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ALTERATION IN IMMUNOLOGICAL PROFILE DURING MALIGNANCY: ROLE OF ENVIRONMENTAL TOXICANTS

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

[1] Department of Biotechnology, University of Engineering and Management, University Area, Plot No. III, B/5, New Town Rd, Action Area III, Newtown, Kolkata, West Bengal 700156;

[2] Department of Zoology, Serampore College, 8, William Carey Sarani, Maniktala, Serampore, West Bengal 712201

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

ABSTRACT

Exposure to environmental toxicants is a well documented predisposing factor for cancer. Many types of carcinogenic toxicants are found in the environment.This review focuses on three types of toxicants - heavy metals, pesticides and pollutants. Through different mechanisms of cell damage, these toxicants cause malignant growth. There is a strong correlation found between malignancy and cytokines. This work establishes the link between environmental toxicants and changes in cytokine levels with cancer progression.

Keyword: carcinogens, cytokines, chemokine, toxicants

1. INTRODUCTION

Environmental toxicants are simply toxic materials in the environment, involving a wide range of chemical and physical agents discharged into the environment [1]. A broad variety of toxicants are present in the environment, of them many are carcinogens. Immunoprofiling is a quantification tool which studies the human immune cells based upon their functional biomarkers [2]. Immunoprofiling is useful for studying progonosis in various types of malignancy and delivers target for immunotherapy. Quantitative multispectral imaging system, which allows concurrent detection of multiple immune markers, is a novel technique for examination of the tumor immune environment[3].

2. MALIGNANCY

This is term for uncontrolled cell growth. Through blood and lymph system malignant cells has a power to disperse to the other body parts. There are many main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or covers the interior organs. Leukemia begins in the blood forming tissues like bone marrow. Lymphoma and multiple myolema start in the immune system cells.Central nervous system malignancies starts in the tissue of the spinal cord and the brain [4].

3. IMMUNOPROFILING

The human immune system protects from many infectious diseases including cancer. Major approaches in our comprehension of the immune system have largely appeared from studies using animal models such as mice. However, this mouse-centric research has also restricted our potential to comprehend the human immune system and how it differences with age and disease state. The fact that we are yet to define what develops a normal human immune system has obstructed our potential to diagnose, treat, and forestall many human diseases. Immunoprofiling is a measurement state. It calculates the frequency of human immune cells by the help of the functional biomarkers. Flow cytometry, mass cytometry and imaging technology are involved in immunoprofiling.

4. ENVIRONMENTAL TOXICANTS

Environmental toxicants are simply toxic materials including many chemical and physical factors. Pollution of the abiotic ecosystem components (water,land and air) occur through discharging the harmful factors into the environment.

5. ENVIRONMENTAL TOXICANTS WHICH ARE INVOLVED IN MALIGNANCY AND THEIR CARCINOGENIC MECHANISM

5.1.HEAVY METALS

Almost all heavy metals are carcinogenic toxicants. Under the IARC (International agency for Research on Cancer), Arsenic (As), cadmium (Cd), chromium (Cr), and nickel (Ni) are categorised as category 1 heavy metals [5].

5.1.1. Arsenic (As)

Arsenic is a cytotoxic element [6]. Contact with arsenic generally results from ingesting contaminated food and water [7, 8, 9, 10]. As carries role in the development of lung, bladder and skin cancer [11].There is a strong association between As exposure and mortality rate of cancers including Colon,Gastric, Kidney,Lung and Nasopharyngeal [12].Epidemological studies

have also suggested an association between chronic low level As exposure and pancreatic cancer development and non - Hodgkin's lymphoma[13,14].

Carcinogenic mechanism :

Arsenic follows carcinogenesis process by means of Generation of reactive oxygen species (ROS),epigenetic alterations and by damaging the dynamic DNA maintenance repair system. [15]. Further examination of As revealed its ability to reduce intracellular concentration of gluthaione, carrying the potential for carcinogenic activity by oxidative stress of the cell[16, 17]. Another novel pathway for tumorigenic activity was found in human bladder cell. This study determined that the chronic exposure of As had the potential to induce morphological changes and alter protein gene expression which regulate proliferation[18].

5.1.2.Cadmium (Cd)

Cadmium is an immensely toxic heavy metal. Exposure to Cd leads to carcinogenesis in multiple tissue including breast, esophagus, stomach, intestine, prostate, lungs and testes[19,20,21].Increased concentration of Cd were detected in malignant gliomas, suggesting a potential role in brain carcinogenesis[22].Cd also plays a carcinogenic role in pancreatic cancer[23].A study strongly correlated the increased Cd concentration in urine with the risk of development of gastrointestinal cancer[24].

Carcinogenic mechanism :

Cadmium exposure causes malignancy through the mechanisms of ROS generation, genetic alterations, inhibition of the cellular DNA damage repair process [25,26]. It has been found that both chronic and acute cadmium exposure causes dysregulation of the cellular functions leading to malignancy [27]. Oxidative stress following Cd exposure stimulate transcriptional activity of the metallothionein (MT) coding gene. [28]. Chronic exposure of Cd effects especially the kidney by the Cd -MT complex formation, causing conformational changes in renal tubular cells and degradation of glomerular cells that effects the calcium metabolism resulting in kidney stone and cancer [29,30]. Cd also act as an endocrine disrupter, mainly in reproductive hormones[31,32].By mimicking the zinc’s divalent chemical state, Cd can enter the DNA -Zn binding site. It discards the ovarian steroidogenic pathway and mimics endogenous estrogen thus increasing the risk of ovarian cancer and breast cancer [33,34].

5.1.3.Chromium (Cr)

Chromium is a toxic heavy metal. Hexavalent chromium is an occupational carcinogen which cause lung cancer and nasal cancer.Cr also causes cancer in buccal cavity,pharynx,prostate and stomach in humans. Cr increases the risk of overall mortality in cases of lung, larynx, testicular,bladder, bone,kidney and thyroid cancer[35]

Carcinogenic mechanism:

Role of Cr dust in carcinogenesis has been studied since the 1980s.It has been found in a case study that there is a correlation between lung cancer and the chromate-producing industry workers [36,37,38,39] . High concentrations of trivalent Cr leads to cellular damage[40]. Hexavalent Cr is also a strong toxicant which produces reactive hydroxyl radicals. High levels of hexavalent Cr in the bloodstream leads to the destruction of blood cell, followed by the degradation of the liver and kidney[41,42,43]. If reductionof hexavalent Cr compounds to the pentavalent form take place, they can bind DNA and integrate within cellular processes[44].

5.1.4.Nickel (Ni)

There are a variety of cancers associated with nickel exposure. Epidemiological studies have revealed a correlation between Ni exposure and the carcinogenesis of lung, nasal and sinus tissue[45,46,47].In another study, high level of serum Ni were significantly determined in patients with breast cancer[48]. An experiment suggests that Ni exposure plays an important role in acute leukemia[49].

Carcinogenic mechanism :

Ni has an extensive range of carcinogenic mechanism. One carcinogenic mechanism of Ni was that it affected the expression of specific long noncoding RNAs. Ni has the capacity to induce the downregulation of Maternally Expressed Gene 3 (MEG3) by the process of the methylation. It also been revealed that as a carcinogen, Ni can generate free redicals [50].The exposure of Ni alters the transcription of several mRNAs and microRNAs and plays a vital role in immunity as well as inflammation, promotes malignant growth [51]. Ni has the ability to activate epigenetic changes resulting in malignancy. It was observed Ni 2+ had the capacity to induce the trimethylation of histone H3K4. [52].

5.2.PESTICIDES

Epidemiologic evidence established the relationship between chemical pesticides and cancer. There are many pesticides which are found to be carcinogenic, (e.g., organochlorines, creosote, and sulfallate) where others (particularly, the

organochlorines DDT, chlordane, lindane) act as tumor promoters. Some contaminants in commercial pesticide formulations also may lead to carcinogenic risk. Epidemiologic studies has revealed the relationship between various malignancy and pesticides leading to soft tissue sarcoma (STS) and malignant lymphoma, non-Hodgkin's lymphoma (NHL), leukemia, and, less frequently , with cancers of the lung and breast, organophosphorous compounds with NHL and leukemia connection, and triazine herbicides with ovarian cancer[53].

Carcinogenic mechanism:

Consumption of the Pesticides into the liver leads to liver carcinogenesis via the mechanisms of adhesion, alteration, oxidative stress, genotoxicity, immunotoxicity, tumor promotion, and hormonal action [54,55,56,57]. Experimental studies reveal that the exposure to dichlorodiphenyltrichloroethane (DDT),an organochlorine insecticide and its metabolite,
dichlorodiphenyldichloroethylene(DDE)
effects the growth of liver tumors in rodents [58,59,60].

5.3. POLLUTANTS

5.3.1. Water pollutants

Exposure of water pollutants through drinking polluted water,bathing,showering or swimming is responsible for cancer development. The effect of Radon in drinking water significantly increases the risk of lung cancer by increasing the radiation levels inside buildings[61,62,63].Exposure of As in water effects in bladder, lung, kidney, and non-melanoma skin cancers .

5.3.2. Air pollutants

Different outdoor and indoor air pollutants act as carcinogens. Outdoor air pollutants from industrial sources, power plants and motor vehicles increase the risk of cancer [64,65,66].Indoor air pollutants including radon,envinmental tobacco smoke, asbestos, formaldehyde, chloroform and pesticides can cause a wide range of acute and chronic health disorders including cancer[67,68,69,70]. Environmental tobacco smoke alone contains approximately 50 known carcinogens. Broadly air pollutants are linked with many types of cancers such as
breast,Esophageal,LaryngealBladder,Leukomia, mesothelioma, Non Hodgkin's Lymphoma, prostate, soft tissue sarcoma and skin cancer[71].

Carcinogenic mechanism :

Experiments strongly suggests that there is a strong correlation between exposure of air pollutants and epigenomic changes in carcinogenesis, of them hypermethylation of cytosine in CpG-rich islands of gene promoter regions is most common [72, 73]. In cancer, hypermethylation leads to transcriptional inactivation and loss of expression of tumour suppressor and other regulatory genes [74]. In human cancer, aberrant promoter methylation and other epigenetic modifications takes place in a tumour-type and gene-specific manner [75].

6. PROFILING IN VARIOUS TYPES OF MALIGNANCY

6.1. Melanoma brain metastasis

The incidence of melanoma is believed to be correlated with tumor–stroma-associated immune cells. Cytokines and chemokines modulate the activities of these cells,which ultimately leads to development of diseases . Immunoprofiling of cytokines revealed that Chemokine CCL22 and cytokines IL1α, IL4, and IL5 were reduced in most samples, whereas a subset including CXCL10, CCL4, CCL17, and IL8 showed increased expression. Further, clusters survey identified within the melanoma patient set comparing the prognosis of the patients propose that suppression of IL1α, IL4, IL5, and CCL22, with related increase of CXCL10, CCL4, and CCL17, may correlate with more truculent development of brain metastasis. [76].

6.2. Multiple myeloma

Multiple myeloma (MM) is simply characterised as a desynchronized cytokine system with upsurge levels of inflammatory cytokines.It is thought that the proinflammatory cytokines like IL-6 and IL-1 plays a role in cancer development , and anti-inflammatory drugs are necessary to treat tumors.

In this opposite view, it is recommended that cancer-specific Th1 cells helps to inhibit tumour onset and progression. In a Th1 atmosphere, proinflammatory cytokines (e.g., IL-6, IL-1α, and IL-1β) may allocate to tumour elimination through leucocytes from the circulation and by booming the function of $CD4^+$ T cell .

Ben-Sasson et al. assess topically produced cytokines throughout the primary immune response against MM in mice [77]. Notably effective tumour immunosurveillance due to tumour-specific $CD4^+$ T cells, was found to be constantly connected to increased local concentrations of both proinflammatory cytokines (IL-6, IL-1α, and IL-1β) and Th1-associated cytokines (IL-2, IL-12, and IFN-γ).

Tumour suppression is accomplished by the collaboration of cancer-specific Th1 cells and cancer-infiltrating, antigen-presenting macrophages. Th1 cells stimulate the secretion of IL-6 and IL-1β by macrophages. Thus, inflammation, when guided by cancer-specific Th1 cells, may supress rather than provoke tumours.

To confirm this description, Haabeth et al. utilized a technique to calculate locally produced cytokines during primary anticancer immune responses in mice [78]. To operate this approach, they approved a core of nine cytokines, continually correlated with efficacious tumour suppression:IL-1α, IL-1β, IL-2, IL-3, IL-6,IL12 p17,IFN-γ, CXCL10, and CXCL9. It can be found that IL-12 and IFN-γ are eternally connected with tumour rejection which is related with a Th1 polarization of the immune response [79,80]. Oppositely, the proinflammatory cytokines IL-6, IL-1α, and IL-1β may seem to be related to the tumour by chronic inflammation [81,82,83,84].

The finding that increased concentrations of IL-1 were associated with efficacious tumour immune-surveillance is of special interest. IL-1 is a canonical proinflammatory cytokine, that acts as a positive feedback loop in inflammation. It has been determined that IL1 is connected to increased growth and differentiation of $CD4^+$ T cells and to activated macrophage tumouricidal activity *in vitro* [85]. The release of IL-1β by macrophages is dependent on IFN-γ [86].

6.3. Non small cell lung cancer

In the last decade, many clinicopathological studies tried to find whether there are interrelation between the expression level of chemokines and/or their receptors in tumor tissue, with patient survival or NSCLC progression. In this regard, it has been reported that the raised expression of the chemokine CCL5 in grade I lung adenocarcinoma lead to an increase in the survival rate [87]. Side by side, high expression of CXCL8 is responsible for disease[88]From the above mentioned information, the pro-angiogenic effect of CXCL8 could provoke the neoplastic process through tumor cell survival and tumor growth, where the higher expression of CCL5 could be associated to a more well organised anti-tumor response by an increase recruitment of T lymphocytes [89]. There seems a remarkable variation found in the expression of chemokine receptors in the stromal region and in the tumor foci of neoplastic tissue. Ohri and colleagues considered the correlation of expression of CXCR2-5 and CCR1 receptors with the

survival, in a cohort of 20 NSCLC patients. The increase expression level of CXCR2, CXCR3 and CCR1 in the foci of tumor cells and increased expression level of CXCR4,CXCR3and CXCR2 in stromal cells was connected with greater and lower survival respectively [90].

6.4. Gastric Cancer

Gastric adenocarcinoma is the third most common cause of cancer related death. *Helicobacter pylori* infection turns on a signaling cascade that induces release of cytokines and chemokines that are involved in the chronic inflammatory response that operate carcinogenesis. Here circulating cytokines and chemokines were potential diagnostic biomarkers for gastric cancer.

At Mexico city, among the patients who underwent primary surgery from 2009 to 2012, 201 healthy controls and 162 patients with distal gastric cancer were included. The clinical and pathological data of patients were recorded through questionnaire, and the cancer subtype was categorised as intestinal or diffuse. Levels of IL-1β, IL-6, IFN-γ, and IL-10were remarkably higher and level of MCP-1 was lower in gastric cancer patients as compared with controls. No difference in IL-8 or TNF-α levels, were observed between gastric cancer and controls. Level of IFN-γ and IL-10 were remarkably higher in both intestinal and diffuse gastric cancer, while the level of IL-1β and IL-6 were higher and TGF-β was lower only in intestinal gastric cancer; MCP-1 was lower only in diffuse gastric cancer. IFN-γ and IL-10 levels were remarkably higher in early (I/II) and late stage (III/IV) gastric cancer; IL-1β and IL-8 were higher and MCP-1 was lower only in late stage (IV) patients. Thus IFN-γ and IL-10 might be useful markers for diagnosis of early stage gastric cancer, and IL-1β, IL-8, and MCP-1 for late stages of the disease [91].

7. CONCLUSION

The present study analyzes how the different environmental contaminants lead to the incidence of the immunological dysregulation in varied cancer cases globally

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