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Environmental Toxicant and Immune cells: A Review

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Abstract:

Immune system is the adaptive defense mechanism which is evolved in vertebrates to keep them from invading pathogenic microorganisms and cancer. In immune system consists of some specialized cells like: lymphocytes, neutrophils, NK cells, basophils, macrophages, eiosinophils, mast cells, etc.

Ecotoxicology is a subdisicipline of environmental toxicology concerd with studing the damaging effects of toxicants at the population and nature. Environmental toxicants are simply toxic substances in the nature. Environmental toxicant which is effect on ecosystem very badly.

In this paper we discuss that how environmental toxicant effect on immune system or immune cells.

Keywords: Immune system, Ecotoxicology, Immune cells.

1. Introduction:

Immunity is a reaction to foreign substance, including microbes, as well as to macromolecules such as proteins and polysaccharides, regardless of the physiologic or pathogenic consequence of such a reaction[2]. Blood and lymph system participate a essential role in coordinating the function of immune system[3].

The immune system is two types. They are innate and adaptive immunity. Innate immunity represent a rapid and stereotype response to large but limited number of

stimuli. It is contained by physical, chemical, and biological barriers , specialized cells and soluble molecules present in all individual, irrespective of previous contact with offending agents or immunogens and does not change quantitative or quantitatively after contact[1]. This immunity is nonspecific.

Adaptive immune system is able to recognizing and can be eliminate specific foreign microorganisms and molecules. Adaptive immunity develops as a response to infection and adapts to the infective agents [2].

Immune system conveys its work through different cells and soluble molecule secreted by them. Different type of immune cells involve in immune system[1]. Those immune cells are: natural killer cells(NK), macrophages, lymphocyte (B&T lymphocytes), dendritric cells, mast cells, neutrophills, eioshinophils, basophils, antigen presenting cells etc.

Heavy metals are well known environmental pollutant. Heavy metal can be defined those metallic element that has a relatively high concentration. It is harmful or dangerous at low concentration. Example of heavy metals are: mercury(Hg), cadmium(Cd), chromium(Cr), arsenic(As), lead(Pb) etc.

Environmental toxicants especially heavy metals primary or secondary effect on immune cells and immune system of vertebrate animals.

2. Immune cells:

Natural Killer Cells:

Natural Killer cells or NK cells can be defined as those cells who are non phagotic & non adherent in nature but it can release perforin in close proximity to a cells that is selected for destroying. Natural Killer cells or NK cells originate from bone marrow.They are about 15 micrometer in diameter with a kidney shaped nucleus and azurophilic granules in their cytoplasm. Perforin forms pores in the cell membrane of the target cell through which the granzymes and associated molecules can enter inducing apoptosis.

The NK cells are important line of nonspecific defense, detecting, and lysine cells infected by viruses, bacteria and protozoa as well as tumor cell. Furthermore, they recruit neutrophils and macrophages activate DCs & T and B lymphocyte[4].

They are capable of identifying alterations in surface marker of the auto cells, NK cells provide natural toxicity.There are different types of surface receptors who are activated and inhibitory signals are identified. The inhibitory receptor identify the cells MHC class I molecules, expressed on the surface of all nucleated. In general, there is dominance of inhibitory receptor preventing lysis of host's normal cells that express MHC class I . Viruses and tumor infected cells have low expression of MHC class I protein, becoming vulnerable to the action of NK. The tumoricidial capacity of NK is increased by cytokines such as interferons and interleukins [4].

Macrophage:

Macrophages are mononueclear phagocytic leucocytes that play important roles in adaptive as well as in Innate immunities. They are the 1st line defense against bacterial infections and are indispensible participants in the immunological defense by processing and are indispensable participants in the immunological defense by processing and presenting antigens to lymphocytes.

Unlike neutrophils, macrophages can remain in tissue for 4 month to year acting as a true sentinels. In Innate immunity, macrophages process &present antigen via MHC molecules, which stimulating the response mediated by TL [5].

Three type of macrophages are present: activated, tissue repair, and regulator macrophage. Activated macrophage act by tumoricidial and microbial activity, which secrete large amount of proinflamatory mediators and cytokine. They are involved in cellular immune response. Tissue repair macrophage activated by IL-4 which help tissue repair by stimulating fibroblasts and promoting extracellular matrix deposition. Regulatory macrophage release of IL-10 which help in regulatory activity[5].

In inflammation macrophages activate of TL and LB by costimulatory molecule.They release proinflammatory cytokines such as IL-1, IL-6, IL-12, and chemokines[6].

Lymphocyte:

Lymphocytes are originated from pleuripotent hemopoietic stem cells. Lymphocytes circulate in blood and lymph. These cells are the cheif constitunents of the immune system. 3 types of lymphocyte cells found in body on the basis of immunological function & cells membrane components;

these are T lymphocyte/ T cells, B lymphocytes/ B cells & null cells [3].

It is not possible to differentiate morphologically similar T & B lymphovytes in peripheral blood smear but they are functionally different in nature & different surface marker [3].

B lymphocyte:

B lymphocytes are develop in bursa of fabricus (birds) or bursaequivalent regions in bone marrow. The B cels following their maturation express unique antigen binding receptors on its membrane [3]. These receptors are membrane bound antibodu molecules. When naïve B cells 1st encounters antigen that matches its membrane-bound antibody , it get differentiated into memory B cells and effector B cells called plasma cells. Each plasma cell can secrete enormous amount of one of the 5 classes of antibody within its short lifespan. In humoral immunity, secreted antibodies act as a major effectors molecules. In addition to membrane antibody molecules which serve as the antigen receptors some other molecules having immunological importances are also expressed on the membrane of mature B cells.Some of these are: Class II MHC molecules- help the B cells to act as an antigen presenting cell [2].

B7-1 (CD80) and B7-2 (CD86) – these molecule interact with surface molecules of different T cells [2].

T lymphocytes:

T lymphocytes are differentiate and mature in thymus before their release into circulation. On the basis of surface marker different subsets are noticed in T cells. T cells play an vital role in cell mediated immunity [3]. T cells receptor cannot recognize free antigens, rather they recognize only antigens which are bound to the particular cell membrane proteins called major histocompatibility complex molecules. All T cells on their membrane express the T cell receptor a complex of polypeptide that includes CD3 and CD4 or CD8 molecules. There are two well defined populations of T cells : T helper cells T cytotoxic cells. T helper cells express the membrane glycoprotein called CD4 wherease t cytotoxic cells express a membrane glycoprotein called CD8. It is activated by antigens then the native T cells helps to begin to divide & give rise to a clone of effector cells each & it specific antigen class II MHC complex . These T

heleper cells secrete various effector molecules or cytokines that play a central role in the activation of B cells, T cells and other cells that participate in immune response [2].

After the interaction with an antigenic class I MHC complex on the surface of an altered self cells in presence of appropriate cytokines the T cytotoxic cells are activated.

T cells also express distinctive membrane molecules in addition to T cell receptors CD4 and CD8 molecules. Few of these are: The receptor CD28 belongs co-stimulatory B7 families of molecules that present on B cells & other antigen presenting cells [2].

CD45- act as signal transduction molecules [2].

Antigen-presenting cells (APCs):

Antigen presenting cells (APCs) are specialized cells group that are able to capture microbial & other antigen & display them to T lymphocytes. They stimulate the proliferation & differentiation of the lymphovytes by the providing signals [2]. Most important APC in initiating T cell responses is the dendritric cells. Others include macrophages that present antigens to T cells during cell mediated immune responses B lymphocytes that act as APC for helper T cells during humoral immune response, follicular dendritic cell that display antigens to B cells during particular phases of humoral immune responses. Many of these cells function in antigen presentation for a small time duration during a substance inflammatory response [2].

Dendritic Cells:

Dendritic cells play vital roles in antigen capture. The stimulation of T lymphocyte responses in protein antigen. Most of dendritic cells procedure and near antigen to T_H cells. These cells are found under epithelia of many organs[2]. According to the location these can be classified as:

Langerhans cells:

These are present in the epidermis and mucous membrane. They are act as sentinels for the detection of invading pathogens. Interaction with pathogens implient langerhans cells migration to lymphoid regions to prime T cell immunity [3].

Interdigitating Cells:

These cells are occurred in T cells areas of secondary lymphoid tissue and thymic medulla.

Interstitial dendritric cells:

These cells are present in lung, heart, kidney, liver and gastrointestinal tract. They are efficient in presenting soluable antigen. Circulating of antigen and antibody complexes fasten to the receptors on follicular dendritic cells and they helping in activating the B cells in lymph nodes.

Follicular dentritic cells:

These cells are create in the germinal centers of lymphoid follicles in lymph nodes, spleen and mucosal lymphoid tissues. They don't express class II MHC molecules. They trap antigen complex to antibodies or complement products. B lymphocytes recognize the antigens by the help of follicular dendritic cells. High affinity antigens displayed to the antigen bound receptors of activated B cells [3].

Neutrophils:

Neutrophils are the most abundant type granulocytes in peripheral blood, with an important role in the early stages of inflammatory reaction & sensitive to chemotactic agents such as cleavage product of complement fractions & substance released by mast cells & basophils . One liter of human blood contains about 5 billion neutrophils.

The neutrophil phagocytc ability is encouraged by binding of its receptors for opsonins IgE-Fc, C3b, TRLs. These cells also undergo degranulation, releasing 3 classes of granules in the extracellular environment.

Primary granules contain important mediators , such as myeloperoxidase defensins, neutrophils elastase, permeability increasing protein and bacterial cathepsinG[7].

Secondary granules with components specifically secreated by neutrophils with lactoferin is a prime example[7].

Tertiary granules with cathepsins &gelatinous are main protein[7].

The collective function of the grabules helps in digestion and elimination of pathogens phagocytised by the cell. The chemotactic mode of cytokine at the site of inflammation initiates the marginalization & extravasculation in neutrophils to attract near the infected area.

When neutrophils have received the accurate signals, they take 30 minutes to leave the blood. Then they reach the infected area. When they reach the spot of infection then they do not return to the blood. They turn into pus cells and die.

Modern studies we known that netrophils also generate the neutrophils extracellular traps(NETs) which is destroying extracellular bacteria. The NETs are presents in huge amount in inflammatory site acting directly on microorganism also serving as a physical barrier which prevent spreading. In medical terminology the raise of neutrophils is known as leucocytosis[7].

Eosinophils:

Eosinophils with bilobed nucleus and granular cytoplasm are motile phagocytes. They found about 2-5% of total blood leucocytes in normal healthy individuals. They show extravasations and phagocytosis during inflammation reaction. Granules contain toxic protein & cationic protein called cathepsin which help in the inhibition of a big parasite. The receptor bind IgE antibody help in this tasks[3]. In addition to that they assist in the removal of immune complexes through phagocytosis and regulate functions of other immune cell. In healthy individuals raise of eosinphils is a general immunological response to intestinal parasites. Granules of eosinophils are membrane bound. When the parasite is too big for phagocytosis then plasma membrane of granules release their toxic protein and histamine in the adjacent of parasite. The released substances of eosinophils bind to the membrane of the parasite to kill and eliminated [3].

Basophils:

Basophils are one of the least abundant cells in blood . They are non phagocytic in nature. They work by releasing their pharmacologically active substance such as histamine, sertonine, heparin, peroxides etc. Basophils release histamine which help in inflammatory response & fighting with invading organisms [3]. In general the released substance of basophils result in Type I hypersensitivity / allergic reaction. Basophils have receptors that allow binding f IgE, IgG, histamine. They have receptors for Fc region of IgE antibodies the IgE antibodies produced against an allergen bind to basophils. Antigen react with basophil bound IgE antibody which induce to release of histamine. For this interaction, permeability of capillaries are increased.

Another substance prostaglandins which increased blood flow to the site of infection [3]. Then blood clotting elements to be delivered at the infected area, which prevents further spread of pathogens [3].

Mast cells:

Mast cells play an important role in allergic reaction. Mast cells are created in the bone marrow. It is released into blood as undifferentiated cells. These cells enter a wide variety of tissue and become mature [2]. Mast cells are found in almost all parts of the body along with the endothelisl cells of the blood vessels as well as mucosal cells. IgE antibodies are present on the surface of mast cells. The IgE antibodies secreted against specific allergen bind to the mast cells and induce mast cells secretions on antigen binding. These chemicals are harmful to the parasite & also serve as signals to other immune cells to come and join in the reaction. The action of mast cells and the effect of their secretion are similar to the action of basophils [3].

3.Environmental Toxicant:

The pollution is one of the major challenges in this modern society[8]. Environmental corruption and pollution by heavy metals is a threat to the environment and it is the serious concern[9,10].Combination caused by rapid industrialization and urbanization by heavy metals of environment. Their mobilization and transport rates have greatly increased from 1940s[11,12]. The environmental natural sources associated with metal-containing rocks and volcanic eruptions, industrial emissions, mining, smelting, and agricultural activities such as application of pesticides and phosphate fertilizers. Anticipation of fossil fuels also participates to the release of heavy particles or metals like cadmium to the nature [13]. Heavy metals that can be resolute in the environment, corrupt the food chains, and cause different health problems due to their toxicity [14]. Metal concentrations above threshold levels affect the microbiological balance of soils and it can also reduce their fertility [15]. Both animals and humans bioaccumulation of toxic heavy metals of rapture ecosystem may have similar effect[16]. In biota such heavy metals may show negative effect on the ecological health of aquatic animal species & may contribute to collapse their reproduction. Heavy metals are strongly neurolysin in fish species[17]. And those heavy metals with chemical also damage their communication

process with their environment [18]. Generally, such distortion has negative effects on fish populations because deformities affect their daily survival process, growth rates, welfare, and external image. On environmental heavy metal pollution such as deformities in fish can distribute as excellent biomarkers[19]. In aquatic environment, metal of natural or anthropogenic resources are ubiquitous & interaction with particularly fishes a main source of protein for human consumption which is vital socioeconomic impotence [20].

4. Effect of Toxic Heavy Metals On Fish:

Aquatic biota is reveal to heavy metals through their different way such as water, sediments, and food [21]. Freshwater fish are different toxic which is released to industrial sources. Contamination of fish for those heavy metals has become a very important global issue because it is a threat to fish and it's a health risk to fish consumers[22]. The important things is assessment of bioaccumulation of heavy metal & we need to know the heavy metal in fish tissues for management of aquatic ecosystem & human consumption of fish[25]. Fish have fatty acids at high level and cholesterol at low level. This is the important source of proteins[26]. Edible fish is good for human diet, it is beneficial and therefore it's recommended for balanced diet. Moreover, contamination of fish by toxic heavy metals is know to be a risk for human health which can be raised concerns about their consumption especially in more sensitive group of human population like woman, children, & people having risk of disease from other causes. Various factor play several role in bioaccumulation of metals in freshwater fish, factor like fish character & external natural factors. Factor included fish age, size(weight, length), feeding habits 7 body physiology, including metal concentration & metal bioavailability in the water colum & responsible as well as involve environmental factor. The accumulation of heavy metals in different tissues of fish is differently depending on the structure and function of tissues. Metabolically tissue like skin & muscles has lower aggregation active tissue like gills,liver, & kidneys. Fish gills are acting as a target tissue for increasing gathering & remove of heavy metal like Ni[26]. For poor heavy metal accumulation, fish ,uscle are target tissue [27]. They are vital because of humans consumption, trace metals

bioaccumulation in fish muscles is specific [28]. Several studies of bioaccumulation in fish have observed tissues are edible because of metal concentration of fish muscles & most relevant associating human health [29-36].

5. Human Exposure to Heavy Metals:

Humans are release the toxic heavy metals in the environment through their different way including ingestion, inhalation, and dermal absorption. In developing countries people are more exposed to toxic metals[37] because people are not aware & knowledgeable about the effect of heavy metals on human health [38]. People may be exposed to heavy metals in the work place and as usual in their daily life. Occupational exposure can be defined as human revelation to toxic chemicals at work place while non occupational exposure is the revelation to such chemical in the natural environmental people can expose to such heavy metals in different ways like mining & industrial operation they may inhale dust & particulate matter containing metal particles or the peoples who are extracted gold through amalgamation are exposed to Hg vapors. From the study it has been reported that welders with prolonged expouser to welding fumes had higher levels of Cr, Cd, Pb, in blood which increased oxidative stress[39].Cd & other toxic heavy metals which are present in tobacco leaves have the bad effect on smokers[40]. The major exposure source for the general human population is Ingestion of heavy metals through food and drinking water. Industrial and agricultural activities are the rapid economic development around the globe has led to intensification. This may lead to contamination of soil, air, 7water with toxic heavy metals. Producing human food in heavy metals contaminated media may cause bioaccumulation of these element in the human food through which the heavy metals ultimately reach to the human body[40].

6. Effects of Toxic Heavy Metals on Human Health:

Major antioxidents of cells mainly the antioxidant & enzyme which have the thiol group (-SH) are depleted by heavy metal like Cd, Pb, Hg, As. These type of metals may increase the generation of reactive oxygen species (ROS) likeb hydroxyl radical(HO_), superoxide radical, & hydrogen peroxide. Oxidative stress can be defined by the increased generation of

reactive oxygen species which can destroy the inherent antioxidant barrier of cells[41]. Heavy metals with Cd, Pb, and Hg, are nephrotoxic, especially in the renal cortex[42]. In toxicity the chemical form of heavy metal is essential. Mercury toxicity largely depends on Hg convergence[43]. In the cancer & diabetes patients toxic heavy metal like chromium(Cr), cadmium(Cd), lead(Pb), have been found in relatively higher concentration compared to those in the normal subject in Lahor city, Pakistan [44].

7. Consequence of Arsenic on fish innate immunity:

As many components of innate immunity are evolutionary conserved and arsenic is one of them that often accumulate most rapidly in aquatic habitats. Monitoring arsenic levels & their associated health effects in fish may not only provide insight into overall ecosystem health [60] but may also act as a senital for potential impacts on human health.

Metallothionein (MT) has been induced arsenic resulting the oxidative stress response and also reducing reactive oxygen species(ROS) scavenging enzyme production[61]. And the final outcome is extention of the exposure of unregulated enzymatic activity [62].

Innate immune system is very drastically effected by arsenic:

i) Antiviral gene expression causing adequet respiratory burst response.
ii) TNF production.
iii) Antiviral response in fish effecting the indigrients of innate immunity.

8. Consequence of Chromium on human:

A large number of biologically active substance like heavy metals, have direct effect on human immune system. In environment chromium trivalent Cr(III) and hexavalent Cr(VI) forms are found. Vegetables', meat, urban air hip & cigarettes are the major source of chromium for the humans[46,47].Chromium enters to the body by the help of lungs gastrointestinal tract and to a lesser extent to skin. When chromium enters by dermal and inhalation routes then it is toxic and causes lung

cancer, nasal irritation, nasal ulcer and contact dermatitis [48].

Effect of chromium on lymphocytes:

The effect of chromium on lymphocytes has been investigated in many trials. Borella et al. [49] looked at how toxic metals like Cr(III) and Cr(VI) affected phytohemeagglutinin-induced blastogenesis of human lymphocytes in vitro. Cr(VI) has a biphasic effect with stimulatory effects at low concentrations and inhibitory effects at higher concentrations. Faleiro et al.[50] investigated the influence of CoCrMo disc samples on the CD3 mediated in vitro reaction of human peripheral blood T lymphocytes in vitro. In the presence of CoCrMo disc samples, lymphyocyte differentiation is inhibited. Scanning electron microscopy ultrastructural tests showed that the variations in the no of blast cells on CoCrMo discs after a 4 day culture are associated with the proliferation findings . After intraperitoneal injection in mice or in vitrostudies on murine lymphocytes, cobaltchromium particles greatly inhibit the proliferation of both T and B cells as well as the generation of immunoglobulins can play a role in the development of implant associated infection in patients with prosthesis[51].

Several tests, on the other hand, have shown that chromium salts /alloys have little effect on immune system cells. In vitro, yucesoy et al.[52] looked at the immunotoxic effects of the lead, cadmium, and chromium on natural killer cell function. The metal salts have little effects on the activity of NK cells. Likewise for the kinetics of cell division in culture of peripheral blood lymphocytes , no effect is shown in stainless steel welders subjected to chromium and nickel present in welding fumes[53-56].

consequence of chromium on macrophages:

Chromium inhalation has little effect on lung morphology, but macrophages become swollen, multinucleated, , or vacuolated and collect as nodules in intra-alveolar spaces. Higher Cr(VI) doses suppress alveolar macrophage phagocytic activity and the humoral immune response, while lower Cr(VI) does activate alveolar macrophage phagocytic activity and improve humoral immune response[54, 57-61]. Macrophages may be stimulated to produce nitric oxide(NO), which is needed for a variety of functions. Tian and Lawrence [55, 62-65]

investigated the effect of different metals, including chromium, and discovered that chromium does not modulate NO development by cytokine-stimulated murine macrophages (IFN-Q, TNK-K). Chromium mildly inhibits inducible NO synthase, implying that it can directly alter the enzyme or cofactor. Metals may thereforebe pathogenic by inhibiting or increasing NO development, suppressive defense mechanism ,or inducing hypersensitivity. Howie et al.[56] analysed the literature on animal and cellular models used to research the reaction of cobaltchrome alloy implants to wear and corrosion materials. Huge amounts of particles injected in a single bolus cause acute inflammation and necrosis, accompanied by a chronic inflammatory response. Macrophages are the most common cell type that can live in tissue for years. In vitro experiments indicate that cobaltchrome alloy particles macrophage to release inflammatory meditaors before causing cell death. Apart from causing bone resorption, these mediators have significant effects on osteoblast-like cells. Lee et al.[57] demonstrated does-dependent effects of chromium chloride and CrP on glucose uptake , supero0xide anion formation activity of glucose-6-phosphate dehydrogenase, and Escherichia coli phagocytosisby incubating pulmonary alveolar macrophages in medium in the presence or absence of insulin. Gatta et al. [58-62, 66] investigated the effects of nutritional chromium yeast supplementation on rainbow trout immuneresponse (Oncorhynchusmykiss). A flavorable influence on serum lysozyme production is found in fed a figh-chromium diet. Significant differences are observed in ability to phagocytose and level of respiratory burst elicited by sh fe3d supplemented chromium-fed macrophages. Chromium supplementation inhibits TRNF-K secretion in U937 monocytes cultured in high-glucose medium, according to Jain and Kannan, [59-63]and this effect appears to mediated by its antioxidative effect.

9. Conclusion:

The environmental toxicant is one of the major challenges in this modern society. Environmental pollution by heavy metal is a threat to environment and ecosystem.

On this basis of the paper, I came to known that immune cells and immune system badly effect by heavy metals toxicants. Example: Arsenic disrupts the immune response of

fish, and Chromium affects various components of the immune system & may results in immunostimulation or immunosupression.

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