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The immune system-A sensitive target for environmental stress

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The biography of an individual is determined by the genetic background or the constitutional factors on one hand and by the environment or the stress conditions on the other hand. The genetic background of an individual does not finally determine the phenotypic expression of structure and function of organs or organ systems such as the musculo-skelettal system, the vascular system, the respiratory system the nervous system, the endocrine system, or the immune system structure and function of all the systems can be modified by environmental stress load.

Individual health is the result of an equilibrium between the total body stress load of an individual and the stress tolerance of the exposed cells, tissues and organs. If stress load and stress tolerance are balanced in an individual a healthy state is very likely under imbalanced conditions a large number of disorders can occur.

In order to balance stress load and stress tolerance and by that to prevent disorders, two different strategies are available.

（1）passive avoidance of peak stress load

（2）active training of the organ systems.

For maintenance of good health over many decades a combination of both strategies seems to be very successful. For training purposes mild stress conditions are required in order to expand the structural and functional capacity of the organ systems（eustress）. Peak stress exposure, in contrast, to which structural and functional adaptation is not possible will always cause disorder, injury and damage（disstress）.

The number of different stressors is very large and it is very rarely that an individual is exposed to an isolated single stress factor such as:

（1）mechanical trauma

（2）thermal injury

（3）acoustic overload

（4）chemical toxicity

（5）ionizing or non-ionizing irradiation

（6）psycho-social problems

Despite of the multiplicity of different stress conditions to which cells and tissues can be exposed there are very few basic mechanisms by which the secondary tissue damage is mediated. Stress-mediated production and release of activated oxygen species such as superoxide, peroxide, hydroxyl radical, singlet oxygen is a very significant process connected to ionic disturbances and changes in protein function such as enzyme activity or receptor specificity.

Highly sensitive molecular targets of the toxic metabolites of molecular oxygen are unsaturated phospholipids and glycolipids of biomembranes or of the circulating lipoproteins（LDL）, but also structural proteins such as collagen or elastin, glycoproteins, carbohydrates and nucleic acids are targets for the stress-induced oxidants and radicals.

Oxidative alterations in essential biomolecules such as lipids, proteins, carbohydrates or nucleic acids have consequences on the more complex cellular level as well. The oxidative attack against a single biomolecule is a microtrauma which is easily compensated or repaired but under peak stress conditions extremely large numbers of reactive oxygen species are produced the sum of which can cause secondary cell and tissue damage if the antioxidative defense systems are not optimally trained and activated.

This holds, particularly, true for highly sensitive cells and tissues such as cells of the immune system. These are characterized by extreme sensitivity on the one hand and at the same time high efficacy of the cellular and humoral responses. In addition to very high sensitivity at the recognition sites and high efficacy at the effector sites the immune system is strictly regulated by intrinsic mechanisms but also by mechanisms

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involving other integrated gystems such as the vascular system, the endocrine system or the nervous system. The immune system as a whole as well as single cellular or humoral components are therefore sensitive targets under a variety of stress conditions and this, in turn, can cause a number of specific pathologies.

There is a continuously growing body of evidence that exogenous stress factors are capable of modulating the immune responses of the exposed individuals. Due to the fact that the immune system is a self regulated system designed to react to external stress conditions the stress-induced alterations in the immunocompetence cannot simply be deseribed as immunotoxic efects. Careful evaluation in required whether or not the stress-induced changes in the immunocompetence are part of the self-regulated functional reserve of the immune system. Also, this evaluation has to consider not only aspeets of individual response to stress but also evolutionary concequences for the species and the whole biosphere.

The human health implications of stress exposure with regard to immunocompetence as the affected function have to be differentiated into those connected to an impaired, depressed, deficient functional capacity and those in which overstimulation or loss of self-tolerance do cause the pathologies. From a vast number of studies it is clear that stress-induced impairment of immune functions is connected to an increased risk of infectlons and mallgnancles whereas stress-induced overstumulation enhances the incidence of allergic reactions and autoimmune disorders.

Sensitivity and specificity of the stress induced responess of the immune system depend very much upon the basic cell-biological mechanisms by which the stressors do interact with the immune cells. From the fact that the immune response involves a large number of basic biological functions such as proliferation, differentiation, receptor expression, ligand-receptor interaction, membrane transport, protein biosynthesis, adhesion, chemotaxis, phagocytosis, killing etc it is clear that many physical, chemical, biological and other factors can interact.

Host defense is organized in different functional components such as specific and sensitive recognition causing adaptive responses of the cells involved the principal features of which are antigenic specificity, memory, as well as the capability to expand the capacity on demand. Antigenic specificity is connected to the ability to distinguish foreign, and potentially hazardous, antigens from self-information expressed undor normal conditions in the organism. Immunological research of the last decades has revealed that with regard to antigenic specificity the immune cells are clonally distributed each clone expressing a unique membrane receptor for the antigen.

On exposure to antigens the cell clones expressing the complementary receptors on the membrane respond selectively. Proliferation of the specific clones is induced thus expanding the number and capacity of competent immuno cells a proportion of which undergoes differentiation into effector cells directly or indirectly capable of eliminating the antigen. The rest of the cell pool are memory cells reacting more quickly and profoundly after a second exposure to the same antigen.

Clonal distribution is only one biological principle upon which the extremely complex adaptive reponse of the immune system to antigens is based. The functional heterogeneity of the lymphocytes such as the B-cells or the T-cells is another characteristic property. Following activation by antigen exposure B-cells differentiate into plama cells with the consequence of a massive production and release of specific antibody molecules designed to interact with extracellular antigens.

Antigen-exposed T cells can differentiate into effector T cells capable of recognising and killing infected or transformed cells and of releasing soluble mediators such as cytokines by which the cellular immune response is up-or down-regulated.

From the extreme complexity of the molecular and cellular events comprising the controlled immune response and host defense to foreign antigens it is clear that like in other finely-tuned biological systems the functional integrity of the immune response is highly sensitive to disruption by a large number of stress conditions. Relatively subtle changes in the delicately balanced functional network of the immune system can cause a severe loss of homeostatic regulation with potentially serious clinical consequences as it is observed in many hereditary or acquired immune disorders.

External stress conditions such as single nutrient malnutrition

can cause severe imbalaces in the immune response. As an example, zinc deficieny is connected to atrophy of the lymphoid tissue, to reduced antibody production and many other changes in immune functions due to the fact that this element is an essential cofactors for more than 70 enzymes involved in cell proliferation, cell differentiation, biosynthesis of biomacromolecules etc. Also, protein malnutrition or loss of protein by hypercatabolism, enteropathy or renal disorders is known to cause acquired immune disorders. Mechanical, thermal or radiological trauma also is capable of changing the normal immune response. Infection by certain viruses is an additional condition under which imbalances in the immune functions are frequently observed.
Finally chemical exposure such as anesthesia, drug abuse or exposure to environmental or occupational chemicals is a significant influential factor in many immune disorders.

The field of immunotoxicology has attracted considerable attention during the last decade and the list of chemicals reported to impair immune functions is continuously growing. Selective and apecific immunotoxicity of a chemical, however, has not been documented in the literature although the existance of immunotoxins has been portulated. It is very likely that immunotoxic effects of chemicals are a consequence of chemical interaction with fundamental biological functions of the cells involved in the immuno response.
Among the studies on immunotoxic effects of polyhalogenated hydrocarbons the impaired differentiation of T-cells to cytotoxic effector cells by TCDD at doses of 1 ng/kg is a very significant fact. Another finding after exposure to polyhalogenated hydrocorbons is thymic atrophy. Polychlorinated hiohenyls have also been reported to affect lymphocyte function. Some of the data were measured in rats or mice but also in man immune functions have been identified as the target for chemical toxicity.
Immunosuppressive or immunotoxic effects have also been detected as a consequence of heavy metal exposure although detailed studies on the immunotoxic mechanisms are lacking.

In addition to the impairment of immune functions by toxic interaction chemical stress can also sensitize immune functions thus enhancing the risk of allergic reactions and autoimmune disorders. Almost every tissue or organ can be become the target for autoimmune attack and the catalog of clinical manifestations is long. A potential mechanism by which chemicals can cause autoimmune disorders is chemical modification of self antigens which subsequently stimulate T-helper cell mediated production of autoantibodies by B-cells and plasma cells. Many of the clinical manifestations are positively of negatively connected to certain HLA alleles. In chemically induced autoimmune disorders, however, the mechanistic details are very often not elucidated although some progress has been made in the last few years.

From the point of clinical ecology the situation is even more depressing owing to the fact that in most of the individual autoimmune disorders the chemical stressor causing the modification of the self antigen is not identified. The chance is much better if the chemical is a drug and the symptoms do disappear after withdrawal but frequently environmental chemicals are involved causing idiopathic autoimmune diseases the etiology of which remains obscure. In addition autoimmune disorders can also be caused by errers in immunoregulotory machanigms without direct exogenous stress conditions.

Life in a world characterized by a large number of stress factors challenges the immune responses with an enhanced risk of immunodeficiency or autoimmune disorders. Much more research efforts are required in immunotoxicology as well as clinical ecology in order to establish appropriate preventive and/or therapeutic intervention.