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Autoimmune Diseases: The Role of Environment and Gene Interactions

Wellington K. Ayensu[1,3], Emmanuel O. Keku[2], Raphael D. Isokpehi[1,3], Ibrahim O. Farah[1], Chris A. Arthur[4] and Sophia S. Leggett[4]
[1]*College of Science, Engineering & Technology, Jackson State University, Jackson,*
[2]*Department of Public Health and Preventive Medicine, School of Medicine, St. George's University, St. George, Grenada,*
[3]*Bioinformatics Section; Jackson State University, Jackson,*
[4]*School of Health Sciences, College of Public Service, Jackson State University, Jackson,*
[1,3,4]*USA*
[2]*West Indies*

1. Introduction

Data from epidemiological studies indicate global increase in the incidence and prevalence of numerous autoimmune diseases (AD) as seen in the United States (Jacobson et al.1997). According to estimate from the US National Institute of Health (NIH) the prevalence of AD is in the range of 23.5 billion. From 1996 to date at least 237,203 cases per year of AD are diagnosed in the US; and of this, 42,137 are new cases of primary glomerulonephritis, multiple sclerosis, polymyositis/dermatomyositis and systemic lupus erythematosus (SLE). Early in 1996 alone 6,722,573 women and 1,789,273 men suffered from varieties of diseases that had components of autoimmunity. Currently up to 150 autoimmune based diseases have been identified and approximately 40 more are awaiting confirmation. Similarly the incidence of several autoallergic diseases, type 1 insulin dependent diabetes mellitus (IDDM), rheumatoid arthritis, and Graves' disease, hyperthyroidism included are on the increase. Of the 1.2 million new cases of AD diagnosed every 5 years, at least one or more cases will include these autoimmune disease components. (Jacobson et al.1997)

The global incidence and prevalence for each AD is currently lacking and that calls for improvement on data collection and reporting. Nearly 10% of developed world's population suffer from AD and contribute significantly to chronic diseases and mortality. Women are three times more likely to be at risk than men in acquiring these diseases with non-Caucasians at higher risk. We are also seeing global prevalence of allergic respiratory diseases on the increase for the past 20-30 years. Over 15 million people in US suffer from asthma alone; approximately 50 million are diagnosed with some form of allergic diseases (Smith et al, 1997). Presently the direct annual health care cost for AD in US is in excess of $100 billion US dollars as compared to $57 billion for cancer. Hospitalization alone takes over half the cost of the direct expenditures. Almost 20% of the population classified as 'high-cost patients' consume more than 80% of the resources. Consequently the cost to public health from clinical management of these conditions is on the increase. All indications point to future better

management of asthmatics through research and interventional efforts directed at communities, hospitalizations and high-cost patients in order to decrease health care resource use and provide cost savings. This calls for rigorous investigations into the role of environmental xenobiotics/substances and/or pollutants that are risk factors in the development of autoimmune diseases. In this chapter we intend to survey the public health concerns imposed by pollutants of the air, water and the food chain with concentration on typical examples of the effects of mercury on health to demonstrate the likelihood of dangers imposed through environmental and genetic disturbances in health.

2. Environmental chemicals and autoimmune diseases

Many scientists concur that several species within mammals to amphibians, birds, reptiles, and fish so far under monitoring systems are close to total extinction; well over 30,000 plant and animal species are estimated to be lost each year, a morbidity rate generally agreed to be much faster than at any time. Loss of species seems to be explained in most cases through the global weather changes as well as pollutional activities of man. But industrial activities seem to play major role in this problem; the latest data emanating from the industrial front estimate that at least 85,000 possible pollutants are currently being released into the environment through industrial activities alone http://www.epa.gov/glnpo/lmmb/substs.html (FDA/EPA).

2.1 Chemicals and substances of public health concern

These pollutants cover the heavy metals like thallium, aluminium, cadmium, lead, gold and mercury as well as pesticides, herbicides, preservatives, dyes, plastics, bisphenol A and rubber products. The Environmental Working Group indicated from studies in 2005 that a cocktail of 287 pollutants are measured in new born US fetal cord blood (http://www.ewg.org/reports/bodyburden2/execsumm.php). Perfluorooctanoic acid (*PFOA or* C8), and perfluorooctanoate, a synthetic but stable perfluorinated carboxylic acid and fluorosurfactant PFOA's were included in the findings as well as pesticides, dioxins, flame retardants. Recently another concern has been brought to the limelight by the internal Florida Department of Environmental Protection (DEP) Workgroup. It is stated that the current update of the American Chemical Society's Abstract Service reveals that as of August 2007 over 98% of the commercially available compounds are not under regulatory practices as they should be. This amounts to about 15 million out of over 32 million substances commonly referred to as Emerging Substances of Concern, or ESOC that have been registered for regulation (Chemical Abstract Service [CAS] website): http://www.cas.org/cgi-bin/cas/regreport.pl.

Much uncertainty surrounds the outcome from releases of these substances into the environment. No information about the pharmacokinetics or pharmacodynamics interactions among life forms on these substances are available. No available information on transport and toxicological effects are on record. Within two years between 2005 and 2007 over 5 million new chemicals have been reported to be registered and 5 million more chemicals became commercially available. Currently CAS informs that within each week more than 50 new substances or additions to existing substances to the database is the norm; http://www.cas.org/index.html. Apparently the ratio of unregulated to regulated chemicals keeps growing exponentially. The ESOC chemicals fall under various categories of organic groups encompassing from flame retardants (PBDEs), pharmaceuticals to endocrine-modulating chemicals (EMCs), nanoparticles to biological metabolites as well as newly discovered Industrial chemicals and toxins. They are constantly being discharged into

the environment where they find their way into our water bodies posing an unknown level of risk to life forms including humans, animals, and plants.
Regulatory Agencies are therefore challenged to find answers to solve what may be an unknown outcome of these ESOC substances being continually released into the biosphere. In the absence of detail knowledge on the environmental outcome and without effective regulation no useful assessment can be made on the environmental risk posed. Thus vast majority of ESOC substances have to be non-traditionally managed by other means such as prevention and effects-based environmental assessment methods. That effort is even more tasking and presents difficulties in monitoring the trends of the etiology of diseases now becoming prevalent in the environment under such practices. ESOC substances are now recognized to be of global concern; among these are included polybromina -teddiphenyl ethers (PBDEs), perfluorooctanoic acid (PFOA), siloxanes, perfluorooctanesulfonate (PFOS) and hexa- bromocyclododecanes (HBCDs). PBDEs and HBCDs come under flame-retardant chemicals that are moderately long-lived and volatile; readily released to the atmosphere because they do not strongly bind to substrates. Once in the atmosphere they are globally transported and readily bioaccumulate in biological tissues.

2.1.1 Nanoparticles

Human activities now have added sources of environmental contaminants. Human-originated nanomaterials are naturally man-made structures that differ in size range from 1 to 100 nanometers (nm). They are commonly used in drug delivery nanotherapeutic pharmaceuticals, cosmetics, personal care products, energy storage products, fabrics, lubricants and equipments like golf balls. The use of nanomaterials has been on the increase and now it is ubiquitous. Their minuscule sizes allow traversing not only biological membranes but also the blood/brain barrier (BBB) and display physical and chemical properties different from parental compounds. Examples are gold or silver metals known to be inducers of autoimmunity but also possess magnetic properties.
The intrinsic stereospecificity of these substances allow these molecules to play significant toxicological role in the environment (Donaldson et al 2004) and are therefore of public health concern. Carbon black displays enhanced severe effect than titanium dioxide (Renwick et al 2004), while the nanoparticle sizes of both chemicals are inducers of increased lung inflammation and destruction of the epithelial linings than their larger size. Adsorptions onto the surface of nanoparticles may play synergistic role in the reactivity; in vitro studies with fractions of diesel exhaust particles showed effects on cells (Xia et al 2004). Atmospheric nanoparticles may be complex enough to form interactions with organics and metals capable of higher levels of toxicity; metallic iron potentiates the effect of carbon black nanoparticles resulting in enhanced reactivity displayed as oxidative stress (Wilson et al 2002). Conversely other combinations with pullulan (polysaccharide polymer of maltotriose units, also known as α-1,4- ;α-1,6-glucan) and dextran tend to reduce toxicity of the respective nanoparticles (Gupta and Gupta 2005, Berry et al 2003).
Some nanoscale materials may be catalytic or behave as semiconductors, properties that can only increase the likelihood that nanomaterial could produce unanticipated toxicological effects. Nonbiodegradable ceramics, metals and metal oxides within nanomaterials are quite environmentally stable and persistent (EPA, 2007) and therefore undergo bioaccumulation in the food chain (Biswas and Wu, 2005). They are currently implicated in the induction of acute and chronic biological toxicity (Oberdörster, 2004a and 2004b; Lovern and Klaper, 2005; Lam et al., 2004; Shvedovaet al., 2005; Fortner et al., 2005) of unknown physiological mechanisms and hence consequences.

2.1.2 Particulate matter

Nanoparticles compare with particle pollution or particulate matter (PM), a group of complex mixture of extremely small air-borne particles and liquid droplets in air suspensions. There are a number of components covering acids (nitrates and sulfates, organic chemicals, metals, soil or dust and sulfates, organic chemicals, metals, soil or dust or mold spores). Particles less than 10 micrometers in diameter (PM_{10}) pose an even worse health concern because of their inhalation properties that allow for accumulation in the respiratory system; they are found in all types of combustion (motor vehicles, power plants, wood burning, etc.) and some industrial processes. Severe health risks are posed among fine particles less than 2.5 micrometers in diameter ($PM_{2.5}$). Fine particles easily lodge and penetrate deeply into the bronchial tree and into the deepest alveolar areas of the lung upon inhalation. Coarse particles measuring between 2.5 and 10 micrometers are derived from crushing or grinding operations, and dust from paved or unpaved roads.

Properties of PM link them to a variety of significant health problems starting from offensive asthma to early mortality of exposed patients who suffer from cardiac and bronchial diseases. Exposures to PM result in high rate of respiratory symptoms involving irritation of the airways, coughing, or difficulty breathing, decline in lung functions, aggravated asthma, and development of chronic bronchitis, irregular heartbeat and nonfatal heart attacks. Individuals with a variety of health issues particularly those with prior heart or lung diseases tend to suffer premature deaths on exposure to PM. Children and older adults are the most likely to be affected by particle pollution exposure but healthy individuals are found to experience temporary symptoms from exposure to elevated levels www.epa.gov/asthma; and plays esthetic role by significantly effecting visibility impairment in the nation's cities and national parks. To protect public health and welfare, EPA has continually issued National Ambient Air Quality Standards (NAAQS) since 1971 for six criteria pollutants among which are particulate matter and Sulfur Dioxide (SO_2), Ozone (O_3), Nitrogen Dioxide (NO_2), Lead (Pb), and Carbon Monoxide (CO). The NAAQS from EPA has undergone revisions in 1987 and 1997 and again in September 2006 and it is helpful to familiarize oneself; there is an urgent need for studies to unravel the pharmacokinetics and pharmacodynamics of these particles to help disclose the role played in disease pathogenesis especially concerning the autoimmune state- asthma being one of the priorities.

3. Autoimmune diseases: etiologies and mechanisms

All indications show that tissue burdens of PBDE in life forms including humans are doubling in every two to five years. Human breast milk has been found to contain as much as 419 ng/g lipid weight of PBDE (Schecter et al., 2003). The question then arises whether these molecules contribute to what we measure in the increases in the incidence of ADs. These substances are known to interfere with the reproductive and developmental stages of mammals as well as in birds and invertebrates (McKernan *et al.,* 2006, Wollenberger 2005); they are carcinogenic, endocrine-modulating, and have neurotoxicological effects (Birnbaum, 2005). Autoimmune diseases present a major affront to the health of Americans as well as of global concern. Vast arrays of diseases come under auto-allergic/–immunity; these cover maladies that may present as localized to be organ specific or systemically distributed to the extremities to involve all organ systems typically noted in systemic lupus erythematosus (SLE). In health the Immune System guards us against invasion of foreign

substances including harmful bacteria, viruses, and parasites quite well without any perturbation. At times, however this machinery loses control and begins to attack even the self itself. Hypersensitivity responses resulting from direct attack of body components by antibodies or immune cells instead of attacking foreign substances alone generally come under autoimmunity or autoallergic responses. Autoimmune state becomes apparent with rise of demonstrable presence of autoantibodies or complexes of these with body substances or the presence of cells, T lymphocytes that attack self-constituents. Minor and harmless autoimmune states exist in normal persons in general; it is part component of the defense system as envisaged by Jerne's hypothesis (<http://www.enotes.com/microbiology encyclopedia/). In the disease state, however, autoimmunity becomes defined when the benign state results rather in pathology; it sets in motion homeostatic deterioration. The process is dependent on both genetic influences and environmental triggers.

For the past decades it has been conclusively demonstrated that alleles of the major histocompatibility complex (*MHC*) contribute to the susceptibility to autoimmunity but relatively recently there is an unparalleled discovery of novel genes in molecular pathways implicated in autoimmunity. Some of the variants identified clearly participate in the modulation of T-lymphocyte (T-cell) activation and do contribute to many different forms of human autoimmunity. Other genes tend to have restricted roles, with susceptibility apparently confined to one autoimmune condition or to a specific ethnic group. To gain insight into the initiation mechanisms of autoimmune diseases requires identification of the genetic determinants underlying disease pathogenesis and this implicates new biochemical pathways. The Autoimmune state may be either the direct originator of disease itself or arise as a secondary disease from perturbations from other chronic diseases. Direct autoimmune states are phenotypically demonstrated in patients that have antibodies in the active disease phase: examples are represented by idiopathic thrombocytopenia (ITP), Grave's disease and myasthenia gravis, pemphigus vulgaris and bullous pemphigoid, diseases that can be transferred among species through antibody transfers.

Disease transfer through T lymphocytes exchanges have not conclusively been demonstrated to lead to pathology but with the aid of cytokines may rather alleviate or exacerbate disease state. Indirect cause of autoimmunity has been defined by Rose and Bona, 1993 as when disease can be induced in an animal model. SLE is well represented by several genetically determined mouse models which, while not exactly clinical replica of the human disease do very closely replicate pathological and serological characteristics clinically seen to occur. Hashimoto's thyroiditis and multiple sclerosis can be reproduced by immunizing animals with an antigen analogous to the putative autoantigen of the human disease. Absence of direct and indirect evidence with markers describing the state of autoimmunity become circumstantial: positive family histories for disease, presence of certain MHC class II alleles are examples.

Currently it takes a great effort to assess accurately the initiation levels of these diseases in humans; the very initiating factors are difficult to focus on and in which stage/s or area of the metabolic processes gets initially disturbed becomes challenging to screen and allow for therapeutic management. Majority of ADs such as multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and thyroiditis one finds representative spectrum of autoimmune diseases that appear to have etiological background in dysregulated immune system. Enough supporting evidence exist to confirm the autoimmune nature of many of these disorders but still it is gravely challenging to decipher their precise etiology and/or the initiating factors. Of late a small fraction of the T cells, the regulatory T cells are among the focal area of studies and have become recognized as

particularly crucial for control of autoreactive immune responses. Normally the processing of a self antigen by the antigen presenting cells (APC) allow binding of processed antigenic fragments to the MHC molecules within the APC followed by display of these MHC-peptide complexes on APC's membrane surface for presentation to the appropriate T cells; this eventually terminates in activation of antigen-specific T cells. These T cells are then capable of attacking the self tissues expressing that particular self antigen. The process is believed to be the critical steps in the initiation of anti-self T cell responses.

Genome wide studies indicate that costimulatory signals examplified by CTLA4 or PD1 and the modulators of T-cell receptor signaling (LYP, encoded by *PTPN22*), somehow must be confirmatory key checkpoint for human autoimmunity as happens in the T-cell during the period of T-cell receptor training to eliminate self-antigen carrying T cells in the thymus. This notion of the crypticity of self antigenic determinants (Sercarz et al., 1993; Moudgil and Sercarz, 2005) takes strength from the premise that rely on potentially immunogenic regions (determinants/epitopes) within a self antigen that are processed and presented by the MHC molecule to T cells at different levels of immunogenecity. This means that certain 'dominant self' epitopes are well processed and presented, whereas others, the (cryptic or recessive self) (Sercarz et al., 1993) ones are poorly or never processed and presented. Thus this type of staging of determinants (dominance/crypticity) in turn plays a critical role in thymus gradation of the T cell repertoire: the T cells specific for dominant self epitopes are tolerized with ease while those purportly aimed at cryptic self epitopes evade tolerance induction and become part of the mature T cell repertoire (Gammon and Sercarz, 1989; Cibotti et al., 1992; Sinha et al., 2004).

T cells that evade tolerance induction are capable of being activated in the periphery under certain stressful inflammatory circumstances such as occur during infection; this has the consequence of enhanced processing and presentation of once latent (cryptic) determinants (Lehmann et al., 1992; Lanzavecchia, 1995). These activated T cells at times are capable of escaping appropriate constraint from regulatory T cells and permitted to execute their effector function of initiating autoimmune damage. The unveiling of previously cryptic determinants leading to activation of self-reactive T cells that escaped tolerance induction during thymic selection, owing to the crypticity of self determinants is considered a primary cornerstone of a theory of autoimmunity (Moudgil and Sercarz, 2005). The idea of determinant hierarchy provides a vital link between the thymic selection of potentially autoreactive T cells and the subsequent activation of these T cells in the periphery under conditions that facilitate the revelation of previously cryptic determinants. Peripheral ongoing immune tolerance of the mature immune system also attracts attention as another source of autoimmune initiation. This idea is supported by variations seen in the expressions of "self-antigen" in the thymus (e.g., insulin in T1D); in this instance T-cells are selected for survival according to the affinity of their cell surface receptors for self-antigen. This may represent a major key step in the genesis of autoimmune disease.

Other means of autoimmune genesis stem from APCs. These cells play crucial role in antigen processing and presentation to the T-helper (Th) cells. Dendritic cells for example are key cells in the initiation and perpetuation of immune responses. Highly polymorphic genes within the *MHC*, with links to autoimmune inductions, encode proteins to which antigens bind and presented directly to T-cells by APCs. Another source of autoimmune initiation focus on the cell surface marker CD4-positive Th cells; they are the conductors of the adaptive immune response and many genes with an established role in autoimmune disease have their expression in this cell type.

Autoimmune diseases present specific issues that need attention. Drugs used to manage known chronic and acute diseases are implicated in triggering and are therefore thought to be indirect causes of various autoimmune diseases following administration. Many of the prescription drugs commonly used for highly prevalent diseases come under this category: these inexhaustively include drugs like Alferon N, Allopurinol, Atenolol, Atorvastatin, captopril, Penicillin, Carbamazepine, chlorpromazine, Chlorthalidone, cimetidine, Ethosuximide, gold salts, griseofulvin, Hydralazine, Interleukins, Infergen, Interferons, Interferon Alfa, Hydrochlorothiazide, Intron A, Isoniazid, Levodopa, Lithium, Lovastatin, Mesantoin, Methimazole, Methyldopa, Methylsergide, Metoprolol, Minocycline, Minoxidil, Ophthalmic timolol, Nitrofurantoin, Oral contraceptives, Quinidine, Phenytoin, PegIntron, P-aminobenzoic, Penicillamine, Perphenazine, Trimethadione, Pravostatin, Phenylbutazone, Procainamide, Valproic acid, Propylthiouracil, Simvastatin, sulfasalazine, sulfonamides, streptomycin, Sulfonamide antimicrobials, Tetracyclines, Tiotropium Bromide inhaler and Tumor Necrosis factor.

The concern here can well be summarized with the incidence and/or prevalence of asthma, one of the most common chronic diseases of childhood estimated to affect 6 million children. More than 22 million Americans are diagnosed with asthma, and approximately 50 million of individuals are diagnosed with some form of allergic diseases. Presently in US the annual direct health care cost for AD in general is in excess of $100 billion US dollars as compared to $57 billion for cancer. Hospitalization alone takes over half the cost of the direct expenditures. “High- cost patients” that form about 20% of the population spend more than 80% of the resources. As a result, the cost to public health from clinical management of these conditions is on the increase.

4. Global problems associated with asthma and COPD

Epidemiological data following the natural history of asthma reveal that in 1999 mortality rates from the disease declined in comparison to previous years. This was followed by a surge in recent decades in asthma prevalence also in the United States and other Western countries; data suggest this trend may also be reaching a plateau. The general trend of global asthma incidence is rising worldwide but looking at US data we see increased morbidity and mortality from asthma from 1980s -1990s with plateau in the 1990s. This finding is the reverse of what was seen in the 1978-1980 where an increase in mortality due to asthma was measured: from 1990-1999 mortality declined. Commencing from 1995 the rate of outpatient visits for asthma increased; whereas the rates of hospital admissions declined *from 19.5 per 10,000* of the population in 1995 to *15.7 in 1998* attributed to enhanced rates of dispensed steroid prescriptions for inhaled medications. This finding has been interpreted as due to the improved treatment of asthma responsible for these favorable developments.

The implication, if it holds supports explanations of certain changes in environmental chemicals releases. Recent increases in asthmatic conditions in the population may be linked to many causes the cardinal one being the amount and types of substances that are being released increasingly into the biosphere. Releases of substances most of which have an unknown effect and still others closely linked to inductions of asthmatic features in the ever increasing population with genetic predispositions present ominous threat to the very survival of several species including man himself.

Exposures to environmental factors early on in childhood play significant role in the risk in developing asthma. Clinicians have known for quite a while that asthma is not a single disease. Risk to asthma stems from early environmental factors as well as the presence of

susceptibility genes; subsequent disease induction and progression from inflammation as well as response to therapeutic agents plays big roles in disease etiology. It is a typical consequence of environmentally induced autoallergic disease known to be heterogeneous (Asosingh et al 2007, Dompeling et al, 2000, Dweik et al, 2001, Kharitonov and Barnes, 2001, Weiss, 2002, Pascual and Peters 2005, Salvato, 2001, Wu et al, 2000) existing in many forms. The immunologic profile of the asthmatic airways presents as proliferation and activation of helper T lymphocytes (CD4+) of the subtype T_H2 responsible for the allergic inflammation in atopic asthmatics. Upon stimulation these cells release a number of cytokines covering IL-4, agent for IgE synthesis, IL-5, essential for eosinophils' maturation, and IL-3 and granulocyte-macrophage colony-stimulating factor, GMCSF (Bolland and Ravetch 2000, Candore et al, 2002, Lang et al, 2010, Pollard et al 1997).

In allergic as well as nonallergic individuals we observe populations of eosinophils in the airways with increased levels in asthmatics with allergies http://www. clevelandclinicmeded .com/ medical pubs/disease management/allergy/ bronchial-asthma/that have higher rates of asthmatic attacks. These cells serve as the source of mediators that exert damaging effects on the airways. Ultimately, mediators lead to degranulation of effector/proinflammatory cells in the airways that release other mediators and oxidants, a common final pathway that culminates in chronic injury and inflammation commonly seen in asthma. Chronicity of the asthmatic condition has been confirmed by several parameters. Low pH and high output of reactive oxygen and nitrogen species (ROS) during asthmatic exacerbations are specific biomarkers in expired air reflecting altered airway redox problems (Clynes et al, 1988, Comhair et al, 2000, De Raeve et al, 1997, Dweik et al 2001). Superoxide, hydrogen peroxide, and hydroxyl radicals are among ROS agents that are responsible for the inflammatory changes in the asthmatic airway (Candore et al 2002, Bolland and Ravetch 2000, Pollard et al, 1997). These ROS originate from the lungs of asthmatic patients induced by activated inflammatory cells (ie, eosinophils, alveolar macrophages, and neutrophils) (Holgate et al, 2000).

Pathogenicity in asthma in particular is portrayed by overall interactions between neural mechanisms, inflammatory cell mediators such as leukotrienes and prostaglandins, and intrinsic abnormalities of the arachidonic acid pathway and smooth muscle; all these cells play significant roles in the initial as well as disease progression. Inflammation is the most likely etiological basis of airway hyperreactivity and variable airflow obstruction.

Asthma usually persists into later childhood and adulthood from early childhood in the presence of the appropriate genetic background. Tolerance to allergens is a normal security that prevents such responses, but the specific immunological events that mediate tolerance in this setting are still under scrutiny. Despite the explosion of information about asthma, the nature of the basic pathogenesis has not been established. However, asthma clearly does not result from a single genetic abnormality, but is rather a complex multigenic disease with a strong environmental contribution. For example, asthmatic children and adults sensitive to inhalant allergens such as dust mites, mold spores, cat dander, etc portray such reactions right from childhood compared with adult-onset asthmatics. Local epithelial environment within the connective tissue is believed to be actively involved in regulation of events and the relation between the airway epithelium and the subepithelial mesenchyme is proposed to be a key determinant in the concept of *airway remodeling* (Davies et al, 2003; Weiss, 2002; Li and Wilson 1997, Pascual and Peters, 2005, Salvato 2001). Difficulties and/or problems underlying diagnosis and classification of these diseases are simply due to the fact that most of the ADs become apparent only at variable phases of several chronic stages of organic ailments. Some ADs present as auto allergies covering several fields of diseases: the

incidence of several of these diseases is also on the increase and covers type 1 insulin dependent diabetes mellitus (IDDM), rheumatoid arthritis, and Graves' disease, hyperthyroidism included. There is scarcity of information on the global incidence and prevalence for each AD. Some autoimmune/allergic diseases (AD) can be seen in cases of chronic obstructive pulmonary diseases (COPD). As such the incidence of these disorders has not been well defined. However, sharp global increases in the prevalence have been observed in the United States.

Etiological initiators of and pathogenesis of most ADs are obscure; they are presumed to be numerous with cigarette smoking a typical COPD-associated. Cigarette smoking is clearly the major risk factor for COPD but exposures to other noxious substances including dusts and chemicals found under occupational settings are known to contribute to the development of the disease (Pauwels et al, 2001).The attributable fraction contributing to COPD cases caused by occupational exposures is estimated to be in the range of less than 15% to as high as 31% among those who never smoked (Hnizdo et al, 2004). We find that minority groups have been historically overexposed to hazardous industrial substances and are candidates with increased risk for work-related airflow obstruction putting them highly in the AD group as well; making it necessary to improve on data collection and reporting. Estimation shows, however that nearly 10% of developed world's population suffer from AD and contribute significantly to chronic diseases and mortality. Women are three times more likely at risk than men in acquiring these diseases with non-Caucasians in the higher risk groups. The global prevalence of allergic respiratory diseases including COPD has been also on the increase for the past 20-30 years.

5. Mercury as environmental inducer of autoimmunity

Psychoneuroimmunological studies demonstrate in various ways that homeostatic regulation of the internal milieu links the soma with the neural pathways; stressors effects relate the two in bidirectional pathways. Current Naturopathic Medical view of diseases also links the involvement of the genes to autoimmune proneness. In this wise the authors concentrate on the metal mercury as a representative highly reactive toxic agent within the body as a means of gaining an insight into the problem of etiologies of autoimmune diseases. Mercury has a high affinity binding to *sulfhydryl* as well as to *hydroxyl*, *carboxyl*, and *phosphoryl* functional groups very commonly displayed on macromolecules, proteins and the genetic materials. It is widely distributed as an environmental and industrial pollutant. No known beneficial metabolomic effect is assigned to mercury in the physiology of humans, yet a 70 kg man is loaded with an equivalent of 13mg mercury (Pier, 1975) distributed in the skin, nails, hair, and kidneys. The net outcome of exposure to mercury is dose-dependent and at low concentrations mercury is the agent for the induction of several diseases that affect most systems of the body.

The central nervous system (CNS), the brain and the kidneys suffer most where Mercury Induced Autoimmunity (MeIA) can be particularly threatening in onset and severe among especially non-Caucasians that manifest *defined* major histocompatibility complex (MHC) haplotypes. Several data confirm that mercury is also associated with polyclonal cell stimulation. Mercury Induced Autoimmunity (MeIA) engages helper T lymphocytes in the induction of disease process in responder animals (Jiang YG, Möller G 1995, Horwitz and Stohl, 1993; Puck JM, Sneller MC. 1997) and in humans (Liossis et al 1996). It is suggested there is a genetic basis for airway hyperresponsiveness with linkage to chromosomes 5q, 11q (Li and

Wilson1997) and 12q24 in Hispanic subgroups (Salvato 2001). While MeIA is well characterized into different arrays of disease susceptibility in animal studies (De Raeve et al 1997) and in humans (Holgate et al, 2000, Li and Wilson 1997,) the role of mercury in the pathogenesis of autoallergic/immune syndromes like asthma and SLE is not well characterized.

Our Microarray data resulting from low doses (1-3 µg/mL) exposures of human cell lines to mercury indicate differential expressions of several genes located on many human chromosomes. Most genes affected were expressed more than twice the control level; several genes were also down-regulated with mercury treatment. We found close to a total of two hundred highly up-regulated genes with greater than a two-fold change difference ($p \leq 0.002$) in the lowest mercury concentration (1µg/mL); 12 genes were moderately over-expressed with an increase of more than one fold ($p \leq 0.005$); and a total of more than two thousand genes were down-regulated albeit most repressions were not statistically significant ($p>0.05$) according to the Wilcoxon's Signed Rank test. Only forty of these genes were down regulated to statistically significant levels at $p \leq 0.05$ according to the Welch's ANOVA/- Welch's test. Clear distinctions were seen in the gene expression profiles of the experimental versus controls. Affected genes distributed among almost all of human chromosomes with higher than normal effects on genes associated with chromosomes 1-10, 12, 14-18, 20 (sex-determining region Y), 21 (splicing factor and ATP-binding), X (including BCL-co-repressor). Genes affected include potassium voltage-gated channel–subfamily H member 2 (KCNH2), stress responses, G-protein signal transduction, putative MAPK activating protein (PM20, PM21), *ras* homolog gene family, cytokine receptor activity and polymerase (DNA directed), regulatory subunit (50kDa), leptin receptor involved in hematopoietin/interferon-class (D200-domain), and thymidine kinase 2, mitochondrial TK2 (HGNC) and related genes. Closely associated genes on a chromosome tend to be influenced for expression perhaps due to the availability of close and adjacent *phosphorylation* receptors found by bioinformatics tools.

Identified genes of interest that were over- or under-expressed operate in several pathways including principally the immune and cell cycle (cyclin-dependent kinases) pathways, apoptosis, and cytokine expressions (Figs 1-3) as well as the TGF-beta and the GABA, NMDA receptor subtypes. We have since confirmed that mercury has significant effect on GABA receptors in microarray experimentations in murine cell lines (unpublished data). Our lab results reinforce the capability of mercury exerting significant influence in most metabolic processes probably generating ROS (Kavuru et al 1998; Lang 2000, 2006, Montuschi and Barnes 2002, Wu et al 2000) that participate in the degree of disease outcome of the autoallergic/asthmatic syndromes. The auto allergic phase is the body's adverse response to the onslaught resulting in signs and symptoms invariably difficult to definitively differentially diagnose early on in disease. Estimates from the National Institute of Health (NIH) data indicate that in US alone the prevalence of AD to be about 23.5 billion (Jacobson et al, 1997); in 1996 approximately 1 in 31(3.13%) or 8.5 million people were afflicted with one form or other of AD. Since then at least 237,203 cases of AD are diagnosed annually; of this 42,137 are new cases of primary glomerulonephritis, multiple sclerosis, polymyositis/ dermatomyositis and systemic lupus erythematosus (SLE). Of the total 6,722,573 are women and 1,789,273 men suffering from varieties of diseases that had autoimmune components (Jacobson et al, 1997, Smith et al, 1997). Currently almost 100 types of AD have been identified and approximately 40 more autoimmune-based diseases are awaiting clarification and confirmation.

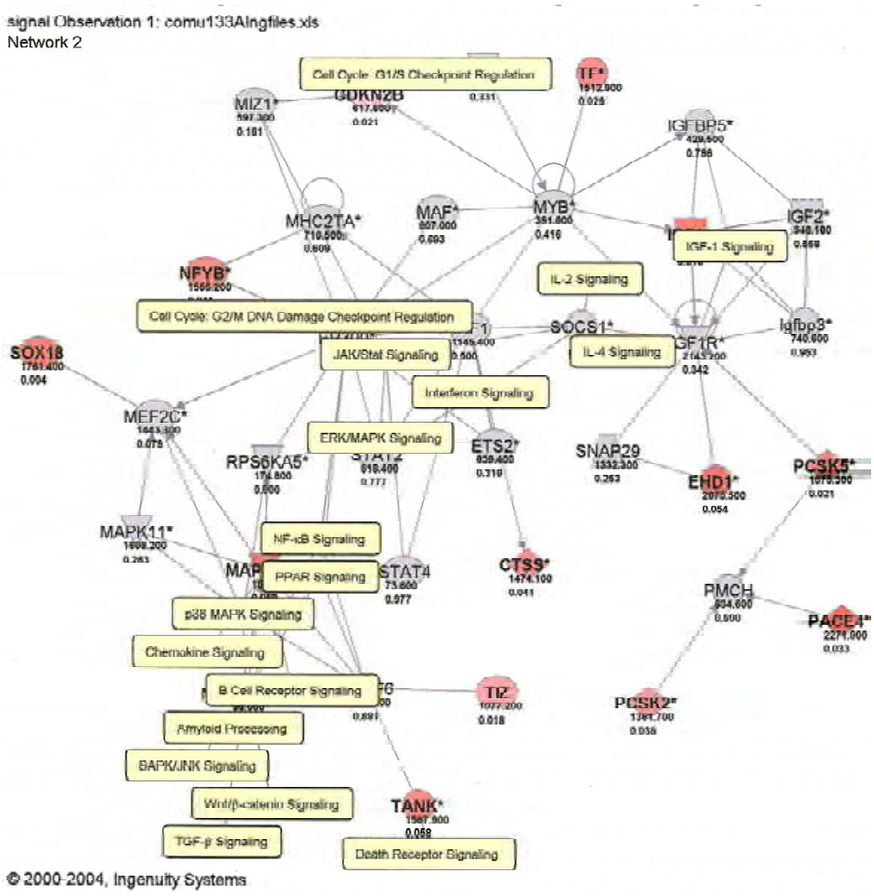

Fig. 1. Results: HepG2 Genes affected by Mercury exposure

5.1 Mercury toxicity: evidence for autoimmunity and neural problems

Mercury (Hg) has long been recognized as a neurotoxicant; however, many experiments with murine models have conclusively implicated this heavy metal as inducer of autoallergies as well as immunotoxicant. In particular Hg has consistently been shown to induce autoimmune disease in susceptible animals with phenotypic consequence of autoantibodies overproduction and pathophysiological signs of lupus-like diseases. This finding has been endorsed by epidemiological studies demonstrating links between occupational Hg exposure and lupus. Mercury rather may interact with triggering events, such as genetic predisposition, exposure to antigens, or infection, to exacerbate disease. Non mercury-susceptible mice that are exposed to mercury do succumb to mercury-induced autoimmune disease (MeIA) with very low doses and short term exposures of inorganic Hg (20-200 μg/kg) exacerbates disease and accelerates mortality in the graft versus host disease model of chronic lupus in C57Bl/6 x DBA/2 mice.

Furthermore, low dose Hg exposure increases the severity and prevalence of experimental autoimmune myocarditis (induced by immunization with cardiac myosin peptide in adjuvant) in A/J mice. Immunosuppression as well as immuno-stimulatory signals results from exposure to the metal in many species humans and rodents included (Pollard et al., 1999). MeIA is prominent among some genetically predisposed individuals that carry syntenic genes as haplotypes in linkage disequilibrium. Some of these individuals are

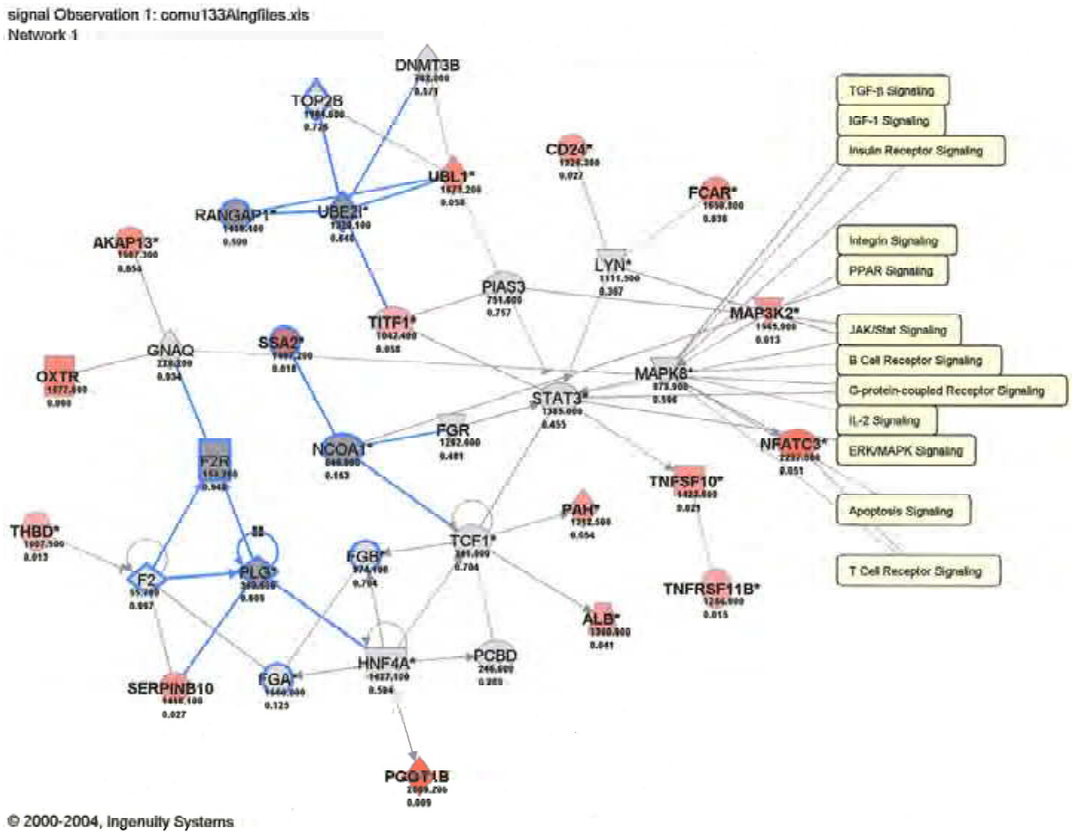

Fig. 2. Results: HepG2 Genes affected by Mercury exposure

genetically prone to develop spontaneous autoimmune diseases. The etiology and pathogenicity of these, mostly systenic, autoimmune states have been difficult to trace. Immunological findings support the notion that the origins of majority of these idiopathic autoimmune diseases can be traced to environmental contaminants of the biosphere with xenobiotic compounds like silver, gold and mercury strongly implicated. *Exposure t*o low levels of mercury (<40µg/kg body weight) in susceptible persons may be unsafe; predisposed individuals develop all types of AD typically systemic lupus erythematosus (SLE). Evidence is derived not only from experiments of nature as happened in Miamata in Japan but also from many strains of inbred mice described below. These strains of animals do develop lupus-like disease that imitate closely a simplified version of human systemic lupus erythematous (SLE), with the production of autoantibodies and the subsequent development of immune-complex mediated glomerulonephritis (Theofilopoulos et al., 1985).

The general consensus is that the dose of mercury, duration of exposure as well as the genetic background of the exposed animal (Hanley et al., 2002; Hultman et al., 1992, 1993; Jiang and Möller, 1995; Kono et al., 1998; Pollard et al., 2002) contributes to disease outcome. The H-2 haplotype plays important role in the specificity of resulting autoantibody as well as susceptibility to immune complex generation; but there is a role for involvement of non-MHC genes in MeIA susceptibility also. Acute renal tubular lesions and immunosuppression follow exposure to large doses, whereas chronic administration of smaller doses of mercury leads to the development of SLE (Bariety et al., 1971; Kasturi et al., 1995; Roman-Franco et al., 1978). Mercury-induced autoimmunity shares the same pathogenicity and clinical

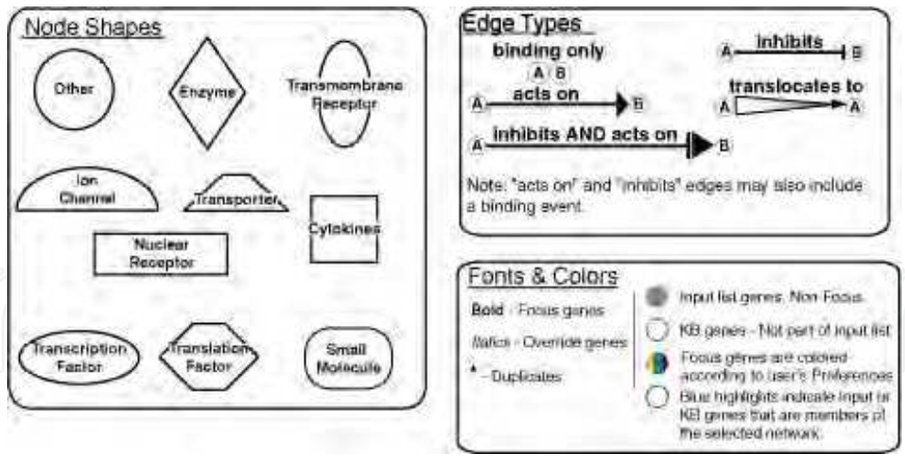

Fig. 3. Key for Both Figs 1 and 2

manifestations seen in patients suffering from clinically diagnosed systemic lupus erythematosus (SLE) (Dubey et al., 1991; Hirsch et al., 1982; Mathieson et al., 1992); the symptomatology is also the same (Biancone et al., 1996; Jiang and Möller, 1995; Kono et al., 1998) with very minor differences.

In humans most of the genes participating in immunity are located on the major histocompatibility complex (MHC) on chromosome 6 with its equivalent on the H-2 region on chromosome 17 in mice. The complexity of the interactions leading to disease state are reflected in the arrays of disease manifestations. Various susceptibility modes are demonstrated by different combinations of gene haplotypes in different strains of animals. BALB/c mice of $H\text{-}2^d$ haplotype are highly susceptible to MeIA phenotypically demonstrated as lymphoproliferation without accompanying immune-complex glomerulonephritis (ICGN) (Jiang and Möller, 1995). Mice with *B10.D2* haplotype specificity are capable of lymphoproliferation but with less severe ICGN than BALB/c mice on exposure to mercury. The $H\text{-}2^d$ haplotype *DBA/2* strain of mice is however, resistant to both lymphoproliferation and ICGN (Hultman et al., 1992; Jiang and Möller, 1995; Kono et al., 1998; Takeuchi et al., 1995). $RT\text{-}1^n$ rats are susceptible, whereas $RT\text{-}1^1$ haplotypes are resistant (Eneström and Hultman, 1995; Sapin et al., 1984). An $H\text{-}2^s$ haplotype carrying A.SW mice and others show high susceptibility to Hg-induced autoantibodies, whereas *C57BL/6* strains ($H\text{-}2^b$) are less susceptible. DBA/2 mice strains bearing $H\text{-}2^d$ haplotypes are not responsive while $H\text{-}2^k$–bearing mice show intermediate susceptibility (Dubey et al., 1991; Hultman et al., 1993; Jiang and Möller, 1995; Kono et al., 1998).

Most SLE susceptibility loci have been mapped in New Zealand hybrid models; at least 12 of them are located outside the H-1, the murine major histocompatibility complex, H-2. Three regions commonly noted by linkage studies in New Zealand models are found on murine chromosomes 1, 4, and 7 (Drake 1995, Kono et al., 1994, Morel et al., 1994); these have equivalent syntenies in human loci (Duits et al., 1995; Moser et al., 1998; Salmon et al., 1996) that seem to be *ethnically* distinct (Duits et al., 1995: Salmon et al., 1996). Another region along both *H-2 class II* and *TNF-*_ gene polymorphisms have been described to act as H-2-linked predisposing genetic elements for the development of SLE; a very strong evidence suggests the contribution of *TNF-* polymorphism that may be the modulator of the initial steps of disease development (The *Wbw2* locus (telomeric to H-2)) which was not linked with autoantibody production might play a role in determining lupus susceptibility; this reaffirms the clustering of functionally related H-2 and non-H-2 genes in the H-2 region on

chromosome 17 to be active players in the induction of SLE, a typical example of AD usually quoted. Genetic variants do exist in autoimmune susceptibility that may be a basis for health disparity among races and forewarns that in dealing with xenobiotics like mercury, susceptibility among different racial groups may exhibit differences enough to be taken into account in therapeutic managements.

It has been determined that mercury is immunologically processed uniquely in disease pathogenesis. The process involves the antinuclear autoantibody, (AnoA Abs) response directed against fibrillarin. The AnoA Abs response directed against fibrillarin is one of the most representative manifestations of MeIA that is linked to *H-2*^{s} (Hanley et al., 2002; Hultman et al., 1992; Hultman et al., 1993; Pollard et al., 2002) and, more specifically, to the class *II I-A*^{s} molecule, by analysis of H-2 congenic mice (Pollard et al., 2002) and is described below. The discovery of potential SLE inducibility on mercury exposure in humans offers the opportunity for comparison with data from murine models of SLE. This means that identification of potential SLE susceptibility loci in humans offers the chance to compare data from murine models of SLE induced by xenobiotics such as mercury.

Mercury-induced cell death (MeICD) is processed through proteolytic breakdown of fibrillarin, a 34kDa MWt macrophage degradable protein component of small nucleolarribonucleoprotein particles (snRNPs); the generation of a unique (19kDa) proteolytic fragment required no pre-interaction between mercury and fibrillarin (Pollard et al, 1997, 2002).

MeICD was associated with a novel protease transiently synthesized and that stimulate *self-reactivity* quite differently from that elicited by full-length protein. Above all *xenobiotic-induced autoimmunity characterized by autoantibody responses against native self-Ag did not require pre-interaction between xenobiotic and Ag*. The genetically restricted anti-fibrillarin autoantibody response of MeIA was not found directed against a fibrillarin-Hg complex as expected of MHC-dependent antigen processing although a metal-protein interaction occurred (Pollard et al., 1997, 2002). This finding endorses a longstanding belief that SLE-prone patients could generate self-autoantibodies spontaneously even without any physical presence of observable inducers of auto-antigens. Cell demise through MeICD was found to be mediated through both nonapoptotic and apoptotic protease activities but the processing pathway of fibrillarin was different enough to suggest the action of different *proteases* (Casiano et al., 1996; Pollard et al., 1997, 2002). It was surmised that the cleavage patterns for a number of auto-antigens must differ between non-apoptosis ($HgCl_2$, heat, ethanol) and apoptosis (anti-Fas) induced cell death (Casiola-Rosen et al., 1995; Pollard et al., 1997). Apparently an MHC-restricted autoantibody response and interaction with $HgCl_2$ are characteristics that differentiate fibrillarin as an autoantigen in $HgCl_2$-induced autoimmunity. The observation that specific cleavage fragments of fibrillarin result from $HgCl_2$ induced death and not other forms of cell death means that *novel* cleavage fragments probably act as *autoimmunogens*. Besides other effects of mercury on the immune system including specific cytokine requirements (Gillespie et al., 1995; Ochel et al., 1991; Van Vliet et al., 1993), inhibition of Fas-mediated cell death are possible means of terminating self-tolerance leading to the equivalent of the SLE state (Whitekus et al., 1999).

As detected in Asthmatic states MeIA is one of the autoimmune models in which T_H1/T_H2 imbalance play critical roles (Biancone et al., 1996; Dubey et al., 1991; Hirsch et al., 1982; Jiang and Möller, 1995; Mirtcheva et al., 1989; Sapin et al., 1984). Although the mechanism by which mercury modifies the immune system is obscure, cationic mercury has a high affinity for *sulfhydryl* groups as the principal site for binding and also has a substantial affinity for *amines, phosphoryl, carboxyl, and hydroxyl groups* (ATSDR, 1999). Mercury is

capable of linking with macromolecules including the genetic materials and proteins to form complexes that can activate the immune system. Some of the modified proteins may have epitopes closely resembling self-immunogens (*cryptic antigens*) easily leading to autoimmune disorders in predisposed individuals (Pollard et al., 1997, 2002; Takeuchi et al., 1995). The activation of $CD4^+$ and $CD8^+$ T cells requires a prior induction of antigen presenting cells (APC) (Jiang and Möller, 1995). Mercury binds to molecules on accessory APC cells and transforms molecules on these cells to superantigens capable of activating T cells with a particular set of Vβ Ag-binding receptors (Jiang and Möller, 1995). The mechanism of MeIA can therefore be differentiated from mechanisms induced by polyclonal cell-activators (PCA) such as pokeweed mitogen, PWM. These PCA do not require helper T cells assistance in antibody/cellular inductions.

The presence or absence of IFN-γ on the responder or the non-responder T_H1/T_H2 cell types respectively is thought to be prerequisite in the response to or failure of response respectively (Kono et al., 1998). The balance between the T_H1/T_H2-type responses does not contribute directly to autoimmune susceptibility. Rather IFN-γ has been found to be necessary for the activation of the immune system to respond to poor epitopes, including both self and non-self Ags leading to humoral and cellular auto responses. Dose differentials of IFN-γ appear to directly contribute to disease proneness. High dose immunization with Ag and a strong adjuvant tend to override the IFN-γ requirement (Ferber et al., 1996; Jones et al., 1997). Similarly, a strong genetic predisposition may decrease the threshold for susceptibility enough to overcome the IFN-γ requirement (Abbas et al., 1996). Susceptibility to autoimmune diseases therefore is generally considered a multi-process with many stages or focal barriers evidenced by clinical observations in SLE patients (Andre et al., 1996; Hultgren et al., 1996; Manoury-Schwartz et al., 1997; Vermeire et al., 1997). Lupus is therefore not inherited as a simple Mendelian trait but inherited as a multifactorial and complex trait.

Latest information confirms that the steps to disease state are characterized by unknown, but a large number of susceptibility alleles that give rise to quantitative phenotypic effects. Dose effect allows each of the susceptibility alleles to have partial contribution to probability of increased disease severity. Still nongenetic factors do contribute to disease susceptibility. Recent linkage analyses have revealed over 100 large genomic regions, each represented as a quantitative trait locus (QTL)http://www.discoverymedicine.com/tag/quantitative-trait-locus/ that are associated with increased susceptibility to lupus in mice (Kono et al., 2006) and at least 8 validated QTLs in families of lupus patients (Tsao, 2003) that partially overlap with the mouse QTLs. Some of the genes contribute to the murine lupus QTLs and participate in human SLE. Analysis of these genes is providing insight into pathogenesis of human SLE. Use has been made of linkage analyses on some model murine species that spontaneously get the lupus; these have involved analyses using 129, MRL-*Fas*^{lpr}, BXSB.*Yaa*, and the F_1 hybrid between NZB and NZW (BWF1) and their recombinant inbred derivatives, NZM2410 and NZM2328.

Statistically significant associations between over 100 genomic regions and a lupus-related phenotype covering most commonly lupus nephritis or anti-nuclear autoantibody (ANA) synthesis have been analyzed. Through substitution techniques whereby for example a QTL located in a lupus susceptible strain was replaced with the corresponding genomic interval from a resistant strain only 35 of the 100 genomic regions have been so far confirmed (Morel, 2010). Substitution of the *Adnz1* region (in NZM.C57Lc4 congenic strain) in lupus-prone NZM2328 mice with the appropriate genomic interval from a non-autoimmune genome led to the predicted and expected milder form of glomerulonephritis (Waters et al., 2004). Conversely

when the susceptible QTL was bred into a non-autoimmune genome such as B6.NZM2410.*Sle1* mice, which carry the NZM2410-derived*Sle1* QTL that showed the strongest association with lupus nephritis, produced the expected high levels of ANA (Mohan et al., 1998). The implication was that none of the susceptibility loci was sufficient for the induction of full-blown lupus pathology; each of these loci directed the expression of typical phenotypes such as ANA or increased lymphocyte activation (Morel et al., 1997). Therefore each of these component phenotypes itself has an independent genetic basis, at least in the mouse.

In human SLE, risk haplotypes of some of the susceptibility genes such as *STAT4* (Sigurdsson et al., 2008) or *IRF7/PHRF1* (Salloum et al., 2010) correspond to production of specific autoantibody profiles, suggesting that, as in mice, component phenotypes have unique genetic basis also. Confounders make the human analyses harder and difficult to explore due to the unavoidable co-expressivity of all other susceptibility alleles. Intersections of gene-function properties have been identified among the 35 validated murine susceptibility loci. High overlaps have been detected on chromosomes 1, 4, 7, and 13; longer areas are seen on chromosome 1; where 16 independent loci have been identified in 6 strains. The overlap is very conspicuous in the telomeric portion of chromosome 1 with its equivalent region localized in the human *1q23-42* site, a region identified to have many known linkages to human SLE (Tsao, 2003). These results tend to imply that at least some lupus-prone genes are shared among lupus-prone mouse strains and humans as well in that region.

Characterization of the original QTLs lupus congenic strains corresponded to a cluster of susceptibility loci best demonstrated for *Sle1*: this corresponds to at least 7 independent loci. Phenotypic expressions of *Sle1*, ANA synthesis have been linked with 3 independent sub-loci, *Sle1a*, *Sle1b,* and *Sle1c* (Morel et al., 2001). Further studies demonstrated that ANA production was feasible by the way of various distinct paths in each of these 3 sub loci. *Sle1a* regulates inducement of activated, nucleosome-reactive $CD4^+$ T cells and inhibits the number of $CD4^+$ $Foxp3^+$ http://www.discoverymedicine.com/tag/foxp3/regulatory T cells (Chen et al., 2005a; Cuda et al., 2007) with contribution from two independent sub-loci within *Sle1a*, *Sle1a1* and *Sle1a2* (Cuda et al., 2010). Findings indicate *Sle1b* function to regulate tolerance in immature B cells (Kumar et al., 2006; Wandstrat et al., 2004). *Sle1c*, with its two subloci, *Sle1c1* affects germinal center B-cell responses, and *Sle1c2*, that induces appearance of autoreactive $CD4^+$ T cells respectively (Boackle et al., 2001; Chen et al., 2005b). *Sle1d*, sandwiched between*Sle1b* and *Sle1c2*, enhances the severity of glomerulonephritis when mice carrying this allele are crossed with NZW mice (Morel et al., 2001). Also interlocked between *Sle1a* and *Sle1b* is the *Fcgr2b* the presence of which reduces expression on germinal-center B cells and plasma cells (Rahman et al., 2007): a phenotype known to have links with lupus patients (Mackay et al., 2006). The obvious deduction is that other lupus-prone strains may express identical state of genetic complexity in that region and at other loci and therefore is an avenue of either common or strain-specific genes, possible determinant of individual gene level and hence probable disparity among races.

Synergistic interactions between specific loci were also found to be linked with co-expressivity found in *Sle1* and *Yaa* on a B6 background that led to severe lupus nephritis (Croker et al., 2003); the co-expression of either *Sle2* or *Sle3* with *Yaa* achieved only the phenotypes of either parent strains. In humans genetic interactions have been harder to identify for SLE (Harley et al., 2009) partly due to the extreme genetic diversity co-segregating with any gene or locus of interest. Additive effects have, however, been identified between risk variants of*STAT4* and *IRF5* (Abelson et al., 2009; Sigurdsson et al., 2008), suggestive of specific genetic interactions in human SLE. The co-expression of *Sle1*, *Sle2*, and *Sle3* on a B6 background has been seen to give rise to fully penetrant lupus nephritis (Morel et al., 2000).

A clear demonstration of mercury's possible influence on several metabolic pathways is seen in the number of possible pathways affected Figures 1-3: red coloration indicates upregulated genes and blue coloration indicates inhibition of gene expression on exposure to mercury. Mercury exposure leads to effects on several of biochemical pathways involving products of genes in cell cycle signaling: G2/M checkpoint regulation, TGF-β, IGF-1, insulin receptor activity, chemokine, Wint/ β-catenin, integrin, PPAR, SAPK/JNK, JAK/Stat, B and T cell receptor, G-protein-coupled receptor, IL-2, ERK/MAPK, death receptor signaling such as apoptosis, NF-κB, cell cycle and above all immune responses regulated by most of these genes. Pathways indicated are examples of mercury's potential to affect susceptible individuals that carry MHC haplotype combinations and who are prone to develop not only autoimmune and/or cancerous diseases but risk factors for obesity and other chronic associated diseases yet to be evaluated through mercury toxicity.

Our studies confirm that several genes in haplotype combinations are subjected to pronounced changes on exposure to environmental mercury. Among these genes we mention the transforming factor beta (TGF-β) superfamily of cytokines. This group of family genes is associated with regulating the cell cycle essentially for maintenance of normal immunological homeostasis and lymphocyte proliferation. Proteins synthesized from these genes play important roles in regulating essential cellular functions such as differentiation and apoptosis. TGF-β superfamily of cytokines is over expressed on mercury exposure. Some cells, lymphocytes among them are known to respond to TGF-β by undergoing apoptosis. Apoptosis may lead up to accumulation of self-antigens within a localized part of the body and break the body's immunological tolerance to give rise to the autoimmune state. The mechanisms regulating this process are yet to be clarified. Over expression of TGF-β cytokines induced by mercury may lead to transcription of Smad6 and Smad7; these molecules act as inhibitors of TG apoptosis is necessary for maintenance of tolerance. Failure to eliminate immature B cells has the consequence of autoimmune diseases and cancer development. Several aberrant functions associated with many pathways involving the cell cycle and the immune responses are therefore possible through intoxication with mercury. Such wide effects of mercury translate to risk associations when disease susceptibility is our prime concern. This means that it is only at the right genetic combinations and the appropriate line-up of associated genes that disease susceptibility ensues. That goes to argue for severity of disease as well. Mercury-exposed individuals carrying the appropriate allelic-combinations located on specific haplotypes are prone to develop autoimmune diseases.

Not only do some metals induce autoimmunity but can also affect the nervous system when present during fetal development. Mercury readily crosses the human placenta and accumulates in fetal tissue during gestation (David et al., 1972). Mercury can concentrate in umbilical cord blood significantly more than in the maternal blood (Sakamoto et al., 2004). This could affect various developmental processes (Clarkson, 1997; Hassett-Sipple et al., 1997; Pendergrass et al., 1997) leading to behavioral dysfunctions associated with autism (Bernard et al., 2001) and others. Arrhythmias and cardiomyopathies have also been associated with mercury toxicity. Mercury intoxication can result in mental retardation, cerebral palsy, seizures and ultimately death (WHO, 1990). For the early protection of children, it becomes necessary to come up with reliable and relevant tools that identify chemicals with developmental neurotoxicity potential. Once identified, these neurotoxicants need to come under regulatory practices in order to restrict their use and to control exposure as, for example in the case of lead (Silbergeld, 1997).

5.2 Spontaneous lupus: who are at risk

To date genetic mappings endorse genetic susceptibility to autoimmunity and confirms it to be highly associated with individuals with certain combinations of genes in MHC-haplotype linkages: *Fasl* (CD95/L), *Sap* (serum amyloid P-component), *Fcγr2b* (FcγRIIB), *Cr2* (CD21/CD35) and *Ptprc* (CD45) amongst them. Deficiency in individuals of Fcer1g (FcR*γ*-chain) results in resistance to autoimmunity. These genes are not by any means exhaustive. As mentioned above gene type and dosage seem to determine severity of autoimmune diseases. This indicates that susceptibility and/or initiation factors operate via multiple pathways subjected to regulatory or focal checkpoints that finally give rise to the pathological state. The situation is exemplified by SLE, type 1 diabetes, IDDM and RA patients. In genetically predisposed patients the synthesis of autoantibodies and/or the generation of cellular attack of self-antigens may follow different pathways. Such mechanisms are known to be influenced by gene dosage and contributions from *ethnic* and environmental background. Clinical management or treatment schedules need to vary accordingly.

Thus lupus susceptibility genes are now of deep interest to immunologists/allergists and are being identified in the mouse and their contribution to the disease state is being actively sought through analysis of rare or common variants. Discoveries of the roles of the susceptible lupus genes mainly in the mouse have given insights and critical lead to links with human SLE disease patterns. However the molecular mechanisms by which they contribute to autoimmune pathogenesis are yet to be clearly defined. The multifactorial complex nature of lupus disease susceptibility is currently thought to operate via a combination of common genetic variants that result in small phenotypic effects; rare variants end in large phenotypic effects (Cirulli et al., 2010). So far identified common variants in lupus susceptibility genes include the PTPN22 or *IRF5* among others. Genome wide Association studies (GWAS) and analysis also reveals scarce variants such as C4 and TREX (Graham et al., 2009). Rare *SIAE* variants responsible for the loss-of-function have been linked with autoreactive B cells (Surolia et al., 2010); the *lpr* and *gld* in humans represented in lupus-prone murine strains lead to a functional decline in CD95 or C95L, respectively (Cohen et al., 1992); the *Yaa* mutation, an equivalent of a *Tlr7* gene duplication (Pisitkun et al., 2006), and a mutation in the Coronin A1 gene in the B6.Fas^{lpr}/Scr strain that regulates CD4$^+$ T cell activation (Haraldsson et al., 2008) have all been located.

The murine equivalent of humans common variant genes have now been identified for SLE. NZB and NZW allele of *Fcgr2b* encode a negative regulator of B-cell signaling and predicates an autoimmune phenotype (Rahman et al., 2007; Xiu et al., 2002). Studies currently endorse links between *FCGR2B* variants and human SLE (Lee et al., 2009). *Cr2* polymorphism that function to encode the complement receptor type 2, a B-cell co-receptor known to contribute to the *Sle1c1* phenotypes (Boackle et al., 2001; Chen et al., 2005b). SLE patients do carry a common *CR2* haplotype more frequently than in healthy controls; and follicular dendritic cells (FDC) express a novel CR2 splice variants of SLE patients (Douglas et al., 2009; Wu et al., 2007). *Sle1b* corresponds to polymorphisms in four signaling lymphocytic activation molecule (SLAM) family member genes (Wandstrat et al., 2004), including *Ly108* directly implicated in the regulation of B-cell tolerance (Kumar et al., 2006). Variants of *SLAMF3* (*LY9*) and *SLAMF4* (*CD244*) have also been linked with human SLE (Graham et al., 2008; Suzuki et al., 2008). For the *Sle1* sub-loci, *Sle1a.1* corresponds to the expression of a novel splice isoform of the *Pbx1* gene that is associated with increased CD4$^+$ T cell activation in both mice and humans (Cuda et al.,2007, 2010). Searches are still going on to reveal the mechanisms linking *Pbx1* expression and T cell phenotypes. Complex

phenotypic expressions are associated with *Sle3* locus that includes myeloid cell-induced $CD4^+$ T-cell activation (Zhu et al., 2005) and mild glomerulonephritis (Mohan et al., 1999). Kallikrein (*Klk*) polymorphic genes, serine esterases that regulate a wide spectrum of biological functions in the kidney including inflammation, apoptosis, redox balance, fibrosis, and local blood pressure located in the *Sle3* interval have been linked with increased susceptibility to nephritis in SLE mice and SLE patients (Liu et al., 2009).

To date close to 22 identified and validated loci with confirmed associations with SLE susceptibility (Graham et al., 2009) have been mentioned in the literature. These loci are placed in one of four groups on the basis of mouse characteristics (Morel, 2010). Group one genes are thought to be directly implicated in lupus pathogenesis through their capacity to either induce or modulate disease in the mouse. A representative one is *STAT4*, a transcription factor linked with signal transduction of the IL-12 and IL-23 receptors that has a critical role in regulating the effector functions of helper T cells (Korman et al., 2008). In addition, *Stat4* deficiency modifies disease severity in the NZM lupus models (Jacob et al., 2003; Xu et al., 2006). The *IRF5* whose risk alleles are associated with an increased production of interferon alpha (IFNα) in SLE patients (Niewold et al., 2008) is a puzzling piece. In two different murine models (Richez et al., 2010; Savitsky et al., 2010) *IRF5* however, failed to establish a link between IRF5 and IFNα, pointing instead to a transcriptional control of the IgG2a locus. It is still not clarified if these discrepancies reflect species-specific functions of IRF5 or whether the association between *IRF5* polymorphisms and IFNα production does not involve a direct mechanistic link between the two genes. The second group covers GWAS-identified SLE susceptibility genes with known functions in the murine immune system but without current established link with lupus pathogenesis in man. For example, tumor necrosis factor alpha-induced protein 3 (TNFAIP3) and its binding partner TNFAIP3-interacting protein 1 (TNIP1) are negative regulators of nuclear factor κB signaling and tumor necrosis factor (TNF)-mediated apoptosis (Vereecke et al., 2009).

These findings imply that overexpression of TNFAIP3 would inhibit pathogenesis in lupus-prone mice; its deficiency would exacerbate disease. Newly discovered genes without a known function are placed in the third category of genes associated with SLE in GWAS. The *JAZF1* in this group has now been associated with multiple human phenotypes (Gateva et al., 2009) still awaiting detailed basic functions workout. *FCGR2A* belongs to the fourth group of genes and is associated with SLE risk in GWAS but has no equivalent ancestral gene in the mouse, and therefore cannot yield information for human SLE analysis.

6. Conclusions

The Biosphere is gradually being overwhelmed with several substances from industrial and other activities that has direct role in changes in the incidence and prevalent measures in various diseases. Among these diseases the autoimmune state seems to be a major avenue that impacts and disrupts the homeostatic mechanisms. Autoimmune diseases like asthma are excellent representation of environmental problems acting as indicators of atmospheric as well as the air, the soil and water bodies that are affected by pollutional activities. Thus rises in the incidence and the prevalence of AD within the communities count as direct role of the environmental pollution affecting the gene pool and becomes public health concern. It is important to follow the effects of these substances and the pathways of disease pathogenesis. Currently GWAS is becoming a powerful tool or vehicle that is helping in the understanding the functional roles of the polymorphic alleles particularly those alleles

prevailing across ethnic groups. Analyses of population differences in autoimmune state is a first and important step *in* unraveling the complexity of these genes affected by environmental pollutants represented by mercury. It is common knowledge now that environmental contaminants through the food chains occur; pesticides are found in fruits, vegetables and cereals of European origin estimated to contain about 300 biocides in food products (Commission of the European Communities, 2007, Suñol, 2009), also seen in the urine in majority of US population (Mage *et al*., 2004); and human adipose tissue, serum, and placenta in agricultural areas (López-Espinosa *et al*., 2007).

Studies in the laboratory reveal increasing concern as to whether pesticides currently used can cause neurodevelopmental toxicity (Bjorling-Poulsen *et al*., 2008). Similar concerns go for several substances released into the environment. Regulatory checks help to determine the role they play in diseases seen in the population. We are at a time that full-genome association analyses can produce equivocal array of data, some of which are likely to provide vital new biological insights into autoimmunity that may hold the key to novel therapies. The state of the matter is that susceptibility alleles of autoimmune diseases are now believed to fall into two general groups: (1) those genes that confer susceptibility to multiple autoimmune phenotypes (*CTLA4, TPN22*, *PDCD1*, *FCRL3*); and (2) those that confer tissue specificity to autoimmunity (*INS* in T1D, *PADI4* in RA). Of note also is that allelic diversity within the *MHC* is also a major determinant of tissue specificity. Having a clear understanding of the genetic basis of autoimmunity and the application of this knowledge to appropriate clinical therapies may provide clinical social medicine benefits in several ways. It may be possible to have early diagnostic tools to detect high risk individuals at the highest genetic risk in prospective longitudinal studies aimed at defining the role of manageable/preventable environmental influences on disease. Also the identification of genetically susceptible individuals will enable targeting of preventive therapy once it becomes available at or evasion of detrimental environmental influences. It may also be helpful to align genetic profiles with prognosis as seen in degrees of disease severity in SLE, RA, IDDM etc or response to specific therapies so that more appropriate or aggressive treatments can be selectively targeted. This will particularly be of unimaginable use in health disparity studies.

7. Acknowledgments

This work was supported in part by the Mississippi IDeA Network for Biomedical Excellence, (NIH-NCRR-P20RR0 16476); Arkansas IDeA Network for Biomedical Excellence (NIH-NCRR-P20RR016460); Research Centers in Minority Institutions (RCMI)—Center for Environmental Health at Jackson State University (NIH-NCRR G12RR013459); Pittsburgh Supercomputing Centre's National Resource for Biomedical Supercomputing (T36GM095335); and National Center for Integrative Biomedical Informatics, University of Michigan (NIH-U54DA021519).

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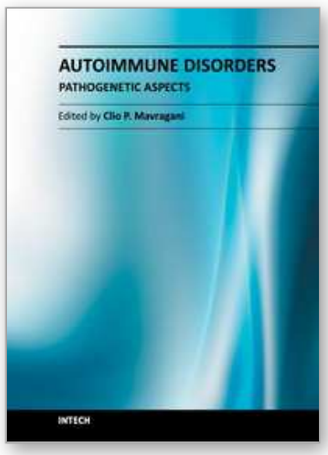

Autoimmune Disorders - Pathogenetic Aspects

Edited by Dr. Clio Mavragani

ISBN 978-953-307-643-0
Hard cover, 508 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

The present edition entitled "Autoimmune disorders - Pathogenetic aspects" aims to present the current available evidence of etiopathogenetic insights of both systemic and organ specific autoimmune disorders, the crossover interactions among autoimmunity, cardiovascular morbidity and malignancy as well as novel findings in the exciting fields of osteoimmunology and immunology of pregnancy.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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