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# Environmental toxicants and autoimmunity

Susmita Mukherjee[1], Swagata Mukherjee[2], Chiranjeeb Dey[2] , Sonali Paul[1*]

[1] Department of Biotechnology, University of Engineering and Management, Kolkata

[2]Department of Zoology, Serampore College, Calcutta University

* corresponding: sonali.paul@uem.edu.in

**Abstract:** Autoimmunity is a condition where structural and functional damage happen by the immunologically competent cells or antibodies to self-antigens . Autoimmune diseases result from destruction of self – proteins, cells, organs by autoantibodies or self- reactive T cells. There are certain factors that can trigger the autoimmunity, like – Genetic factors, Toxic chemicals (Environmental factors), Viral, Hormonal, stress and neurochemicals. In this review there are several aspects that come across the fact that Environmental toxicants has important contribution in autoimmunity. Many pesticides, and Hg also has a definite role in autoimmunity. This review paper provides us elaborate predisposition of environmental toxicants to autoimmunity. This review paper is also consists of little discussion of genetic factors and how they interlinked to autoimmunity.

**Keywords:** Autoimmunity, Environment, Toxic chemicals, Genetic interactions.

## 1 . Introduction:

Autoimmunity literally means protection against self but it implies to injury to self. The body can differentiate antigens, in between self and non self. And it does not establish any immunologic attack against self -antigens .This phenomena is called immune tolerance. Due to fail or disfunction of Immune tolerance, autoimmunity happens. The disease caused by autoimmunity is called autoimmune diseases [1].

The cause of autoimmunity is multifactorial, with both environmental and genetically risk factors. Currently, studies exhibited that, approximately thirty percent of all autoimmune diseases considered by the account of genetical. The rest seventy percent (70%) is due to environmental factors, including toxic

chemicals, dietary components, gut microbes. [2]

In the era of system biology, we have to consider genetic interactions. In this topic it's very important to establish gene – gene or gene-environment interaction. And we found here a strong genetic connection towards autoimmunity. Autoimmune diseases are a several group of complex disorder, which caused by breakdown of self – tolerance, and have a strong genetic element. [3]

There are many ways that multifactorial pathogenesis of autoimmune diseases has confirmed. Some genetic interactions can be [4]:

A. The proteins encoded by genes related with autoimmune diseases are involved in varied inflammatory mechanisms, like antigen presentation, type I interferon, Toll-like receptor and NF-κB signalling, B-cell and T-cell function, apoptosis, and salvation of immune complexes, and cellular debris . [5]

B. Protein modifications could stimulate by genetic variants, in terms of production rate and function, with changes in the related processes. Moreover, different autoimmune diseases are connected with the same genetic modifications, which suggests a shared genetic pathway to decrease of tolerance and induction of autoimmunity.

C . The role of genetic factors in pathogenesis of many autoimmune diseases are ensured by the higher resemblance ratio between monozygotic twins compared to dizygotic twins or other siblings .

**1a. .Gender may play a role in Systemic Lupus Erythematosus (SLE)**

We can consider gender , as a genetic factor , which play a profound role in the incidence of autoimmunity.[6] Systemic Lupus Erythematosus occurs much more frequently in females than in males in both mice and man. Some individuals are susceptible to autoimmunity and some are protected because of the genetic differences , which could act in many ways and affect many tissues . [6]

**1b . Role of FOXP3 in autoimmunity**

Recent studies showed that FOXP3 is an epithelial cell-intrinsic tumour suppressor for breast,[7] prostate,[8] ovary [9]and other cancers[10,11,12]. FOXP3 has an important role in maintenance of self-tolerance , and also in preventing of autoimmune diseases . [13] Inactivating mutations of FOXP3 cause immune dysregulation, polyendocrinopathy, and enteropathy, X-linked syndrome. FOXP3-expressing regulatory T cells help to reduce autoimmunity and immunity against cancer as well as infection. In mouse and human genome FOXP3 binds and thousands of target genes are regulated by FOXP3. FOXP3 is known to activate and as well as repress target genes by the help of epigenetically regulating histone modifications of target promoters.

This types of disruptions confirms growth benefit to cancer cells as Foxp3 gene repress oncogenes while activating other tumour suppressor genes [14,15,16].

Since FOXP3 emerge as important tumour repressor and as well as important immunological regulators . [17,18]

**1cAssociated genetic factors in Rheumatoid Arthritis (RA**)

The human leukocyte antigen (HLA) region contributes to approximately half of its genetic susceptibility ,particularly where disease characterized by the presence of anti-citrullinated antibodies. A number of alleles in the epitope recognition part of the HLA molecule which is , also known as shared epitope , strongly associated with RA and they share a common cue of amino acid residues .Other variant, likePTPN22, TRAF1-C5, PADI4, and STAT4 genes seem to be implicated in RA susceptibility, next to HLA genes [19] genetic factors likely to contribute to a disease phenotype, specially in terms of defeating loss. Recent data has been suggestedarray between radiographic damage and polymorphisms of genes , which encodes TNF, IL-1, IL-6, IL-4, IL-5, OPN, and PRF1 .[19]

## 2. Effect of Dietary components on Autoimmunity

In todays date diets of industrialized part of the world , is way more different than one or two decades ago . This differences of diet comes from different types of food experiences , which comes from different types of food sources , chemicals , flavours , preservatives ,different breeds of food plant and food animals , and their genetic modifications. Autoimmune diseases like diabetes , Multiple Sclerosis (MS) in industrialized area leads to the fact that diet is potential link to such disorder [20]. There is a connection between gluten ingestion and gluten sensitive enteropathies, which is accepted and well established [21].High levels of dietary sodium can raise blood pressure and adverse cardiovascular health, and also [22] it can affect to the immune system [23].MS, systemic lupus erythematosus (SLE), RA, and other autoimmune disorders are associated with low levels of vitamin D .

## 3. Environmental Toxic chemicals and their effect on Autoimmunity

Autoimmune response and diseases can be induced by solvents and many types of chemicals through the variety of effects at biochemical and genetic level .

i)Chemicals are capable of altering cellular proliferation, Th1, Th2, Th3, Th17, and tissue-specific function , apoptosis.

(ii)For induce the production of IL-17 and IL-21 , Th17 cells which can be activated by proteins and lipid , induced by some chemicals.

(iii)For inducing production of anti-HSP90 autoantibodies chemicals activate HSP90.(iv)Chemicals are potential for inducing DNA-hypermethylation and change in cellular functions. (v)Chemicals can increase ROS production and also the induction of DNA-fragmentation.(vi)Chemicals may compete with thyroid hormones or intervene with iodine transportation and chemicals also able to induce oxidative stress that leads to an inflammatory response to the thyroid gland. (vii)Chemicals not only stimulate the synthesis of nitric oxide by nitric oxide synthase but also induce the release of reactive oxygen species.[24]

Some examples of environmental factors which include anthropogenic chemicals, pesticides, respirable particles, drugs, microbes, and diet . [25]

## 3a . Role of Sodium chloride (NaCl) in autoimmunity

It has been demonstrated that up taking processed foods which contain high amounts of salt may in part be responsible for the increasing incidence of autoimmune diseases. In a recent study it was shown that an excess uptake of salt can affect the innate immune system, particularly in, macrophage function .[26]

Salt may add to the wound of complex autoimmune diseases, it has been shown that, by the activation or induction of pathogenic Th17 cells, sodium chloride can induce autoimmune disease [27].The conversion of naïve $CD4^+$ T cells to $CD4^+$T cells expressing IL-17A induce by increasing NaCl concentration. This effect was dose dependent, and by increasing the concentration of NaCl by 40 mM, maximum IL-17A induction can be achieved.

Since the high salt levels did not significantly change cell death, lymphocyte proliferation, or increasement of Th1 or Th2 differentiations. High salt diet was specific for Th17 conditions .The

mechanism by which a high-salt diet enhances the differentiation of naïve $CD4^+$ cells to Extracellular NaCl concentration . This mechanism needs the help of the activation of IL-23 receptor and which is binding by IL-23 that influences the activity of SGK1 and NFAT5 which is able to move the expression of transcription factor RORγt, IL-23R, IL-17A, and IL-17F, and this is the result in the phenotype that alter from naïve $CD4^+$ T cells to pathogenic Th17 cells .In MS, (multiple sclerosis) ,psoriasis, and other autoimmune disorders .

There are many dietary components and dietary salt is just one of them many which can influence T-helper cell differentiation and the growth of autoimmune disease. The effect of other dietary nutrients, such as, vitamins, and other environmental factors on metabolism and microbiota should be established . [28].

**3b . Role of trichloroethylene (TCE ) as water pollutant in autoimmunity**

Trichloroethylene (TCE), an industrial solvent and also a drinking water pollutant. And it has been involved in $CD4^+$ T cell-mediated autoimmunity. An experiment , in mice, these effects were conveyed and stayed in adult mice after developmental and early life exposure to TCE. that determined whether these effects which are persistent are associated with epigenetic changes, by measuring methylation of CpG sites in autosomal chromosomes in activated effector/memory $CD4^+$ T cells . The investigators found that developmental exposure to TCE and it's methylated binding regions of polycomb group (PcG) proteins in effector/memory $CD4^+$ cells that canstayed into adulthood . [29]

**3c . Role of pesticides in autoimmune diseases**

Farming pesticides generally linked to systemic autoimmunity . Though specific role of pesticides is unclear ,In a study,[30] related to serum antinuclear autoantibodies (ANAs) . ANAs were inversely associated with non-cyclodiene organochlorine insecticides , its but positively associated with exposure to the fumigant methyl bromide . The carbamate insecticide aldicarb which can associated use of four organochlorine insecticides . So that similarly , specific organochlorine insecticides might has a risk of developing systemic autoimmunity .

People who are exposure to respirable crystalline silica in occupations like construction, mining, and farming is connected with development of autoimmune diseases , including systemic lupus erythematosus . It has shown weekly repeated airway exposure over 1 month to silica leads to pulmonary ectopic lymphoid neogenesis, systemic autoantibody elevation, and glomerulonephritis. Recent data says that within 1 week after silica exposure, it increases many events, mRNAs associated like chemokine release, cytokine production, sustained interferon activity, complement activation, and adhesion molecules. which were evident in the lung that increased over the course of the 3-month long experiment. Expression of innate and adaptive immune genes was observed later in the spleen and kidney. These findings suggest that upon silica exposure [30]

**3d . Environmental microbes can cause systemic autoimmunity**

Environmental encounters with microbes including viruses and bacteria can influence development of autoimmunity. It has noted, Epstein-Barr virus (EBV)

infection is a risk factor for multiple rheumatic diseases. [31]After evaluating the association of EBV antibodies with Sjögren's syndrome (SjS) ,its found that patients with SjS had both a significantly higher prevalence. In later studies, analysis of 14 ceroepidemiological studies found the associations between SjS and antibodies to EBV (Epstein Barr Virus ) early antigen and viral capsid antigen.

Gut microbiome dysbiosis has been linked to the different autoimmune diseases. [32] Recent epidemiological and mechanistic evidence showed that associating environmental exposures with several autoimmune diseases.[25] They discuss how gut microbiome composition interchange might influence disease pathogenesis, particularly in response to exposure to environmental chemicals.

**3e . Mercury (Hg) as environmental toxicants**

Mercury (Hg), atoxicant ,as well as an environmental factor Mercury , which reported having a link with autoimmunity .[33]It exists in several chemical forms .And which is faced by humans in dental amalgams, certain vaccines, occupational exposure, atmospheric pollution and seafood. Several studies have investigated that the effect of the various forms of mercury (Hg). Which includes elemental (Hg0), inorganic (I Hg) and organic mercury (oHg) and how they are associated with autoimmunity. Peripheral blood mononuclear cells (PBMC) , which are used in vitro studies, from healthy participants have shown that methylmercury (MeHg) causes cell death , which is shown at lower concentrations than Inorganic Hg(I Hg). Though exposure to I Hg leads to more enhanced pro-inflammatory activity in comparison to MeHg.[34]

One study reported that tolerance to murine Hg-induced autoimmunity 100 (mHgIA) was achieved following exposure to HgCl2, in 24 h old neonatal 101 rats. The authors imputed the observed tolerance to a subset of CD8+ T 102 cells, as rats that were treated with anti-CD8 monoclonal antibodies exhibited a loss of tolerance. [35]

**3f .Zinc and cadmium helps to induce autoimmunity**

According to report, several effects that can induce zinc deficiency on various immune cells. In autoimmune disorders, low plasma zinc levels (hypozincaemia) can leads to an acute phase response ,like RA. Rheumatoid Arthritis (RA) is an autoimmune disease that may results extra-articular expositions .Extra articular expositions primarily affect the lining membrane of the joints, which is called the synovium. The systemic effects of the disease seem to appear at its very onset. To date, cause has been unidentified, only several possibilities have been point out. One factor of zinc metabolism is, zinc has critical cellular and molecular function, it'sin both the innate and adaptive immunity and that affects the susceptibility to infections. [36]

As well as, Rheumatoid arthritis (RA) is strongly connected with microbial infections. [37]

Systemic zinc deficiency is exhibited by low serum zinc, that is involved in the autoimmunity. [38]The immune responses and the inflammation in RA can be associated with some agents. Agents that regulate zinc homoeostasis and clearly is critical for management and treatment of the disease . [39] In an experiment, Patients with rheumatoid arthritis (RA), which express HLA-DRB1 have a higher

activity of zinc-dependent MMP-3. This is an enzyme that can degrade cartilage.[40]

On the other sideCD40 is linked to zinc transporter that is ZnT7, which express in the regulation of immune function of human B lymphocytes. ZnT7 in B lymphocytes decreases the expression of CD40 on the cell surface.[41]

**3g. Stress can be a factor effecting autoimmunity**

Stress is a psychophysiological state, in which steady mental condition is threated, or disturbed [42]. Autoimmune diseases are heterogeneous and group of chronic diseases which is occur secondary to loss of self antigen tolerance. It outcomes when environmental demands exceed an individuals' adaptive capacities. Genetic factors and as well as environmental factors interplay, and cascade of events leading to induce such autoimmune diseases and autoimmune reactivities. It has been shown that stress has a great role on such diseases in genetical susceptible patients. During the stress response, is stimulates catecholamines, glucocorticoids, which are released from locus coeruleus and adrenal gland [43]. some biomolecules exert their action over various immune cells in both innate and adaptive form of immune system. Thus it released cytokine The increase of IL-4 promotes T-helper 2 ($T_h2$) cell differentiation, and on the other hand the decrease in IL-12 and the increased IL-10 production decrease the number of T-helper 1 ($T_h1$) cells.[44]

The relationship of autoimmunity with stress is intertwined. Stress has been shown to be associated with disease onset, and diseases exacerbations in rheumatoid arthritis,[55]and also systemic lupus erythematosus , inflammatory bowl diseases, multiple sclerosis ,graves diseases [45] and other autoimmune conditions .[46]

Finally, psychological therapy and cognitive behavioral therapy thought to reduce stress levels, which was shown to be effective and influencing better outcomes in many autoimmune diseases. [47]

**3h. Smoking is environmental risk factor for inflammation and autoimmune diseases**

Cigarette smoke and hypoxia both lead to enhance oxidative stress and also production of reactive oxygen species and other free radicals, which have several effects ,like the generation of autoreactive pro-inflammatory T cells and autoantibodies, which reduces in T regulatory ($T_{reg}$) cell activity, and increased expression of pro-inflammatory mediators [e.g., interleukin-6 (IL-6), interleukin-4 (IL-4) and interleukin-8 (IL-8)].[48]

Smoking and hypoxic environments may associate as potent environmental risk factors for inflammatory and autoimmune diseases.

In medical science autoimmune diseases has been a hot topic for the last decade. In autoimmunity immune cells unable to recognize self-molecules, and they recognize them as foreign molecules and it becomes hyperactive to remove these molecules, which leads to chronic inflammation, . [49] In today’s date,for the development and progression of inflammatory and autoimmune diseases, environmental factors play vital role. Within such factors, cigarette smoke (CS) and hypoxia are two potent factors. And they are environmental stresses that can cause imbalance in normal immune homeostasis by regulating immune-regulatory activities. This activities may

lead to inflammation and autoimmune diseases. [50]

Cigarette smoking can directed to inflammatory and autoimmune diseases through multiple mechanisms, as following: genetic/epigenetic modifications, over oxidative stress, reactive oxygen species (ROS), and free radical production, and nicotine and heavy metal toxicity. These effects, may enhanced B and T cell proliferation. And they reduce immune suppressive T regulatory (Treg) cell proliferation and activity, as well as they can also able to generate autoantibody production, and also can enhance the expression of some pro-inflammatory mediators, like IL-6, IL-8, tumour necrosis factors (TNFs), Interferon gamma (INF-γ). So we can conclude thatcigarette smoking is a risk factor for being developed inflammatory and autoimmune diseases.[51]

Several toxic components of Cigarette smoking have immunomodulatory effects that evident from genetic/epigenetic changes and which lead to altered gene expression and function; some examples involve changes in pro-inflammatory cytokine expression and histone deacetylase (HDAC) and histone acetylase (HAT) activities.[52]

Several studies have demonstrated cigarette smoking to be a valid environmental risk factor for certain autoimmune diseases, including RA, MS, and SLE. [53]

Adeveloping risk of rheumatoid arthritis (seropositive RA) for individuals who smoked for more than 20 years, and more increased risk for RA in male smokers have been reported. [54]

Increased cero-positivity for dsDNA (i.e., anti-dsDNA antibodies) has been found in current smokersand that serves as a diagnostic tool for SLE. [44,46] demethylation results in anti-dsDNA antibody production. And which sufficiently stimulates lupus-like autoimmunity in genetically predisposed mice and, likely, humans .[55]

Cigarette Smoking cause oxidative stress , which is a potential risk factor for autoantibody production. For example, in red blood cells (RBCs), elevated level of ROSresults in the production of autoantibodies against RBCs. Thiscauses autoimmune haemolytic anaemia (AIHA). [56]

### 3i. Excessive iodine intake can cause autoimmune thyroiditis

Additional iodine intake can cause dysthyroidism, especially in patients who are suffering underlying autoimmune thyroiditis. This phenomena leads to thyroid destruction, hence it leads to presentation of thyroidal antigens to the immune system, which leads to autoimmunity and autoimmune reactivities.[57]

## 4 . Conclusion

Several studies suggest that taking of ω-3 polyunsaturated fatty acids (PUFAs), which found in fish oil might be effective against the development of autoimmune diseases. After many experiments the results are both of positive as well as negative. In today's date it's very important to put a view on this particular topic. Autoimmunity is a condition where body's self tolerance is damaged. In this review paper it has shown that both environment and genetic factors are responsible and as well as we come to know how different factors like dietary components , may help to induce

autoimmunity . And also role of stress that may have a link to induce autoimmunity .

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