress cytotoxicity of NK cells. In particular, it is noteworthy that both NK cells from MM patients and those from a culture of PBMCs derived from HVs with asbestos showed the same characteristic of decreased cytotoxicity with low expression of NKp46.
Silicosis patients suffer from pulmonary fibrosis caused by silica inhalation, as well as autoimmune diseases known as the adjuvant effects of silica. Caplan syndrome complicated with rheumatoid arthritis (RA) is well known epidemiologically, and the incidence of complicated systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and antineutrophilic cytoplasmic antibody (ANCA)-related nephritis have been reported frequently in silicosis patients. To explore the detailed mechanisms of silica-induced dysregulation of autoimmunity, we had focused on Fas/CD95 and Fas-mediated apoptosis because Fas is one of the most important molecules regarding apoptosis of lymphocytes and its alteration makes some T cells survive longer. Additionally, if the long-survived T cells include the self-recognizing T-cell clones, it is easily thought that autoimmune diseases will appear in this situation. Furthermore, regulatory T cells (Treg) showing CD4+25+ and forkhead box P3 (FoxP3)-positive have been a central player in regulating activation of self- and foreign-antigen recognizing T cells, and it has been reported that activation of Treg causes its higher expression of Fas/CD95. Thus, in this review, we introduce the alteration of Fas and related molecules as found in silicosis and also present the Treg function of the CD4+25+ fraction in peripheral blood mononuclear cells derived from silicosis patients.
VALIDATION STUDY OF THE NEW CRITERIA FOR SENSITIZER USING GERMAN SENSITIZERS OF DEUTSCHEN FORSCHUNGSGEMEINSCHAFT (DFG)

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The globally harmonized system of classification and labeling of chemicals (GHS) was recommended by United Nations (UN) and became available in 2008 all over the world. The classification criteria for skin and airway sensitizers in GHS include evidences from animal studies, for example, OECD Guideline 406 (guinea pig maximization test, GPMT and Buhler guinea pig test) and Guideline 429 (local lymph node assay, LLNA). According to Deutschen Forschungsgemeinschaft (DFG) in Germany and European Chemical Bureau (ECB), the criteria for sensitizers also include evidences from validated animal studies. At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. In Japan, the criteria from the Japan Society for Occupational Health (JSOH) for sensitizers do not include evidences from animal studies. We revised the criteria for sensitizers of JSOH and adopted evidences of animal studies. We organized the research group for sensitizer in 2005 and reviewed the criteria of Germany, EU, GHS and so on (19 experts). The meetings were held twelve times and made the revised criteria for sensitizer which adopted animal studies. We tried to validate the criteria using 28 German sensitizers of DFG, which were not sensitizers in JSOH. We could correctly classify 24 sensitizers by our revised criteria, however, four sensitizers could not be classified at first. Therefore, we visited the secretariat of the committee of DFG in Freising, Germany to investigate the evidenced papers of these four sensitizers in October, 2008. We could find out the evidenced papers of two, however, two sensitizers could not be classified at last. We could correctly classify 24 out of 26 sensitizers. We concluded that our revised criteria were appropriate and that this validation study was successful.
IN VIVO TOXICITY OF NANO-ALUMINA ON MICE NEUROBEHAVIORAL PROFILES AND THE POTENTIAL MECHANISMS

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The rapid development and expanding applications of nanotechnology have led to enhanced exposure of human body to nanoparticles. It is, therefore, necessary to address the safety issue via rigorous toxicological evaluation and to understand the underlying interaction mechanism. However, only a few studies to date have evaluated the safety of nano-sized materials and their potential adverse effects on biological systems. In this study, we sought to investigate the potential toxicity of aluminum oxide (alumina) nanoparticles in ICR strained mice, focusing on potential neurobehavioral defects and the possible mechanisms. The results demonstrated that nano-alumina impaired neurobehavioral functions, including lengthened escape latency, shorter time spent in the target quadrant and reductions in the number of platform crossing. In addition, it induced cell necrosis and apoptosis, which were likely mediated by the reduction of MMP and ROS, and the induction of the caspase-3 gene. Our results implicated that mitochondrial impairment plays a key role in neurotoxicity of nano-alumina, sequent oxidative damage and neural cell loss, especially necrosis, may be direct causes for the neurobehavioral defects. Collectively, nano-alumina presents a strong pro-cell death effect on ICR mice in vivo, suggesting that nano-alumina may serve as an inducer for neural toxicology. Findings in the present study indicating that surface chemical characteristics and nanoscale sizes of nano-alumina could co-contribute significantly to neurotoxicity. The impaired neurobehavioral patterns indicate that nano-alumina particles are more toxic to the cerebrum than those of nano-carbon with the same nanoparticle size and micro-alumina with the same surface chemical characteristics.
Clinical evidences and epidemiological studies show that allergic pathologies of the respiratory tract are increasing in the world areas with high pollution impact, demonstrating how many polluting substances favor both allergic sensitization and the bronchial inflammatory changes characteristic of asthma. It has been shown that asthma, as many other diseases, is a complex interaction between genetic predisposition and environmental stimuli that results in clinical expression of various phenotypes of asthma: allergic, “intrinsic” etc. Many pollutants have such a potential. Diesel exhaust particles (DEP) can favor allergic sensitization, induce acute asthma attacks and increase bronchial reactivity, acting both on allergen, on bronchial mucosa and on immune cells. In fact, DEP can favor B lymphocytes to shift to a production of IgE and T cells to produce Th2 cytokines. Asthma can be also induced by high exposure to many other substances as NO2 and first of all ozone (O3): strong oxidizing substance that is synthesized, in absence of ventilation, by photochemical reaction due to the combination of ultraviolet sun radiation on exhaust gases as NO2 and hydrocarbons. Ozone is abundant in cities with minimal concentration in the morning gradually increasing during the day until maximal levels in the afternoon and then decreasing during the night. Epidemiological studies show that the number of access to hospital for acute asthma and even the use of bronchodilator by asthmatics increase during the high level periods when Ozone constitutes almost 90% of the total oxidants in the environment. Particulate matter of very small diameter has a crucial role in favoring asthma attacks, and smaller the substance deeper the penetration in the bronchial tree, with an inflammatory reaction in the peripheral bronchial mucosa characterized by increased vessel permeability, mucosal edema, inflammatory mediator production by damaged epithelium and inflammatory cells that determines acutely a high narrowing of the bronchial lumen and in a long period favor airways remodeling and a rapid decline of respiratory function.
Humans have enjoyed forest environments for ages because of the quiet atmosphere, beautiful scenery, mild climate, and fresh, clean air. In the present study, we found that visiting forest parks, but not a city, enhanced human natural killer (NK) activity, increased anti-cancer proteins, such as perforin, granzymes A and B, and granulysin in NK cells, and reduced the level of stress hormones in both male and female subjects. Moreover, this effect lasted for more than 30 days after the trips, suggesting that visiting a forest park once a month would enable individuals to maintain a higher level of NK activity. Phytoncides released from trees and the decreased production of stress hormones may partially contribute to the increased NK activity. Because NK cells can kill tumor cells by releasing anti-cancer proteins, and visiting forest parks increases NK activity and the amount of anti-cancer proteins; therefore, the above findings suggest that visiting forest parks may have a preventive effect on cancer generation and progression.
Probiotics have been defined as live bacteria beneficial to the host when administered in adequate amounts. To evaluate the effect of probiotics on the prevention of carcinogenesis, Lactobacillus casei Shirota (LcS) was given to the patients who had undergone the resection of superficial bladder cancer, and administration of LcS significantly reduced the recurrence rate of bladder cancer. When LcS was given to the patients whose colonic polyps were surgically removed, the recurrence of colorectal cancer with moderate or severe atypia was suppressed. To assess the putative actions of LcS on innate immune responses, we examined the effect of LcS on natural killer (NK) cell activity in humans. Daily ingestion of fermented milk containing LcS restored NK cell activity in healthy subjects with low NK cell activity as well as human T lymphotropic virus (HTLV)-1-associated myelopathy patients. When peripheral blood mononuclear cells from healthy humans were cultured in the presence of heat-killed LcS, NK cell activity was augmented, which were partly mediated by monocyte-derived interleukin (IL)-12. These findings suggest that LcS may help the reinforcement of our defense system against cancer by modulating innate immune functions.
Several reports highlight the relationship between blood NK cytotoxic activity and lifestyle. Easy lifestyle, including physical activity, healthy dietary habits as well as good mental health are characterized by an efficient immune response. Lifestyle is related to the type of occupational activity since work has a central part in life either as a source of income or contributing to represent the social identity. Not only occupational stress, but also job loss or insecurity are thus considered serious stressful situations, inducing emotional disorders which may affect both neuroendocrine and immune systems; reduced reactivity to mitogens and/or decreased blood NK cytotoxic activity was reported in unemployed workers or in those with a high perception of job insecurity and/or job stress. Although genetic factors have a key role in the pathogenesis of autoimmune disorders, occupational stress (as in night shifts) was reported associated to an increased incidence of autoimmune disorders. Monitoring blood NK response may thus be included in the health programs as an indirect index of stressful job and/or poor lifestyle.
T REGULATORY CELLS IN ALLERGY

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The progressive understanding of the nature and mechanisms of T regulatory (Treg) cells in the last decade has changed the concept of immune tolerance, that is no longer considered as a mere lack of immune reactivity but as a finely regulated process that requires specific activity of cells, adhesion and secreted molecules. Tregs play a key role in maintenance of self-tolerance and induction of tolerance against ubiquitous innocuous non-self antigens, so preventing the onset of autoimmune diseases and allergies. This review will focus on the Treg response in allergy that is characterized by a down-regulation of allergen specific T cell proliferation and inhibition of both Th1 and Th2 cytokines production. Hence, Treg cells suppress allergen-specific Th1 and Th2 cell responses playing an important role in the physiological immune response to allergens. Further, Treg cells are able to suppress IgE production by B lymphocytes and directly or indirectly inhibit the activity of allergic inflammation effector cells, namely eosinophils, basophils and mastcells. Finally, increasing evidence suggests that Treg cells are also implicated in chronicity development of inflammatory diseases. This appears to happen through a fine interaction they entertain with resident tissue cells and has been particularly highlighted in the study of airways remodeling in asthma. The understanding of the mechanisms underlying allergen tolerance has brought new interest in the development of new allergy treatment, able to target Treg cells, both in allergy prevention and in the therapy of established allergy.
The interaction between NPs and immune system factors has been demonstrated. However, the data available are limited. Among all traits, i.e. hydrophilicity, lipophilicity, catalytic activity, composition, electronic structure, capacity to bind or coat surface species and solubility, dimension, and consequently surface area, seems to be the main factors that contribute to the interactions of NPs with biological tissues and immune system in particular. Certain NPs accumulate to regional lymph nodes where they can be taken up and processed by dendritic cells, interact with self-proteins and, hence, modify their antigenicity and elicit altered immune responses and even autoimmunity. Other NPs may induce allergic sensitization, i.e. allergic contact dermatitis to Pd. In vitro studies demonstrated that NPs can modulate cytokine production toward Th1 (Pl, Pd, Ni, Co) or Th2 (Ti, mw and sw Carbon) production patterns. Some NPs have been linked to allergic sensitization, however, it is unlikely that NPs can act as a hapten inducing a specific IgE production, more likely they can act as adjuvant and induce a specific pattern of cytokines, antibody and cells that favor allergic sensitization to environmental allergens. Furthermore, NPs demonstrated pro-inflammatory effects in the lung in experimental animal with increased expression on IL-1β, MIP-1α, MCP-1, MIP-2, keratinocyte chemoattractant, TARC, GM-CSF, MIP-1α and activation of the stress-activated MAPKs p38 and JNKs. All considered, the available data suggest that through the elicitation of an oxidative stress mechanism, engineered NPs may contribute to pro-inflammatory disease processes in the lung, particularly allergy.
Contact dermatitis (CD) is one of the most prevalent work-related diseases, often resulting in an impaired quality of life and a loss of work ability. CD can be divided into allergic (ACD) and irritant contact dermatitis (ICD). Although skin exposure is a prerequisite for the development of CD, there is substantial evidence that under similar exposure conditions some individuals are more prone to acquiring CD than others. Recently, a number of studies have investigated the link between individual susceptibility to CD and variations in the genes that are involved in the maintenance of the skin barrier, inflammatory response and biotransformation. The most important development has been the discovery that loss-of-function mutations in the gene encoding the epidermal protein filaggrin increase the risk for ICD and for nickel sensitization and nickel ACD, emphasizing the importance of the skin barrier in the pathophysiology of CD. Among the inflammatory genes, a TNFA-308 G/A polymorphism has been shown to associate with susceptibility to both ICD and ACD. In studies specifically for ACD, polymorphisms in genes encoding N-acetyltransferases were shown to modify the risk for sensitization to p-phenylenediamine. Although recent studies have identified a number of biologically plausible susceptibility genes, the predictive value of these genetic markers is too low for the reasonable selection of susceptible individuals in occupational health practice. Additional studies in larger cohorts with well-defined disease phenotypes and appropriate control population are needed to confirm and extend our knowledge of the impact of genetic variations on the susceptibility to occupational CD.
ESTABLISHMENT OF A POISONED ANIMAL MODEL OF TOXIC ENCEPHALOPATHY INDUCED BY 1,2-DICHLOROETHANE

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1,2-dichloroethane (1,2-DCE) is toxic, especially by inhalation due to its high vapour pressure. Inhalation of concentrated 1,2-DCE vapor can induce effects on the human nervous system, even encephalopathy. However, 1,2-DCE toxic encephalopathy has seldom been reported, and no adequate data were available to evaluate the encephalopathy of 1,2-DCE in experimental animals. The aim of the present study was to establish a toxic experimental animal model induced by 1,2-DCE. Dose effect and time effect of 1,2-DCE on the nervous system were detected. The rats were treated by 1,2-DCE at various concentrations of 0, 2.5, 5.0, 10.0 g/m³ for 6 h and treatment of rats at 10.0 g/m³ for 0, 3, 6, and 12 h. Morphology of brain tissue was observed by HE staining and TEM under light and electron microscope, besides water contents in the cortex and medulla of rats were analyzed. The results indicated that 1,2-DCE induced abnormal histopathology, and significantly higher water content were confirmed in the cerebral cortex of toxic animal model in a dose- and time-dependent manner. To declare that 1,2-DCE could induce toxic encephalopathy with a pathological feature of cerebral edema is very important for the medical rescue in the urgent toxic accidents.
PERITONEAL MESOTHELIOMA: DESCRIPTION OF A CASE AND REVIEW OF LITERATURE

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PREVENTION OF OCCUPATIONAL DERMATITIS

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Occupational dermatitis is among the most frequent occupational diseases. Dermal exposure risk affects many professional categories such as healthcare workers, hairdressers, bakers, cleaning and kitchen employees. The economical burden of occupational dermatitis (OD) is huge (> 5 billion € year in Europe), comprising direct costs (treatment, compensation) as well as indirect costs due to sick leave and lack of productivity. A scientifically based preventive program consisting of skin protection during work, cleaning and skin care after work has generally been recommended to prevent occupational contact dermatitis. However the rate of reported occupational skin diseases seems unchanged in the recent years. In cases of impaired skin condition the secondary prevention (i.e. therapeutic treatment by dermatologists and health-educational intervention seminars) is fundamental. For cases of occupational dermatoses in which these outpatient prevention measures are not successful, interdisciplinary inpatient rehabilitation measures have been developed (tertiary individual prevention). In the past years, various pilot-concepts to improve occupational dermatitis prevention have been successfully put into practice focussing on interdisciplinary (dermatological/educational) skin protection training programmes for high-risk professions. Currently a multi-step intervention approach is implemented which is aiming at offering quick preventive help at all levels of severity of occupational contact dermatitis. Recent data reveals that there are reliable evidence-based options for multidisciplinary prevention and patient management of occupational dermatitis using a combined approach by a network of clinics, practices and statutory social insurance bodies. At this stage, it seemed reasonable to form a European joint initiative for skin prevention. Recently a European network of preventive dermatology (European Initiative for the Prevention of Occupational Skin Diseases –EPOS) has been organized based on the German experience in the specific field.