CANCER AND IMMUNITY

The term “Cancer Immunology” is the study of body’s protective mechanisms against cancer. This discipline broadly involves the study of (1) the immune responses to the cancer cells, (2) the antigenic properties of these cells, (3) the immunologic consequences to the host of the growth of malignant cells, and (4) the means by which the immune system can be modulated to recognize such cells and promote cancer eradication.

The most important function of the immune system is to provide protection against any cell or molecule recognized as alien in the body including the outgrowth of malignant cells. But this task is likely to be unsuccessful with most of the cancers for many reasons. The tumour cells are immunologically indistinguishable from normal cells, despite exhibiting abnormal propensities to proliferate, to spread throughout the host, and to interfere with normal organ functions. Thus, the immune system finds difficulty in identifying these tumour cells as foreign as compared to other replicating antigens such as bacteria, which can more easily be distinguished as foreign.

Meenu Gill, Assistant Professor, Department of Pathology Pt. B.D. Sharma PGIMS, Rohtak, Haryana.
Reenu Bathla, Dental Surgeon, Balaji Dental Clinic, Approach Road Near Rly. Station, Rohtak, Haryana.
Parmjeet Singh Gill, Assistant Professor, Department of Microbiology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana.
Hitesh Khurana, Associate Professor, Department of Psychiatry, Pt. B.D. Sharma PGIMS, Rohtak, Haryana.
Normal cell activities are systematically coordinated within an organ for an optimal level of functioning. Therefore, the rate of cell loss due to the natural death of mature differentiated cells is equal to the rate of appearance of new cells from the less mature proliferating cell pool. In some pathologic conditions, there occurs a nonmalignant regulated polyclonal cell growth when the stimulus for cell proliferation exceeds the requirement for cell replacement, resulting in organ hypertrophy. Once the stimulus is removed, the organ hypertrophy resolves. In contrast to such growth, an individual cell may undergo a transforming event and acquire the potential to produce daughter cells that proliferate independent of external growth and regulatory signals. The autonomous growth of such transformed cells of monoclonal origin makes the basis of malignant disease. Such growth is mainly characterized by the unrestrained growth of tumour cells that is locally invasive, disrupts normal tissue and has a tendency to metastasize to distant organs.

**DEVELOPMENT OF TUMOURS**

The transformation of a normal cell to a malignant one may occur (i) spontaneously during cell division as random mutations or (ii) as the outcome of gene rearrangements; alternatively, (iii) they may be induced by a chemical, physical, or viral carcinogen.

**Chemical Carcinogens**

Chemically induced tumours were probably noticed in the 18th century for the first time among the European chimney sweepers who had an unusually high incidence of carcinoma of the scrotum. Soot and tar in smoke is rich in polycyclic aromatic hydrocarbons (PAH) which make a major class of carcinogens. Retention of tar and therefore of PAH in the wrinkles of the scrotum was apparently responsible for these tumours. Following this incidental observation, painting tar on epithelial cells became a common experimental technique in laboratories to induce
carcinogenesis. A second major class of carcinogens, the *aromatic amines*, was identified following the observation of a high frequency of bladder cancer among factory workers using aniline dyes. The mechanisms by which most of chemical carcinogens induce endoplasmic malignant transformation predominantly reflect the mutagenic activity of these compounds.

**Physical Carcinogens**

Evidence for the physical factors as carcinogens accumulated following the discovery of *X-rays* and radioactivity in the late 19th century when many of the early radiologists developed skin cancer including the noble laureate Marie Curie. The most eye-catching evidence of radiation-induced cancers has been in survivors of the atomic bomb explosions at the end of World War II in Japan, who had an increased incidence of a wide range of tumours for more than 20 years after the nuclear holocaust in comparison with the unexposed population. Such ionizing radiation induces various genetic changes like injuries to cellular DNA, resulting in mutations, chromosomal breaks, and abnormal rearrangements. The ultraviolet *radiation*, impairs the DNA repair and thereby inducing skin cancer on sun-exposed part of the body, particularly in people with xeroderma pigmentosum.

**Viral Oncogenes**

Many cells undergo unusual transformation by virus particles. Viral oncogenesis is now of particular interest in cancer immunology because of the increased likelihood of cells transformed by the viral genes express many virus-associated antigens that can be recognized as new by the immune system. Oncogenic viruses can be of either DNA or RNA types, depending on the genetic information carried by the intact virus. Most cells infected by the oncogenic DNA viruses, such as *papovaviruses*, *herpesviruses*, and *adenoviruses*, express all of the viral genes and support viral replication which commonly results in cell lysis.
Infection of cells not permitting viral replication can result in integration of viral DNA into the host genome and expression of only some viral genes, so that lytic virus particles are not formed. Transformation results from direct effects on expression or function of the infected host genes or from aberrant splicing of transcribed viral RNA to produce new proteins that promote transformation. Several human DNA viruses have been found to contain potential oncogenes which have been associated with the development of malignancies. These include associations of Epstein-Barr virus (EBV) with Burkitt’s lymphoma, Hodgkin’s disease and nasopharyngeal carcinoma, and of human papillomavirus with cervical and skin carcinomas.

Oncogenic RNA viruses first discovered in chicken tumours contain genes for a polymerase called reverse transcriptase. They deceive the host cell to use the viral RNA as a template for transcription of a DNA copy which can be integrated into the host’s genome. Because of this there is a reversal of the normal DNA-to-RNA transcription of genetic information. For this reason these viruses are often referred to as retroviruses. RNA tumour viruses appear to be responsible for a large number of naturally occurring cancers in many species. Many of these viruses contain directly transforming oncogenes, where as the others need to activate host genes first. A class of human retroviruses, the human T-cell leukemia viruses (HTLV), is responsible for a variety of T-cell leukemia’s, particularly among the cases occurring in southern Japan where the infection is endemic. Many retroviruses such as feline leukemia virus and HTLV can spread horizontally from infected to normal host, and resistance to tumorigenesis in exposed host’s results in part from an immune response to virus-associated antigens.

C-Myc

Molecular biology has provided us valuable tools to understand the events involved in transformation. With the help
of these viral oncogenes, analogues have been identified in the normal cellular genome. *In vitro* studies of the analogues have demonstrated that activation of these cellular oncogenes can transform normal cells under appropriate conditions to produce a carcinogenic response. The role of many cellular oncogenes in normal growth and development too has been demonstrated, but abnormal expression or maintenance of these genes in an abnormally active state can result in malignant transformation. This may occur (i) by mutations which may interfere with regulation of the transcription or with the activity of the protein; or (ii) by a translocation that places the oncogene next to an active cellular gene, as is observed in B-cell tumours (with the translocation of the *c-myc* oncogene next to an immunoglobulin V region gene); or (iii) by insertion of an active promoter that enhances expression, such as may occur following integration of a slowly transforming retrovirus. Oncogenes code for a wide variety of cellular products including membrane receptors, signaling messengers, autocrine growth factors, inhibitors of apoptosis, and regulators of cell cycle progression and gene expression. The expression of some of these products, particularly those resulting from mutations of the normal protein, can render malignant cells sufficiently different from normal cells for detection by immunologic methods and therefore such cells can be potentially eliminated by immunological attack.

**TUMOUR ANTIGENS**

Many experimentally induced tumours and in some human cancers have elicited certain antigens which evoke an immune response. They can be broadly classified into two categories:

1. Tumour Specific Antigens (TSAs)

   They are present only on the membranes of malignant cells. They induce immune response when tumour is transplanted to syngenic animals. Different tumours have different TSAs, even
though they may be induced by the same carcinogen. In contrast, TSA of virus induced tumours is so virus-specific that all tumours produced by one virus possess the same antigen in different animals and in different kinds of tumours.

2. Tumour Associated Antigens (TAAs)

   These are present on tumour cells and also on some normal cells. They do not evoke an immune response as they are also present on normal cells, and therefore are of little significance in tumour rejection. Despite this, detection of these antigens is nevertheless of value in the diagnosis of certain tumours and antibodies raised against them can be useful for immunotherapy. TAAs fall into following three categories:

   (i) Tumour-associated carbohydrate antigens (TACAs)

   These are the abnormal forms of widely expressed glycoproteins and glycolipids such as mucin-associated antigen commonly detected in pancreatic and breast cancers.

   (ii) Oncofoetal antigens

   These are foetal antigens which are found in embryonic (but not in normal adult cells) and malignant cells. The best known examples are alpha-fetoprotein in hepatomas and carinoembryonic antigen in carcinoma of the colon, pancreas, lung, stomach and breast.

   (iii) Differentiation antigens

   They are peculiar to the differentiation state of carcinogenesis at which growth of cancer cells is arrested and they can also be histologically characterized. CD10, an antigen expressed by early B lymphocytes, is expressed in B cell leukaemias and lymphomas is one such example. Similarly, prostate-specific antigen (PSA) is expressed on normal as well as cancerous prostatic epithelium. Both serve as differentiation markers in the diagnosis of lymphoid and prostatic cancers.
All Tumour-Specific Antigens Defined by Immunization and Immune Challenge belong to the Family of Heat Shock Proteins (HSPs)

When tumours were biochemically fractionated and individual protein fractions tested for their ability to elicit protective tumour immunity, a number of tumour-protective antigens were identified in diverse tumour models, such as mouse sarcomas, melanomas, colon and lung carcinomas, and rat hepatomas.

Regardless of the tumour models used, all antigens belong to the family of proteins known as the heat-shock proteins (HSPs), which:

- Consistute a very large family of intracellular soluble proteins that are organized into HSP families based on molecular size.
- Were shown to elicit protective immunity;
- Were of the HSP90 (gp96 and HSP90), HSP70 (HSP 110 and HSP/c70), calreticulin, and HSP170 (also known as grp170) families.

HSPs have to be Isolated Directly from Tumours to be Immunologically Active

Two aspects of HSP elicited tumour immunity are notable.

- First, HSPs are present in normal tissues as well as tumours, and normal tissue derived HSPs do not elicit tumour rejection. HSP of tumour cell origin only are immunologically active
- Second, HSPs’ immune activity is specific for the individual tumours from which they are isolated.

These two observations suggested that HSPs in tumours differ from those in normal tissues and that HSPs in each tumour differ from the same molecules in other tumours.

This conundrum was resolved by the demonstration that the HSP molecules chaperoned peptides in a peptide binding pocket, much as the MHC molecules (though the structural details of the
pockets in HSP and MHC differ). The specificity of immunogenicity derives from the peptides rather than the HSP itself. Dissociation of HSP-associated peptides from HSPs abrogate the tumour rejection activity.

What are the HSP chaperoned tumour antigenic peptides?

HSPs chaperone a large group of peptides generated within the cells from which they are isolated.

HSP chaperoned peptide pools contain cytotoxic T lymphocyte (Tc) epitopes and Tc epitopes precursors for any antigens that the cell express. This evidence comes from mouse and human tumours, normal tissues, and virus infected cells. Hence, the HSP chaperoned peptides contain among them any tumour specific antigenic epitopes present in the tumour cell or the antigenic fingerprint of the tumour from which the HSPs are isolated.

Tumour derived HSPs elicit a CD8 as well as CD4 response against the tumours through immunization derived mechanisms. In addition, the HSP molecules stimulate the APCs to mediate maturation of dendritic cells and secretion of an array of cytokines that provides the innate milieu for the adaptive response. The immunization challenge model has led to the identification of antigen carriers (i.e. HSPs), but not of the antigens themselves. As a result of exogenous administration, immunization with antigens themselves would generally be expected to elicit CD4 response, which is not sufficient to elicit tumour immunity. Despite produced exogenously, the HSP chaperoned antigens were picked up in this assay because they have the ability to elicit CD8 as well as CD4 responses. This response is derived from the ability of HSPs to interact with APCs through receptors such as CD91.

**IMMUNE RESPONSE IN MALIGNANCY**

Both cell-mediated and antibody-mediated immunity have antitumour activity. As with virus-infected cells and foreign grafts,
the T lymphocytes play a major role in the destruction of tumour cells in mammals. T cell activation generates many subclasses e.g. helper T (Th), delayed-type hypersensitivity T (Td) and cytotoxic T (Tc) cells. The role played by Td cells in cancer immunity is considered important. These cells target the tumour cell killing by means of the lymphokines released from them.

NK cells, which are lymphocytes, are capable of destroying tumour cells do not require any prior sensitization. After activation with IL-2, NK cells can destroy a wide range of human tumours, including many which do not appear to be immunogenic for T cells. So, NK cells have a prominent role in providing the first line of defence against many tumours. In addition to direct lysis of tumour cells, NK cells can also participate in antibody-dependent cellular cytotoxicity (ADCC).

Macrophages when activated by suitable antigenic mechanism also exhibit selective cytotoxicity against some tumour cells in vitro. T cell derived cytokine (interferon-gamma) activates macrophages which acquire antitumour activity.

Humoral mechanism may also participate in tumour cell destruction by activation of complement and induction of ADCC by NK cells.

**IMMUNE EFFECTOR MECHANISMS OPERATIVE AGAINST TUMOUR CELLS**

All the effector components of the immune system can potentially contribute to the immunity against carcinogenesis. Each of these effector mechanisms can play a role in the control of tumour growth. However, one particular mechanism may be more or less important than the other, depending on the tumour and setting. The potential for mediating antitumour responses should become more evident by using approaches to augment individual effector responses, such as the adaptive transfer of large number of cells and the administration of cytokines for antibodies.
T-Cells

The T-cell response is the primary host response for the control of growth of antigenic tumour cells. It is responsible for both the direct destruction of tumour cells and the activation of other channels of the immune system. T-cell immunity to tumours is reflected by the functions of the two T-cell subsets *i.e.* class-I and class II-restricted T cells. Class-I cells, largely represent CD4 helper T (Th) cells that mediate their effect by direct interaction with antigen-presenting cells (APC) and by the secretion of lymphokines to activate other effector cells and induce inflammatory responses. Class I-restricted T cells, largely represent CD8 cytotoxic T (Tc) cells that can also secrete lymphokines but mediate their effect mostly by direct lysis of tumour cells.

The contribution of each T-cell subset and function to the antitumour response is quite variable, but tumour-specific T cells from each subset are capable of mediating tumour eradication and have been detected in the peripheral blood of individual patients. Most tumour cells, however, express class I but not class II MHC markers. Further the Th-cell subset cannot directly recognize these tumour cells. Therefore, such Th cell responses usually depend on APCs such as dendritic cells or macrophages to present the relevant tumour antigens in the context of class II molecules for activation. After antigen specific triggering, these T cells activate dendritic cells and secrete lymphokines which activate Tc cells and can produce other lymphokines, such as tumour necrosis factor (TNF), which may be directly lytic to tumour cells. In contrast to Th-cells, the Tc-cell subset recognizes and kills tumour targets directly by disrupting the target membrane and disintegrating the malignant cell nucleus. Only a minor fraction of class I-restricted CD8 T cells provide helper functions, however, and thus effective Tc-cell responses generally depend on class II-restricted CD4 Th-cell response to provide the necessary helper factors to activate and proliferation of Tc-cells.
B Cells & Antibody-Dependent Killing

Experimental evidence suggests a role of host antibody responses in human tumour immunity as seen by the occasional detection of tumour-reactive antibodies in the serum of patients. More recent sensitive approaches have suggested that antibody response to tumour antigens is likely to be more common than expected. Some of these antibodies react with surface antigens, such as the Her2-neu oncogene protein, and could have direct antitumour activity, whereas others targeting the intracellular proteins could facilitate T-cell responses by enhancing processing and presentation by APC of tumour antigens released from dead tumour cells.

Antibodies may mediate tumour cell lysis through two major mechanisms. Complement fixing antibodies bind to the tumour cell membrane and create pores in the membrane through compliment attachment, resulting in osmosis and therefore cell disruption due to altered osmotic and biochemical integrity. An alternative mechanism is antibody dependent cell-mediated cytotoxicity (ADCC), in which antibodies (usually of the IgG class) form an intercellular bridge to a specific determinant on the target cell via their Fc region to effector cells expressing Fc receptors. Many potential effector cells, including NK cells, macrophages, and granulocytes, can mediate the lytic event. ADCC is a more efficient lytic mechanism in vitro than complement-mediated cytotoxicity, requiring fewer antibody molecules per cell to kill. Preclinical immunotherapy studies with monoclonal antibodies of different isotypes have also suggested that ADCC may be the more important in vivo effector mechanism.

Natural Killer Cells

NK cells can kill a wide range of tumour targets in vitro. The mechanism by which NK cells preferentially recognize and lyse transformed rather than normal targets is now becoming more
and clearer with the increasing characterization of a broad array of inhibitory and activating receptors on the NK cells. The cytolytic potential of NK cells is largely contained by off signals delivered via families of inhibitory receptors that bind to class I molecules on potential target cells. NK cells, as a first line of defense, distinguish the cells infected with viruses, which commonly down-regulate class I MHC molecules. Many tumour cells also express low levels of class I molecules and thereby release the inhibitory signal. The precise nature of the activating signal from tumour cells is less certain, but a variety of molecules such as CD48 and surface glycoproteins are the potential candidates. Cytolysis by NK cells is mediated by the release of cytotoxic factor and the use of perforins to puncture holes in the target cell membrane. The cytotoxic activity of NK cells can be augmented both in vitro and in vivo with the lymphokines interleukin-2 (IL-2), interferon, and via cross-linking the activating Fc receptor by antibodies. Thus NK activity can be amplified by both immune T-cell and B-cell responses. Recent studies have demonstrated that augmentation of NK activity in visceral organs enhances resistance to the growth of metastases. Therefore, NK cells may provide a first line of host defense against the growth of transformed cells at both the primary and metastatic sites, as well as represent an effector mechanism recruited by T cells and B cells (or the pharmacologic administration of cytokines and antibodies) to supplement specific antitumour responses.

Cytotoxic effector cells have many similarities with but can be distinguished from classic NK cells, lymphokine activated killer (LAK) cells that can be induced by very high doses of IL-2, are phenotypically heterogeneous (including both NK and CD8 T cells), and kill a much broader spectrum of tumour targets than do NK cells, but their role during physiologic antitumour responses remains yet unclear. NK-T cells, another class of effector cells, express both NK and T-cell markers and appear to be activated by recognition of neoclassical class I molecules via a relatively
invariant T-cell receptor. These cells have been shown to be important in tumour resistance in murine models and may have some role in human tumorigenesis. (Male, Borostoff, Roth, Roitt, 2006)

**Macrophages**

Macrophages act as antigen presenting cells in tumour immunity to stimulate the immune response, and also as potential effector cells to mediate tumour lysis wherever required. Resting macrophages are not cytolytic to tumour cells *in vitro* but can become cytolytic if activated with macrophage-activating factors (MAF), commonly secreted by T cells following antigen specific stimulation, and therefore may participate as effector cells in the absence of administration of cytokines may depend on T-cell immunity. This argument is supported by studies showing that macrophages isolated from immunogenic tumors undergoing regression exhibit tumoricidal activity, whereas macrophages isolated from progressing or nonimmunogenic tumors generally show no cytotoxic activity. T-cell lymphokines with MAF activity include interferon gamma, TNF, IL-4, and granulocyte-macrophage colony-stimulating factor (GM-CSF). (Greenberg 2006)

The mechanisms by which macrophages recognize tumour cells and kill them are not well defined, but activated macrophages may produce cytotoxic factors that mediate killing as well as *bid* to and lyse transformed or carcinogenic cells in preference to normal cells. Binding by activated macrophages is an energy dependent process mediated by trypsin-sensitive membrane molecular structures. Several distinct lytic mechanisms appear to be operative, depending on the MAF that activate the macrophages. These include intercellular transfer of lysosomal products, superoxide production, release of neutral proteinases, and secretion of the TNF. Studies in knockout mice have suggested that production of nitric oxide which is a mediator of tumour apoptosis, may be the most critical effector mechanism employed by macrophages.
TUMOUR ESCAPE MECHANISMS

It is well known that most of cancers develop in persons who do not suffer from any overt immunodeficiency. Tumour cells seem to develop mechanisms to deceive and escape or evade the immune system in immunocompetent hosts. Several such mechanisms may be operative:

- **Weak immunogenicity:** Some tumours are weakly immunogenic, so in small numbers they do not elicit an immune response. But when their numbers increase enough to provoke immune response the tumour load may be already too high to be managed by the host’s immune system to mount an effective response.

- **Making cells immunologically invisible:** Certain tumour cells can transfer antigens from their surface to cytoplasm or they may shed or stop expressing the surface antigens thus making the tumour cells “immunologically invisible”.

- **Masking tumour antigens:** Certain cancers produce copious amounts of a mucoprotein called sialomucin. It binds to the surface of the tumour cells. Sialomucin being a normal component of the cell, the immune system fails to recognize these tumour cells as foreign.

- **Induction of immune tolerance:** Tumour cells may synthesize various immunosuppressants. They may also activate specific Ts cells. Both these suppress the effector T and B cell clones.

- **Production of blocking antibodies:** Some tumour cells invoke immune system to produce blocking antibodies that prevent activation and fixation of complement system, so lysis of tumour cell is not affected. Blocking antibodies also cover the surface of cancer cells, preventing Tc cells from binding to hidden receptors.

- **Reduced levels of HLA class I molecules:** Tumour cells in certain cases express reduced levels of HLA class I molecules. This impairs presentation of antigen peptides to cytotoxic T cells.
CANCER-IMMUNITY AND BEHAVIOUR

The immune system in conjunction with brain also fights against or may even make the person prone to develop cancer. Recent researches have found that whenever there is physical or psychological stress, the brain reacts to it ‘immunologically’. It activates the hypothalamic pituitary adrenal axis (HPA) and sets in the fight-flight response to the stressor. Paradoxically, it suppresses the immune response of body against the stress through an intricate mechanism of neuro-endocrine-autonomic-immune interactions. Emotional status and the psychological meaning of the stressors to the individual plays an important role in determining the directions of immune response of the body. A positive emotional status and attitude of opportunity to prove self has been shown to enhance the immune status whereas the opposite of it may lead to immunosuppression. Such an outcome of immune response may make body prone to or defend against the diseases including cancer. The interplay of behaviour and immunity was recognised a long back by Ader in 1960s when he noticed rats dying as the conditioned response to oral saccharine. But the unquenchable thirst to understand the process of immunity-behaviour interaction what Ader recognised as Psychoneuroimmunology (PNI) is now almost a separate subspeciality (Ader, 2000; Sternberg 2001). The researches have found the immune system as the “sixth sense” of brain having both efferent and afferent pathways, thereby exchanging valuable information about the status of mind and body’s health with brain. (Ader 2000; Pelletier 1992) (Williams, Peterson, Shea, Schmedtje, Bauer, & Felten 1981)

PNI has also an important role in carcinogenesis too. The incidental findings from the history are valuable examples of it. Lance Armstrong, a famous cyclist who had a severe testicular tumour metastasis to brain recovered from his illness to due to his optimism and spirit to fight. This case give a clear human
example how stress, optimism, brain and cancer immunity are related to one and other. Cancer like many other illnesses has a multifactorial etiology. Various evidences have shown that PNI too play an important role in determining the outcome of this disease. (Durak, 2006)

Immune system may not recognize all abnormal cells (vide supra). The cancer cells express a variety of antigens which are not stored in the immunological memory of the T-cells. This discrepancy in the antigen productions helps the T-cells in removing them through *immune surveillance*. A normal immunologic surveillance recognizes altered cell surface (specific and non-specific) tumour antigens and reacts against them. An intact immune system can remove up to millions of malignant cells everyday. As stated above a wide range of cell-mediated and humoral immune responses play a role in immune surveillance which can protect the host against cancer cells - Tc cells, NK cells, macrophages, Th lymphocytes, B lymphocytes, cytotoxic antibodies and complement system.

Stressors may suppress the immune system through several mechanisms (release of catecholamines and corticosteroids, central mechanisms, etc.). The resultant immunosuppression results in increased susceptibility to malignancy with increased incidence and mortality from malignant disease.

**Coping and Cancer**

Coping efforts are important in the process of adaptation to illness. Several consistent findings have emerged from prospective longitudinal studies of breast cancer patients from diagnosis through treatment and recovery (Carver *et al.*, 1993; Epping-Jordan *et al.*, 1999; Stanton & Snider, 1993). Successful coping is facilitated by optimism—the tendency to anticipate positive outcomes through the use of strategies including acceptance, positive thinking, and problem solving. Optimism is associated
with lower psychological distress (reduced symptoms of anxiety and depression). Conversely, pessimistic thinking is associated with coping that involves avoidance and social withdrawal, which are related to higher symptoms of anxiety and depression (Carver et al., 1993; Epping-Jordan et al., 1999). Breast cancer patients who learn to use more direct and confrontational coping strategies are less distressed than are those who use avoidance and denial and have better survival rates (Holland & Rowland, 1990; Green & Berlin, 1987; Greer et al., 1979; Watson et al., 1990). Research suggests that the belief that one has no control over the course of the disease leads to poor outcome, whereas belief in control over the course of the disease leads to better outcome (Watson et al., 1990). Not all studies report significant impact of psychosocial variables on the course of cancer (Angell, 1985; Cassileth et al., 1985; Jamison et al., 1987), but psychosocial stress has been reported to lead to higher relapse rates in metastatic breast cancer (Ramirez et al., 1989).

About thirty years ago it was suggested that the presence of depression predicted a higher subsequent incidence of cancer (Shekelle et al., 1981). Although a large cohort study reported an elevated rate of subsequent cancers among those diagnosed with depression, this finding was not confirmed in a more recent large-scale cohort trial (Zonderman et al., 1989). Zonderman et al. (1989) found no relationship between two measures of depressive symptoms and cancer morbidity or mortality in a large population. The researchers used continuous and non-categorical measures of depression, leaving open the possibility that severe clinical depression could be associated with elevated cancer risk. However, this and earlier studies lend little support to the idea that depression increases cancer risk (Fox, 1989). Fox’s reanalysis of the original observation suggests that a combination of depression and exposure to toxins could have accounted for the apparent association (Fox, 1989). In a study by Penninx et al. (1998) it was found that in a sample of 5000 elderly people that continuous...
symptoms of depression predicted almost 2-fold elevation in risk of cancer incidence.

Overall, there are a good number of studies demonstrating immune suppression and carcinogenesis following stressful situations and such situations also affect the outcome of malignant disease but the evidence so far is not beyond doubt and need to be replicated in methodologically sound studies.

**Personality, Social Factors and Cancer**

Certain personality and social factors also appear correlated with modulation of immune response and therefore carcinogenesis. Any loss of confiding relationships and inability to express the dysphoric emotions (Type C personality behaviour) may induce certain autonomic changes which suppress the natural defense against the carcinogenesis (Weisman & Hackett, 1961).

Some studies conducted have shown stress and poor coping may causally be correlated. In a prospective study, certain personality variables and stress in life were correlated with reduced life expectancy due to persons proneness to develop cancer later on. (Eysenck, & Grossarth-Maticik, 1991) The malignant melanoma patients who in a study design were exposed to mild electric shocks had a tendency to under report the distress, and had a poorer outcome to the physical disease (Goleman & Gurin, 1993).


Personality traits may not be working independent of stress all the time. Personality traits, have a heritability estimates of
51% for neuroticism and 46% for social desirability (Saudino, Pedersen, Lichtenstein, McClearn, and Plomin, R. (1997)). So it may be assumed that to some extent perceived stress might affect how each patient’s immune system interacts with his/her environment, life events, complex chronic stressors of being ill with cancer, etc. The genetically mediated associations between personality and adverse life events may be sufficiently robust that it has been suggested that personality is the cause of life events, stressors, etc. (Saudino et al., 1997; Magnus, Diener, Fujita, & Pavot, 1993; Poulton & Andrews, 1992). It is possible then that these personality traits are the cause of adverse life events and mediate intervention effectiveness in reducing such a stress and enhancing immune function.

In carcinogenesis, many psychosocial explanations centre on chronic dysphoria from life stressors, chronic but marked helplessness/hopelessness, etc., which are described to have negative effects on immune process (Holland & Rowland, 1990; Schmale, & Iker, 1966). These studies suggest that stress (negative emotions, inefficiently coped with or suppressed as a function of personality) weakens immune competency, thereby increasing the likelihood of cancer morbidity and mortality. It is a reasonable assumption that the immune process is one of the important mechanisms of psychosomatic illness such as cancer, linked with the personality traits. There is a growing body of evidence in favour of this assumption predicting the role of these psychosocial factors in cancer prognosis and the immune process (Anderson, Kiecolt-Glaser & Glaser 1994; Holland & Rowland, 1990).

In an attempt to investigate impact of psychological parameters on cancer morbidity, personality and quality of life data were obtained before, and immunological data before and after, the onset of intervention. Number of NK cells, T4 and T8 lymphocytes and rate of lymphocyte proliferation (PHA responsiveness)
significantly increased after (but not before) the onset of intervention. Increase in T4/T8 ratio was greater in repressors. Disregarding the age, NK cells increased regardless of personality, if age was disregarded. Further, T lymphocytes increased in those with better physical, psychological health despite advanced age or cancer stage. Before psychological interventions, low neuroticism and high anger-suppression scores predicted lesser number of lymphocytes after the intervention, only low neuroticism score predicted greater increase in lymphocytes after. Increase in NK cells was greater in low neuroticism or high anger-suppression scorers for younger patients, and this relationship was reversed for older patients. It was therefore concluded that cancer patients’ immunological status varies with personality and age (Shigehisa & Honda, 2006).

In anxiety disorder patients, when compared with controls, the patients with panic disorder too had significantly lower levels of CD4+ than healthy controls and depressive disorder patients. However, lymphocyte proliferative response to mitogens varied within a wide range; from decreased to increased responses have been observed in panic disorder patients compared with normal controls.

In the anxiety disorders the production of IL-2 and lymphocyte proliferation in response to phytohaemagglutinin (PHA) also leads to a reduced cell-mediated immune function in patients with anxiety disorders, compared with normal controls. These findings also imply that a variety of immune measures should be assessed simultaneously in psychoneuroimmunology research. This would help elucidate the relationship between anxiety and immune function, in cancer patients which has been unclear in most previous research using a single immune measure (Koh & Lee, 1998).
Mechanism of Stress Induced Immunomodulation

Lymphocytes and Stress

Most of the studies have suggested that stress is associated with suppression of immunocompetence, such as reduced lymphocyte proliferation in response to mitogen, PHA, lowered NK cell activity, helper/inducer (T4) and suppressor/cytotoxic (T8) lymphocyte levels, and the T4/T8 ratio.

Lymphocytes have been demonstrated to possess certain receptors to respond to the signals from the secretory products including interleukins from the brain. The cancer cells keep developing in the body. These cells are recognized as foreign by the lymphocytes due to altered antigenicity and are continuously destroyed and removed from the body. However in the event of immune suppression which may be mediated through loss of CNS-Immune system interactions or any alteration in that in response to stress can suppress the functioning of lymphocytes. In such situations the lymphocytes fail to recognize the cancer cells and set in the process of carcinogenesis.

Ben-Eliyahu and his colleagues discovered that stress such as forced swimming, surgery, and social isolation decreases lymphocyte activity in rats for as little as one hour and as long as a day or two (Azar, 1999). These types of stresses may also lead to a two-to-five-fold increased risk of carcinogenesis.

Different kind of stress has a differential response on functioning of different cells involved in cancer immunity. In a pre-post study design by Thornton et al. (2007) the breast cancer patients having high levels of initial perceived stress had a poor T-cell blastogenesis response. After interventions, the patients showing improvement in the initial perceived stress had also improved NK cell mediated cytotoxicity. This study showed a
differential response of cell to the stress. The T-cell blastogenesis was strongly suppressed by the initial high level of stress whereas the perceived stress but not the emotional distress had a suppressive response on the NK cell activity, thereby affecting the immunity to cancer cells in response to stress.

**Stress, DNA Repair and other Immunoprotective Mechanisms**

Lymphocytes also play role in DNA repair process which is also the key pathogenetic process in carcinogenesis. Psychiatric patients in comparison to normal subjects has been demonstrated to display lower lymphocytes function indices and lower capability to repair DNA thus proving stress to impair DNA repair process and enhance carcinogenesis (Armandola, 2002).

Another study investigated the possibility that stress could weaken one part of the DNA repair process. Forty-five rats were given dimethylnitrosamine (a carcinogen), and half were assigned to a stress condition. The methyltransferase, a DNA repair enzyme generated in reaction to carcinogen damage, was drastically reduced in stressed animals’ splenic lymphocytes, as compared with splenic lymphocytes obtained from the control rats (Kielcot-Glaser and Glaser, 1999).

Apoptosis or the programmed cell death is also a cancer protective mechanism and is mediated through cytotoxic T lymphocytes. Different kinds of psychological stress suppress these cells leading to impairment of apoptosis of abnormal cancer cells produced following exposure to carcinogens such as phorbol ester.

Tumour necrosis factor-alpha (TNFá) is an important cytokine associated with tumour regression and increased survival time for cancer patients. In a prospective design study on breast cancer patients, it was seen that those enjoying good social relations had higher levels of levels of circulating TNFá and therefore better immunity to cancer (Marucha, Crespin, Shelby, and Andersen, 2005).
Stress and HPA axis

During stressful periods the circadian rhythm abnormalities are also seen along with the release of CRH which stimulates the release of ACTH and then in turn cortisol, noradrenaline and adrenaline. Cortisol levels are high during early morning hours that prepares individual for wakefulness and low at night time during the period of relaxation. Cortisol also suppresses immune response and reduces lymphocyte activity. Studies on the breast cancer patients have shown alteration in the rhythm of CRH release which might have suppressed the immune response leading to carcinogenesis (Diurnal, Kraemer, Sapolsky, Sephton, and Speigal 2000).

FIGURE 1
Psychoneuroimmunology Model for Carcinogenesis
Reiche and others (2005, 2004) in a review concluded that persistent high levels of cortisol and other stress hormones due to persistent stimulation of HPA axis in chronic stress and in depressive symptoms lead to suppression of immune function. This suppression makes the subjects more prone to develop cancer and other infections. The depressed patients had overall leukocytosis, and high concentrations of circulating neutrophils but reduced mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis. They also had high levels of serum basal cortisol, acute phase proteins, specific antibodies against herpes simplex virus type 1 and Epstein Barr virus, plasma concentration of interleukins IL-1, IL-6, and TNF-α. Both stress and depression were associated with the decreased cytotoxic T-cell and natural killer cell activities affecting the processes of the immune surveillance of tumours, and the events that modulate the development and the accumulation of somatic mutations and genomic instability leading to DNA damage. Behavioural strategies, psychological, and psychopharmacotherapeutic interventions that enhance effective coping and reduce affective distress showed beneficial effects in cancer patients.

**CONCLUSION**

A complete model (fig. 1.1) suggests that a better understanding of the bidirectional communication between the neuroendocrine and immune systems could contribute to novel clinical and treatment strategies in oncology.

There is a sufficient evidence that immune mechanisms definitely have a protective role against carcinogenesis. Although, humoral factors *i.e.* antibody mechanisms are also involved in offering such protection, but cancer immunity is largely a cell-mediated immunity. Behaviour and brain mechanism do modulate this defense as seen in many studies but the exact pathway is still not very clear. Stress leads to immunosuppression through suppression of lymphocytic functions, reduced DNA repair and
suppressed cancer surveillance, and then in turn to carcinogenesis. This simple hypothesis is not so simple to formulate. Stress leads to certain behavioural changes. During the stressful periods the person may indulge in self destructive behaviour such as smoking, drinking which itself would lead to carcinogen exposure, delay in help-seeking and therefore increased likelihood of onset of disease. In such situations the immunity or the role of brain in immune modulation gets somewhat blurred. Stress can also lead to increased exposure to carcinogens. Direct exposure in response to stress itself would lead to pathological processes in the body which might suppress immunity. Alternatively the carcinogenesis itself may lead to immune suppression as seen in many studies and the body response to the carcinogenesis may be that of energy conservation which at times may wrongly be interpreted as depression or negative emotional state especially in the early stages of cancer. Treatment such as exposure to radiation, chemotherapeutic agents itself leads to emotional changes and immune suppression which may have independent pathways. We can certainly expose the animals to various kinds of stressful situations for the purpose of studying their immune mechanisms and carcinogenesis. But this approach too is not always free of ethical problems. Exposing human subjects to stress and those suffering from disease and administering them placebos for the purpose of studies involves still more deep ethical controversies. Moreover we can not always extrapolate the animal data to human subjects especially when psychological and other brain mechanisms are the focus of study. PNI studies have put some light on the process of carcinogenesis, but we are still not clear about the direction of cause and effect relationship between the two. Stress or behaviour leads to immune suppression and then in turn cancer. Or cancer may leads to immune suppression thereby modulates certain psychological and physical changes in the body. Clearly, there is an uphill task in front of the psychoimmunologists and oncologists to find the answer to this roundabout puzzle.
REFERENCES


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