CHAPTER

8 Tumor Host Relations

Malignant tumors are essentially autologous parasites. However, whereas ordinary parasites co-exist with their host, malignant tumors are hostile and lethal to their host. Contrary to infectious diseases and organ transplantation, the immune system of the host is far from being effective in eliminating the tumor. However, the study of tumor-host relations is important for several diagnostic and therapeutic reasons. Thus, a malignant tumor may first present by its complications, and these may represent oncologic emergencies. Moreover, better understanding tumor immunology may help to develop efficient therapy in the future. The present coverage of this subject is divided into two sections, the first presents the effects of tumors on host, and the second discusses tumor immunology with its clinical relevance.

Table 8-2 Oncologic Emergencies in Cancer Patients due to Local or Systemic Complications

Local Emergencies
Superior vena cava syndrome
Increased intracranial pressure
Spinal cord compression
Hemorrhage from tumor
Systemic Emergencies
Tumor lysis syndrome
Hyponatremia
Lactic acidosis
Hypercalcemia
Hemolytic uremic syndrome

EFFECTS OF TUMORS ON HOST

It is customary to classify the effects of tumors on host into *local and systemic* (Table 8-1). However, it is practically important to recognize from the list, some local and systemic complications which present as *oncologic emergencies*, since they require urgent treatment (Table 8-2). Important emergencies resulting from local effects of tumor include: (1) Superior vena cava syndrome usually complicating advanced lung cancer with *mediastinal compression*, (2) increased *intracranial pressure* associated with brain tumors resulting from obstructive hydrocephalus or venous thrombosis, (3) *spinal cord compression* due to vertebral metastases or primary spinal tumors, and (4) fatal hemorrhage, either gastrointestinal, pulmonary or cerebral.

Table 8-1 Classification of Effects of Tumors on Host

Local Effects
Obstructive complications
Failure of vital centers
Hemorrhage
Effusions
Systemic Effects
Neoplastic endocrine syndromes
Paraneoplastic syndromes
Infective complications
Complications of therapy

Oncologic emergences due to the metabolic effects of tumors include: (1) *Tumor lysis syndrome* (TLS), a complication of chemotherapy of large tumors resulting in serious release of cellular potassium, (2) *Hyponatremia* (or low serum sodium), a paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone (SIADH). (3) *Lactic acidosis* due to anaerobic glycolysis in tumors, (4) *hypercalcemia* which may be paraneoplastic (due to a parathormone related protein PTHrP) or advanced osteolytic bone metastases, and (5) *Hemolytic uremic syndrome* which is related to chemotherapy and immunotoxic therapy.

LOCAL EFFECTS OF CANCER

The main local complications of malignant tumors include: *obstructive complications,* failure of vital centers, hemorrhage and effusions. Thus, a tumor may obstruct the flow of CSF (hydro-cephalus), bronchus, gastrointestinal tract, urinary passages, superior vena cava, or lymph flow leading to lymphedema, chylous effusion or malabsorption syndrome. *Destruction of a vital structure* is particular-

ly serious in certain locations as: (1) the brain and spinal cord resulting in paralytic complications, and (2) the intestine leading to perforation. Fatal *hemorrhage* may complicate brain tumor, as well as, cancers of gastrointestinal tract. *Effusions* are local complications of tumors in pleural cavities and peritoneum.

SYSTEMIC EFFECTS OF TUMORS

The systemic effects of tumors are classified into 4 distinct groups, namely: (1) *neoplastic hormonal syndromes* resulting from a functioning tumor of the endocrine glands, (2) *paraneoplastic syndromes* resulting from secretion of ectopic hormone-like products by nonendocrine tumors, (3) *infective complications*, and (4) *complications of therapy*.

Neoplastic Endocrine syndromes

The following is a concise description of seven important clinical syndromes and their etiologically related endocrine tumors:

Cushing's syndrome is caused by a pituitary adenoma secreting ACTH or an adrenal-cortical adenoma secreting glucocorticoids (cortisol). The syndrome is characterized by moon face and trunkal obesity, hypertension and diabetes mellitus as a result of enhanced gluconeogenesis. There is evidence of osteoporosis and purplish striae of skin, a result of protein catabolism. Biochemical changes include hypokalemic alkalosis and increased 17-hydroxysteroids in urine.

Hypergrowth syndromes. Excessive somatic growth indicates an acidophil cell adenoma of the anterior pituitary secreting growth hormone. Gigantism occurs if the condition occurs before puberty, prior to the fusion of epiphysis, hence there is progressive increase in height. About 10% of patients develop diabetes mellitus. Ultimately, fatal hypopituitarism occurs as a result of pressure atrophy of the anterior pituitary. Conversely, acromegaly occurs if the tumor develops after adolescence. The individual cannot grow taller due to fusion of epiphysis, but the bone grows in thickness. Enlargement especially affects soft tissue, small bones of hands and feet and membranous bones of the skull.

Hypertension may be associated with three tumors: a) Pheochromocytoma causes paroxysmal or persistent hypertension with attacks of tachycardia, sweating, trembling and hyperglycemia. There is increased level of catecholamines (epinephrine and norepinephrine) in the serum and urine, b) Primary aldosteronism (Conn's syndrome) is due to an aldosterone-secreting adrenal cortical adenoma. The syndrome is characterized by severe muscle weakness, tetany, polyurea with loss of potassium, hypokalemia and low plasma renin activity. Hypokalemia may cause occasional periods of muscle paralysis, c) Primary reninism is caused by a renin-producing renal tumor arising from juxtaglomerular cells. It is characterized by a high plasma renin activity.

Feminizing syndrome. This is caused by tumors secreting estrogens or gonadotropins. The clinical manifestations vary according to the sex and age of the patient. Thus, in females it is caused by granulosa theca tumor of the ovary or adrenal adenoma secreting estrogen. In children, precocious sexual and physical development occur, whereas adult females present by menstrual irregularity. In male patients the syndrome may be caused by estrogen-secreting adrenal tumor or Leydig cell tumor of testis. A choriocarcinoma of the testis secreting estrogens or gonadotropins (LH) may also be responsible. Gynecomastia is the main clinical presentation, but demasculinizing manifestations may occur in adults.

Virilizing syndrome is the result of androgen secreting tumors. The clinical presentation also depends upon the age and sex. Virilism in females is usually caused by Leydig cell tumor, arrhenoblastoma, gynandroblastoma and adrenal tumors. First, defeminizing changes occur (amenorrhea and atrophy of breast), then masculine characteristics develop, namely: hirsutism, deepening of voice, enlargement of clitoris, muscular development and increased 17-keto-steroids in urine. In males virilism is caused by Leydig cell tumor of testis or adrenal tumor. The syndrome is only manifest in children who develop precocious sexual and muscular development. In adult males, the manifestations of virilism are completely obscured by the normally secreted androgens. In both sexes there is early closure of epiphysis.

Hyperthyroidism is usually the result of a functioning thyroid adenoma, less frequently a follicular carcinoma and rarely a struma ovarii in an ovarian teratoma. The manifestations include: exophthalmos, increased basal metabolic rate, loss of weight, tremors, muscle fatigue, retroorbital edema and degeneration of ocular muscles.

Hyperparathyroidism is usually caused by a

parathyroid adenoma which is more common in females. Clinical features include: multiple osteolytic bone defects (osteitis fibrosa cystica), increased blood calcium over 12 mgm/dl with low serum phosphates and rise of parathormone. The hypercalcemia results in depression of the central and peripheral nervous system, muscle weakness, constipation and depressed relaxation of the heart during diastole. Renal calculi and metastatic calcification also occur with deposition of calcium phosphate in kidneys, lungs and stomach. A calcium level of 17 mgm/dl is usually fatal.

Paraneoplastic Syndromes

A paraneoplastic syndrome is defined as a distant effect of a neoplasm upon the host not produced as a direct effect of the primary tumor or its metastases, and not related to hormone secretion by endocrine tumors. So, by definition, the syndrome is related to non-endocrine tumors. It has been estimated that at any given time, about 20% of cancer patients will be suffering from a paraneoplastic syndrome.

Paraneoplastic syndromes are of interest to the oncologist for many reasons, including the following: a) It may be the initial presentation of malignancy, hence its proper diagnosis allows early tumor detection, b) It may simulate metastatic disease, thus preventing patients from having curative treatment. c) They may be an important factor in morbidity and mortality, thus needing appropriate treatment, d) It may provide a useful biochemical marker for follow up of the patients.

The pathogenesis of paraneoplastic syndromes is explained by two main mechanisms. Most of the effects are caused by specific mediators (ectopic hormones or physiologically active substances) that are the products of derepressed genes. Gene derepression occurs when tumor cells as a result of progression begin to accomplish synthetic functions of their precursor immature cells. Autoimmunity is another mechanism for some paraneoplastic syndromes (neurologic and renal) and represents a host recognition reaction to tumor-associated antigens.

Paraneoplastic syndromes are not random function of all tumors (Table 8-3), but are especially common in some tumors. Thus, tumors of neuroendocrine origin (e.g. small cell carcinoma, neuroblastoma and melanoma) have more tendency to develop paraneoplastic endocrine syndromes. Another example of tumor-type functional relationship is the association of squamous carcinoma of foregut structures (lung, larynx, esophagus) with ectopic parathyroid hormone production. Other tumors which tend to develop paraneoplastic syndromes are pancreatic carcinoma, thymomas and large soft tissue sarcomas. Paraneoplastic syndromes are classified into seven main groups according to the system involved.

Table 8-3 Some Paraneoplastic Syndrome and Their Associated Cancers

Paraneoplastic Syndrome	Associated Cancer
Cushing's Syndrome	Lung Cancer (SCCL)
Hypernatremia (SIADH)	
Autonomic neuropathy	
Dermatomyositis	
Myasthenia	
Nephrotic syndrome	
Hypertrophic Osteoarthropathy	
Gynecomastia	
Leucopenia	
Hypercalcemia	Lung Cancer (Squamous) T cell leukemia/lymphoma
Hypoglycemia	Fibrosarcoma Mesothelioma
Acanthosis nigricans	Gastric cancer Lung cancer
Polycythemia	Renal cell carcinoma Hepatocellular carcinoma Cerebellar carcinoma
Anemia, leucopenia, Myasthenia	Thymoma
Migrating thrombophlebitis	Pancreatic carcinoma
Amyloidosis	Multiple myeloma
Precocious puberty	Hepatoblastoma

Endocrine syndromes

Malignant tumors of non-endocrine origin may produce a number of peptide hormones, or hormone-like substances which are not under normal regulatory control. This ectopic secretory product may be identical to normal hormones, or it may represent a hormone precursor (prohormone) which is subsequently metabolized to active hormone. In such cases, the secretory product is associated with clinical syndromes. Conversely, the tumor may produce inactive peptide subunits that are not associated with clinical syndromes, but are detectable by immunoassay, hence, they may serve as useful tumor markers.

Important paraneoplastic endocrine syndromes are discussed below.

1. Cushing's syndrome is characterized by hypokalemia, hyperglycemia, hypertension and muscle weakness. The classical features of Cushing's, namely (trunkal obesity and skin striae) are not found in the para-neoplastic syndrome. The prohormone large molecule secreted by the tumor is called "pro-opiomelanocortin (POMC)" and can be split into three biologically active peptide fragments: with ACTH action, melanocyte-stimulating hormone and opiate-like activity. However, only a few tumors can cleave POMC. Cushing's paraneoplastic syndrome is most commonly seen with neuroendocrine tumors especially small cell carcinoma of the lung (50%), neuroblastoma, pheochromocytoma, carcinoid and medullary carcinoma of thyroid.

2. Hyponatremia, or syndrome of inappropriate antidiuretic hormone (SIADH). The ectopic production of antidiuretic hormone, arginine vasopressin (AVP), causes sodium loss and water retention to such an extent that it is manifested by weakness, confusion, fits and coma. Diagnostic features are: hypotonic plasma, hypertonic urine, inability to excrete a water load and elevated plasma (AVP). The tumors that most often produce the syndrome are small cell carcinoma of the lung and intracranial neoplasms.

3. Hypercalcemia. In cancer patients, the causes of hypercalcemia are: bone metastasis in 50% of cases, paraneoplastic syndrome 40% and parathyroid adenoma in 10%. Two general factors are involved in paraneoplastic hypercalcemia, namely: a) secretion of parathyroid-like hormone by the tumor or b) secretion of tumor growth factor-alpha (TGF-alpha) by the tumor which acts as an osteoclastic activating factor (OAF) leading to mobilization of calcium from bone. The symptoms of hypercalcemia may be acute (vomiting, mental depression and coma) or chronic (renal failure from metastatic calcification). The biochemical abnormality is elevated blood calcium with low or normal phosphate. There is elevation of parathyroid hormone (PTH) in the blood, but below the levels of primary hyperparathyroidism. The most common neoplasms associated with hypercalcemia are: squamous cell bronchogenic carcinoma, adult T-cell leukemia/lymphoma and renal cell carcinoma.

4. Hypophosphatemic osteomalacia. Some benign mesenchymal tumors are complicated by a vitamin D-resistant osteomalacia, characterized by: phosphaturia, low serum phosphate and normal serum calcium levels. This syndrome is usually associated with giant cell tumors of bone and large hemangiomas. The cause is unknown but may involve a vitamin D antagonist, or a direct effect on the renal tubule to inhibit reabsorption of phosphate.

5. Hyperthyroidism. This may be caused by inappropriate secretion of thyroid stimulating hormone (TSH) by cancers of the breast or prostate. The syndrome may also be caused by very high levels of human chorionic gonadotropin (HCG) associated with choriocarcinoma. This hormonal cross reaction is explained by the structural similarity between HCG and TSH.

6. Hypoglycemia. Paraneoplastic causes of hypoglycemia include: a) secretion of insulin-like products by the tumor, or b) secretion by the tumor of tryptophan metabolites that interfere with gluconeogenesis. The tumors associated with this syndrome are: large mesotheliomas and fibrosarcomas and hepatocellular carcinoma.

7. Gonadotropic syndromes. Gonadotropins (LH and HCG) may be secreted by hepatoblastomas in children and cancers of lung, breast and pancreas in adults. High gonadotropin levels lead to precocious puberty in children, gynecomastia in men, and oligomenorrhea in premenopausal women.

Neuromuscular syndromes

About 7% of cancer patients develop neurologic paraneoplastic syndromes. They are most common with Hodgkin's disease, myeloma, lung and breast cancers. The etiology is autoimmune and the histologic lesions are characterized by demyelination and loss of neurones. The following subtypes are observed:

1. Peripheral neuropathy is usually distal and mostly sensory loss. Autonomic neuropathies manifested as orthostatic hypotension, neurogenic bladder and intestinal pseudoobstruction, are associated with small cell carcinoma of the lung.

2. Amytrophic lateral sclerosis may occur with a rapidly ascending motor and sensory paralysis with severe destruction of gray and white matter of the cord.

3. Cerebral complications may present as dementia, or subacute cerebellar degeneration. Multifocal leucoencephalopathy which was thought to be a paraneoplastic syndrome proved to be a viral infection.

4. Dermatomyositis is associated with malignancy in 25% of cases. The association is even more marked (70%) in patients over the age of 50 years. It affects mainly proximal muscles with weakness, arthralgia, dysphagia and associated skin rash. Muscle biopsy reveals eosinophilic necrosis of muscle, loss of cross striations, hyperplasia of sarcolemmal cells and inflammatory reaction.

5. Myasthenic (Eton-Lambert) syndrome is strongly associated with small cell carcinoma of the lung. It is characterized by muscle weakness and fatigue most pronounced in the pelvic girdle and thigh. In contrast to true myasthenia gravis, muscle strength improves with exercise and there is a poor response to anticholinesterase. The association of true myasthenia gravis with thymoma is well recognized.

Dermatologic syndromes

Pigmented lesions and keratosis are well-recognized paraneoplastic effects of which two types are recognized:

1. Acanthosis nigricans, is a cutaneous disorder characterized by hyperkeratosis and pigmentation of axilla, neck, flexures and anogenital region. It is caused by secretion of tumor growth factor alpha (TGF-alpha). More than one half of patients with acanthosis nigricans have cancer, especially cancer of stomach, breast and lymphoma. In 17% of cases, the skin changes appear before the discovery of the tumor.

2. Seborrheic Keratosis may rarely be the first presentation of a paraneoplastic syndrome, with sudden appearance or increase in size of the lesion.

Hematologic and vascular syndromes

These may be unrelated to therapy or local effects of tumor and include the following paraneoplastic disorders:

1. Polycythemia. Cancer associated erythrocytosis may complicate some tumors, particularly renal cell carcinoma, hepatocellular carcinoma and cerebellar hemangioblastoma. Elevated erythropoietin levels are found in the tumor and in the serum in about half of the patients with erythrocytosis. Other mechanisms include: the secretion of adrenal androgens with erythropoeitic effect, or the secretion of prostaglandins which enhance the erythropoietin effect.

2. Anemia. Pure red cell aplasia may be associated with thymoma. Macrocytic anemia may occur with myeloma. Autoimmune hemolytic anemia may be associated with lymphoma or gastrointestinal cancer.

3. Granulocytosis. The peripheral granulocyte count in some cancer patients may rise to over 20,000/mm, a finding that may lead to an erroneous diagnosis of leukemia. The mechanism of this leukemoid reaction is probably a secretion of growth factors (CSF) by the tumor.

4. Granulocytopenia, apart from therapy, may be associated with thymoma and small cell carcinoma of the lung. The tumors secrete products which interfere with the action of colony stimulating factors (CSF) on marrow cells.

5. Eosinophilia is occasionally noted, particularly in Hodgkin's disease (20%) and mycosis fungoides.

6. Thrombocytosis may occur in 30% of cancer patients, with platelet counts above 400,000/mm. Thrombocytopenia with purpura is rarely seen.

7. Migratory thrombophlebitis may occur with cancers of pancreas, lung and gastrointestinal tract.

8. Disseminated intravascular coagulation may complicate acute promyelocytic leukemia and adenocarcinomas. Laboratory tests show thrombocytosis and increased fibrinogen. Hypercoagulability is attributed to release of platelet aggregating factors and procoagulants by the tumor.

9. Nonbacterial thrombotic endocarditis is most common with solid tumors, rarely with leukemias and lymphomas. Emboli to the brain present a great danger.

Osseous syndromes

Hypertrophic osteoarthropathy is encountered in 10% of patients with bronchogenic carcinoma. The pathogenesis is unclear, but bone thickening is due to the secretion of growth hormone-like products. There is deposition of subperiosteal bone along the distal ends of long bones and shaft of digits leading to clubbing of the fingers.

Renal syndrome

About 11% of patients with nephrotic syndrome had cancer. The pathology is either membranous glomerulonephritis or lipid nephrosis and are produced by the deposition of immune complexes.

Other Syndromes

The following three syndromes are of general nature and can not be classified by target system:

1. Cancer cachexia is a common syndrome including: anorexia, weight loss, weakness, anemia and malnutrition. The affected patients have a high rate of protein catabolism, increased metabolic rate and reduced appetite. Cachexia is probably due to the effect of tumor necrosis factor alpha (cachectin) which acts to mobilize adipose tissue.

2. Fever is not uncommon presentation of malignancy . Thus, 40% of patients with cancer has non-infectious fever at some time in their course, also 19% of fevers of unknown origin are caused by a previously unrecognized tumors. Common cancers associated with fever are: Hodgkin's disease (Pel-Ebstein fever), hypernephroma, osteosarcoma and liver metastases. The fever is probably caused by a pyrogen released from necrotic tumors which acts on the temperature regulating center of hypothalamus.

3. Amyloidosis. About 15% of cases of amyloidosis occur in association with cancer, particularly multiple myeloma, renal cell carcinoma and malignant lymphoma. Amyloid is an insoluble protein fibrils of which two types are recognized: *amyloid light protein (AL) type* derived from plasma cells *and amyloid associated (AA) type* synthesized by the liver. Amyloid develops from soluble protein precursors in the blood, immunoglobulin (Ig) in case of myeloma and serum amyloid associated (SAA) protein in case of solid tumors. Tissue destruction by solid tumors leads to the secretion of interleukin-1 (IL-1) by macrophages. The latter stimulates the liver to secrete (SAA).

Amyloid is deposited extracellularly causing pressure atrophy of cells with failure of vital organs (kidney, liver and heart). Hence, the presence of amyloidosis implies poor prognosis. Thus, in myeloma patients, 10% develop systemic amyloidosis and exhibit a median survival of less than one year. Diagnosis is confirmed by gingival biopsy which demonstrates amyloid material, positive by Congo Red stain with green bi-refringence under polarized light.

Infective Complications

The common pathogens which infect cancer patients are listed in (Table 8-4). The most common viral infections are the respiratory DNA viruses of the herpes virus group which include: herpes simplex virus (HSV 1 and 2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6). Such infections are particularly common in patients with hematologic malignancies and stem cell transplantation.

Gram positive bacteria (S. aureus) are the most common cause of septicemia, whereas, gram negative bacteria (E. coli and pseudomonas) are more common at other sites. Polymicrobial infection is frequent. The most common fungal infections in cancer patients are Candida and Aspergillus. The diagnostic morphology of common fungi is demonstrated in (Fig 8-1).

Infections in neutropenic patients is a serious emergency complication that needs urgent treatment, even if culture is negative (which is the case in 50% of patients). Neutropenic fever is defined as fever >38 ^{o}c and neutrophil count <500/mm^{3}.

The pathogen Pneumocystis jiroveci (formerly named P. carinii) is difficult to

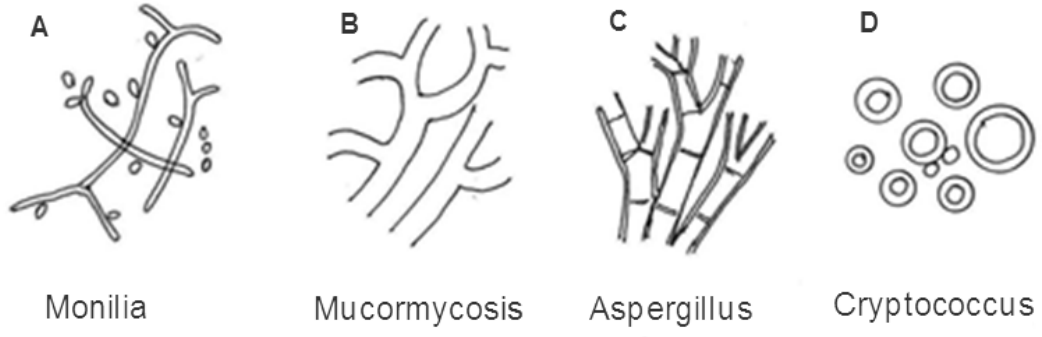

Fig 8-1 *Morphology of common fungal infections in cancer patients. A. Monilia (Candida) exists as pseudohyphae and yeast forms. The former are thin (3-5 microns), nonseptate and branch at wide angle B. Mucormycosis appears as thin walled broad hyphae (6-25 microns) wide, rarely septate, branch at right angle and curved C. Aspergillus is composed of thick walled hyphae (3-6 microns wide), regular septation and branching at acute angles D. Cryptococcus appears as rounded budding yeast forms of variable size (2-20 microns) with thick capsule.*

Table 8-4 Common Pathogens Infecting Cancer Patients

Species	Organism	Site affected
Viruses	Epstein-Barr virus (EBV)	Lymphoid tissue
	Cytomegegalovirus (CMV)	Lung
	Herpes simplex virus (HSV)	Oral mucositis
	Infuenza and Parainfluenza	Lung, sinuses
Bacteria	Staphylococcus aureus	Septicemia, skin
	Streptococci	Septicemia
	Escherichia coli	Intestine
	Corynebacteria	lung
Fungi	Monilia (Candida)	Oral, urinary, systemic
	Aspirgillus	Lung, sinuses
	Mucormycosis	Lung, sinuses
	Cryptococcus	Brain
	Pneumocystis jiroveci	Lung
Protozoa	Giardia	Duodenum
	Toxoplasma	Brain
Nematodes	Strongyloidis stercoralis	Systemic

classify since it combines both fungal and protozoal features. It is an important cause of serious pulmonary infections. It is also noteworthy that strongyloides stercolaris larva in the immunocompromized cancer patients will migrate into the body with fatal outcome.

Complications of therapy

Early complications

The main early complications of chemotherapy are: *Leucopenia*, tumor lysis syndrome (TLS) and the hemolytic uremic syndrome. Leucopenia (neutrophil count <500 mm^3) will predispose to various types of infections. *Tumor lysis syndrome* is most common in rapidly growing, bulky, chemosensitive tumors (e.g. NHL/Leukemia) and results from the breakdown of nucleic acids and release of cellular potassium. The syndrome is characterized by three diagnostic triads, namely: (1) hyperkalemia (Potassium >6 meq/L), (2) hyperphosphatemia (phosphate >4.6 mg/dL) and (3) hyperuricemia (uric acid >8 mg/dL). Hyperkalemia is the greatest immediate risk causing extreme muscle weakness, cardiac arrhythmias and sudden death. The other early metabolic complication is the hemolytic uremic syndrome due to hematologic and renal cytotoxicity of chemo or immunotherapy.

Late Complications

The three main late complications of cancer therapy are: (1) iatrogenic cancer, or therapy induced second malignancy (Table 8 -5), (2) infertility due to therapy induced atrophy of ovaries or testes, and (3) retardation of skeletal growth of children due to destruction of epiphyseal cartilage by irradiation.

Table 8-5 Iatrogenic Cancers

Therapy	Cancer site
Post – Chemotherapy	
Alkylating agents	AML, NHL, Bladder cancer
Estrogen	Endometrium
Tamoxifen	Endometrium
Cyclosporen	Kaposi sarcoma
Post – Radiotherapy	Soft tissue sarcomas*
	Skin carcinoma
	Thyroid carcinoma
	Leukemia

* Common types are hemangioendothelioma and malignant fibrous histiocytoma

TUMOR IMMUNOLOGY

In experimental animals, in which most of the tumors are induced by chemicals or viruses, immune reactions against the tumors are prominent, and lead to tumor rejection. Whereas, in spontaneous human cancers the immune reaction is usually weak and inadequate to control the tumors.

Burnet in 1970 introduced his *immunosurveillance theory* against cancer. According to this concept, cancer cells are continuously arising, but are eradicated by the immune system. Clinical cancer develops as a result of failure of this normal defense mechanism. This theory is supported by the increased cancer risk in the immunodeficiency states. But, the theory is challenged by failure to identify tumor-specific antigens in the grand majority of human cancers.

The concept of tumor immune surveillance has recently been expanded to include the phenomenon of immune selection of tumor cell population during progression. Thus, immunosurveillance will eliminate a sector of tumor cell population with survival of the rest which has escaped immune rejection and hence are more aggressive.

TUMOR ANTIGENS

The initial classification of tumor antigens into tumor specific antigens (present on tumor cells only) and tumor associated antigens (present on both tumor cells and normal cells) has proved to be imperfect. The modern classification of tumor antigens is based on their molecular structure and source (Table 8-6). Most of these antigens are too weak to be used as therapeutic vaccines, but, viral oncoproteins are used in preparing cancer prevention vaccines. Also, some tumor oncoproteins are useful as targets of immunotherapy by monoclonal antibodies.

Table 8-6 Classification of Tumor Antigens Based on Their Source and Molecular Structure

Class	Tumor
I. Oncoproteins of Cancer genes	
BCR – ABL	Myeloid leukemia
RAS	Pancreas
HER – 2	Breast
TP 53	Several cancers
II. Aberrant expression of cellular Proteins	
Tyrosinase and MAGE-1	Melanoma
III. Oncofetal antigens	
Carcinoembryonic antigen (CEA)	Adenocarcinoma
Alpha-Feto-Protein (AFP)	Hepatocellular carcinoma
	Yolk sac tumor
IV. Altered cell surface molecules	
Glycolipids	Melanoma
Glycoproteins : CA-125	Ovary
CA-19-9	Colon, pancreas
CA-15-3, Muc-1	Breast
V. Differentiation antigens	
CD 20	NHL
CD 10	ALL
VI. Antigens of oncogenic viruses	
HPV	Cervical carcinoma
EBV	NHL
HBV	Hepatocellular carcinoma

(Murphy et al., 2008/ Delves et al., 2011)

ANTIGEN PRESENTATION TO T-LYMPHOCYTES

The Major Histocompatability Complex

The human major histocompatibility complex (MHC) antigens (also Known as human leucocyte antigens, HLA) are cell surface glycoproteins essential for antigen presentation to T-lymphocytes. The MHC molecules bind with their peptide antigens intracellularly, carrying it in a groove, and deliver it to the surface where it can be recognized by the appropriate T-cell.

There are two classes of MHC molecules, the MHC class I and MHC class II, which present antigens to activate cytotoxic T lymphocytes (CD8) and T-helper lymphocytes (CD4) respectively. These two classes differ in their biochemical structure, cell distribution and outcome of T-cell activation (Fig 8-2 and Table 8-7). Cancer cells can express MHC-class I molecules, and these carry tumor antigens (peptides) to cell surface to be presented to cytotoxic T-cells.

ANTIGEN PRESENTATION TO B-LYMPHOCYTES

Follicular Dendritic Cells

Antigens are presented to B-cells in the form of whole macromolecules by follicular dendritic cells. These stationary stromal cells are present in germinal centers of lymph nodes and spleen, as well as, in soft tissues. They bear FC surface receptors for the immunoglobulin IgG and can trap antigens bound to antibodies or complement. B-lymphocytes can recognize a variety of antigens, both proteins and nonproteins (Lipids, polysaccharides and small chemicals). Contrary to T-lymphocytes, B-lymphocytes can recognize antigens in their native undegraded form without the help of MHC molecules (Fig 8-3).

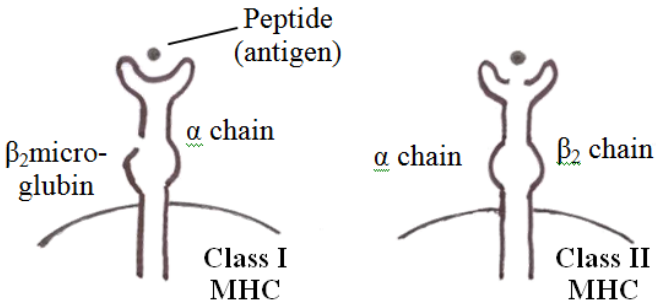

Fig 8-2 *The structure of class-I and class-II major histocompatibility complex (MHC) molecules. Both types have a cleft for binding the peptide antigen. For biological differences refer to Table 8-7.*

Table 8-7 Comparison of Major Histocompatibility Complex Molecules (MHC)

Feature	Class I MHC	Class II MHC
Structure of Peptide chains	α and β_2-microglobulin	α and β chains
Source of antigen	Intracellular	Extracellular
Site of antigen peptide generation	Proteasome	Lysosome
Expressive cells	All cells	Dendritic, macrophages, B. lymphocytes, endothelium, thymic epithelium
Responsive T cells	CD8 (CTL)	CD4 (HTL)
Outcome	Cytotoxicity	Stimulation

(Abbas and Lichtman, 2009)

IMMUNE CELL RECEPTORS AND SIGNAL TRANSDUCTION

The cell receptors of different immune cells are listed in Table 8-8. The T-cell receptor for antigen (TCR) and the CD4 or CD8 co-receptor together recognize the peptide antigens-MHC molecules complex carried by antigen presenting cells (Fig 8-3). This recognition and binding activates tyrosine kinase and provides the first or initiating signal transduction. The second signal is produced after binding of co-stimulatory molecules CD80 or CD86 (formerly E7) of antigen presenting cells with other associated T-cell surface proteins (CD28). The result of both signals is the transcription of cytokines that activates other immune cells in case of T-helper lymphocyte, or lymphotoxins in case of cytotoxic T-lymphocyte. TCR diversity is generated by somatic rearrangement of the genes that encode the TCR and β-chains molecules. T-cells are also equipped with surface adhesion molecules (e.g. LFA-1 and VLA-4) needed for cell migration by chemotaxis.

The B-lymphocyte antigen receptor complex includes surface IgM molecule and associated two immunoglobulins (Fig 8-4). Binding of this complex with the antigen generates the first signal transduction. Subsequent activation of CD21 receptor by antigen, complement or EBV virus will initiate the second signal transduction. After activation, B-lymphocytes develop into plasma cells which secretes antibodies.

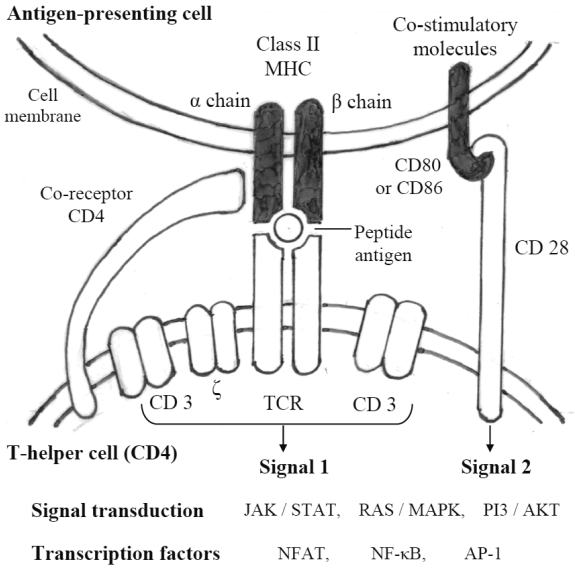

Fig 8-3 *Helper T-cell receptor (TCR) and signal transduction. The TCR complex, assisted by the coreceptor CD4, recognizes peptide antigen in the context of MHC-II molecules and initiates the first signal transduction. The second signal is produced after binding of costimulatory molecule CD80 or CD 86 (formerly E7) with CD28. The same interactions are involved in the activation of cytotoxic T-cells except that the coreceptor is CD8 and TCR recognizes a peptide-MHC-I complex. Abbreviations: JAK=Janus kinase, STAT=signal transducer and activator of transcription, PI-3k-phosphoinositole 3 kinase, AKT=a protein kinase, NFAT=nuclear factor of activated T-cells, NF -kB = nuclear factor-kB, AP-1 =activating protein-1.*

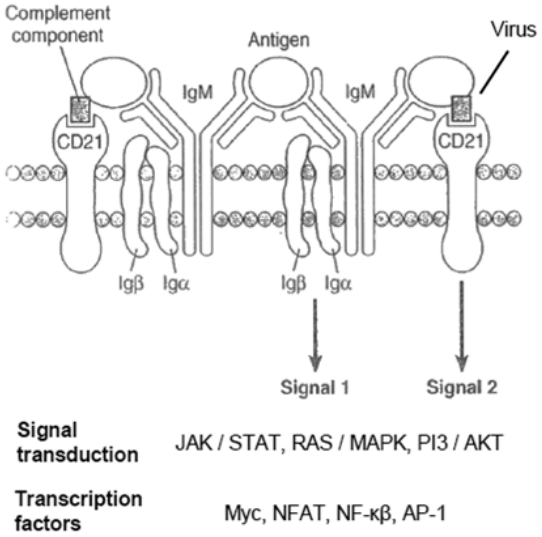

Fig 8-4 *B-lymphocyte antigen receptor and signal transduction. The antigen receptor complex induces surface IgM molecule and associated two immune-globulins (Iga and Igβ). This complex binds with protein antigen producing the first signal transduction. The receptor CD21 activation by antigen, complement or EBV virus will initiate the second signal transduction. After activation, B-lymphocytes develop into plasma cells which secrete antibodies.*

Table 8-8 Cell Surface Receptors of Immune Cells

Cell	Surface Receptor
Antigen Dependent Cells	
Cytotoxic T lymphocyte (CTL)	TCR, CD3, CD8 Costimulatory: CD28
Helper T lymphocyte	TCR, CD3, CD4, CD40 Ligand Costimulatory: CD28
B– lymphocytes	Antigen specific IgM, α and β protein CD40 receptor, CD21 Complement receptor, Fc receptor
Antigen Independent Cells	
Natural Keller cell (NK)	FC (=CD16), NK receptor
Macrophage	MHC-I, MHC-II FC receptor for IgG Complement receptors, Costimulatory molecules CD80 or CD86 (formerly B7)
Langerhans/dendritic Cells	MHC-I, MHC-II
Follicular Dendritic Cells	FC receptor

EFFECTOR IMMUNE CELLS

They are classified into two main classes according to their dependency on antigens (Fig 8-5). Antigen dependent cells are the lymphocytes (T and B sub-types) which are responsible for specific or adaptive immunity. Conversely, antigen -independent cells include: the natural killer (NK) cell, macrophages and neutrophils which are responsible for nonspecific or innate immunity.

Antigen Dependent cells

1. Suppressor/cytotoxic T-lymphocyte (CTL, CD8): These cells recognize only processed antigens (peptides) which are presented in the antigen-binding groove of major histocompatibility complex type I (MHC-I) which binds to CD8 receptor of T-cells. Cytotoxic T-cells are able to induce apoptosis or lysis of tumor cells through perforin or TNF-β (lymphotoxin) mediated mechanisms.

2. Helper/inducer lymphocyte (CD4): These cells also recognize only processed antigens (peptides) which are presented in association with type II MHC that binds with CD 4 receptor of T-helper cell (Fig 8-6). The helper T-lymphocyte is the master cell of the immune system since it activates cytotoxic T-cells, B-cells and macrophages through cytokine-mediated mechanism. Helper T-cells also mediate delayed type hypersensitivity (DTH) reactions.

3. B-lymphocytes: these are antigen dependent, but MHC independent, and are responsible for humoral immunity with production of antibodies by plasma cells. Contrary to T-cells, B-cells can recognize intact unprocessed antigens in their normal tertiary configuration. The antibodies produced are able to mediate: tumor cell phagocytosis by macrophages, complement induced inflammation and antibody-dependent cell-mediated cytotoxicity (ADCC) with lysis of tumor cells.

Antigen Independent Cells

1. Natural killer cell (NK): these are independent on both antigens and MHC for tumor cell killing. Natural killer cells express surface receptor for Ig, hence, they are efficient mediators of (ADCC) reactions. Culture of lymphocytes with IL-2 produce lymphokine-activated killer (LAK) cell which are derived from two sources namely: NK cells and T cells.

2. Macrophages: these are also capable of killing cells in an antigen and MHC independent fashion. Unlike CTL and NK cells, they are phagocytic and process the antigen into linear short peptides

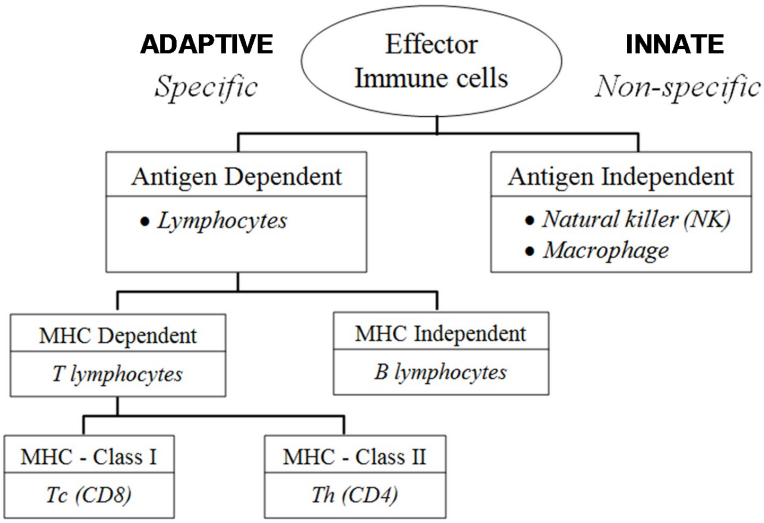

Fig 8-5 *The two arms of immunity and their effective immune cells. Innate (nonspecific) immunity is an immediate short, first line of defense. Adaptive (specific) immunity is a gradual, long-term specific defense, with a memory to the antigen and special cell receptors.*

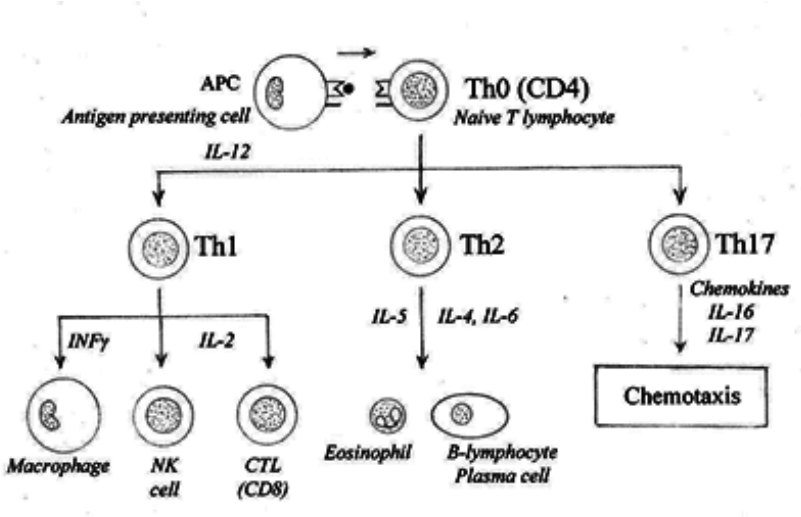

Fig 8-6 *T-helper Lymphocyte (CD-4), the master of immune cells. After binding with the peptide antigen presented on MHC-II by the antigen-presenting cell, the immature (naive) T-helper lymphocyte (Tho) differentiates to three subsets: Th1, Th2 and Th17 which produce cytokines that control cellular immunity, humoral immunity and chemotaxis respectively.*

which are exteriorized with MHC to the cell surface. Like NK cells, they can mediate (ADCC) reaction. Langerhans cells are non-phagocytic histiocytic cells. Both macrophages and Langerhans cells are antigen presenting cells to T-lymphocytes.

3. Neutrophils can also mediate tumor cell killing, either by direct contact or an antibody-dependent mechanism. Their cytotoxic effect, however, requires neutrophil activation by several cytokines, mainly IFN-α and TNF.

CYTOKINES

Cytokines are soluble glycoproteins of low molecular weight (<30 KD) that regulate (modulate) the immune response. Originally, cytokines were classified according to the manufacturing cell of origin (e.g. lymphokines, monokines and interleukins), but, later were classified according to the immune cells affected, as well as, functional effect and given interleukin numbers (Table 8-9). The functional effect may be stimulatory or inhibitory. Moreover, some cytokines may attract immune cells to the location (chemotaxis) and these are called chemokines.

There are three main types of interferons, namely: α, β and γ . The first two interferons have antiviral action, but, interferon gamma (produced by Th-1 lymphocyte) increases the induction of MHC molecule expression, thus increasing the activity of antigen presenting cells, as well as, cytotoxic T cell, hence increases T-lymphocyte cellular immunity. Practically, cytokines may be classified according to their mode of action into the following four main classes:

1. Immunomodulating cytokines: T-helper lymphocytes is the master regulator of all other effector cells of the immune system (Fig 8-6). This is accomplished through the production of the following cytokines: (a) IL-1 through 6 and IFN-gamma to activate B lymphocytes (b) IL-2 to activate cytotoxic T lymphocytes and NK cells. (c) IFN-gamma to activate the antigen presenting cells (macrophages and Langerhans cell) and NK cells.

2. Hematopoietic cytokines: These include the colony stimulating factors (CSF) which stimulate the growth of blood cells in bone marrow. The GM-CSF act on early precursor cell, whereas, G-CSF and M-CSF act exclusively on one cell type, the granulocyte or macrophage respectively.

3. Cytotoxic cytokines: These are involved in cancer cell killing by the effector cells and include: (a) Tumor necrosis factor alpha (TNF- alpha) or cachectin produced by macrophages and (b) TNF-beta (or lymphotoxin) produced by cytotoxic T lymphocytes.

4. Chemotactic cytokines (chemokines): Chemotaxis describes cell mobility (migration) directed by a concentration gradient of chemokines, resulting in recruitment and homing of immune cells into the location. Examples of important chemokines are: (a) SDF-1 produced by stromal cells and chemotactic to stem cells (homing phenomenon), (b) IL-8 produced by stromal cells and chemotactic to leukocytes, and (c) IL -16 and IL-17 produced by T-helper lymphocytes and chemotactic to macrophages.

IMMUNE MECHANISMS

A. Specific (or Adaptive) Immunity

This is an antigen-dependent immunity, characterized by an afferent and efferent arms (or pathways):

1. The afferent arm: The antigen is carried to lymphocytes by the antigen presenting cells which include macrophages and Langerhans cells and other dendritic cells. Macrophages, contrary to Langerhans cells, are phagocytic, and hence, are involved in antigen processing, breaking the proteins into peptides. Antigen is presented to cytotoxic T lymphocytes (CTL) in the form of peptides in association with MHC-class I. Whereas, in case of T-helper lymphocyte (Th) it is also presented as peptides but in association with MHC-class II and the costimulatory molecule B7. Conversely, in case of B cells, the antigen is presented in its native form (protein) by follicular dendritic cells, not associated with any MHC complex.

2. *The efferent arm:*

a. Humeral immunity: B lymphocytes are activated when a native antigen binds to the surface immunoglobulins (IgM) in the presence of lymphokines. This leads to proliferation of B lymphocytes (clonal selection and expansion) and the secretion of antibodies by plasma cells (IgG, IgA or IgM). The FAB ends of the light chains are the antigen binding sites (or paratope) of the immunoglobulin (Fig 8-7). Whereas, the other end of the molecule (FC or fragment crystalline) serves the effector function by binding to FC receptors of macrophages or NK cells; or to complement, leading to elimination of the bound antigen and cell lysis (complement dependent

Table 8-9 Classification of Cytokines According to Their Producing Cells and Target Cells

Cytokine	Producing cell	Target cell	Effect
IL-I	Macrophages and others	THL, B-cells	Stimulator, pyrogenic
IL-2	THL-1	CTL, NK, THL-1	Stimulator
IL-3	T-cells	Stem cells, mast cells, monocytes	Stimulator
IL-4	THL-2	B-Cells	Stimulator
IL-5	THL-2	B-cells, eosinophils	Stimulator
IL-6	THL-2, Macrophages, Tumor cells	B, T cells, stem cell	Stimulator
IL-7	Stromal cells	Pre-B and Pre-T cells	Stimulator
IL-8	Stromal cells	Leukocytes, endothelium	Chemotaxis, angiogenesis
IL-9	T cell	T-cell, mast cells	Stimulator
IL-10	THL-2	THL-1, NK	Stimulator
IL-11	Stromal cells	Megakaryocytes	Stimulator
IL-12	Macrophages	THL-1, NK THL-2	Stimulator inhibitor
IL-13	THL-2, NK, Mast cell	B-cells, THL-2	Stimulator
IL-14	Follicular dendritic	B-cells	Stimulator, but inhibit IgG
IL-16	THL	Macrophages	Chemotaxis
IL-17	THL	Macrophages	Chemotaxis
IL-18	Macrophage	THL-1, NK	Stimulator
IL-27	Macrophages	CTL	Activator
IFN-α and β	Macrophages and T-cell	Tand B cells	Antiviral
IFN-γ	THL-1	Macrophages, tumor cells	MHC, expression
SDF-1	Stromal cell	Stem cells	Chemotaxis (homing)
SCF	Stromal cells	Stem cells	Stimulator
TNF-α	Macrophages	Tumor cells B, T, Macrophages	Cytotoxic stimulator
TNF-B	CTL	Tumor cells	Cytotoxic
GM-CSF	T cells, monocytes	Granulocytes, monocytes	Stimulator
G-CSF	Stromal cells	Granulocytes	Stimulator
M-CSF	T cells, monocytes	Monocytes	Stimulator

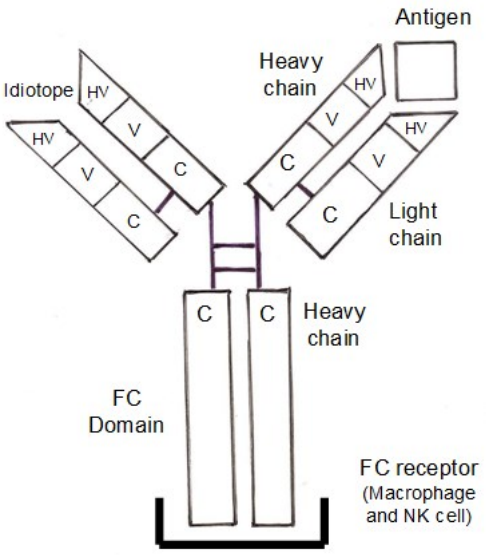

Fig 8-7 *Basic structure of immunoglobulin molecule (IgG). It is a tetramer protein, composed of two light chains and two heavy chains held together by two bisulphide bonds. Each chain is composed of constant (C), Variable (V) and hypervariable (HV) regions. The two adjoining hypervariable regions form the antigen-binding site, whereas, the end of molecule binds with FC receptor on histiocytes and NK cells. The phenomenon of antibody diversely against different antigens depends upon the property of gene rearrangement of Ig gene.*

cellular cytotoxicity CDCC).

(b) *Cellular immunity:* The processed antigen (peptides) is presented to Th in combination with MHC-class II. This activates Th to secrete IL-2 which stimulates Tc (cytotoxic T lymphocyte CTL). The latter cell is capable of recognizing and binding to membranous tumor antigens in association with MHC-class I (with involvement of CD3 and CD8 T cell receptors). This interaction triggers lethal cell damage through the release of lymphotoxin (TNF-beta) (Fig 8-8).

B. Non-specific (or Natural) Immunity

Natural immunity against cancer cells is dependent upon three types of cells, namely: macrophages, natural killer (NK) cells and lymphokine (IL-2) activated killer (LAK) cells. Macrophages are activated by BCG or IFN-gamma. The activated cells destroy cancer cells by one of two mechanisms, namely: (1) cell contact cytotoxicity, or (2) antibody dependent cellular cytotoxicity (ADCC). Antibody and complement coat the antigen on cell surface (opsonisation) leading to its phagocytosis by macrophages via binding to their complement receptors (CR) and FC receptors.

COOPERATION AMONG IMMUNE CELLS

The complex interaction and cooperation among immune cells is demonstrated in Fig 8-9.

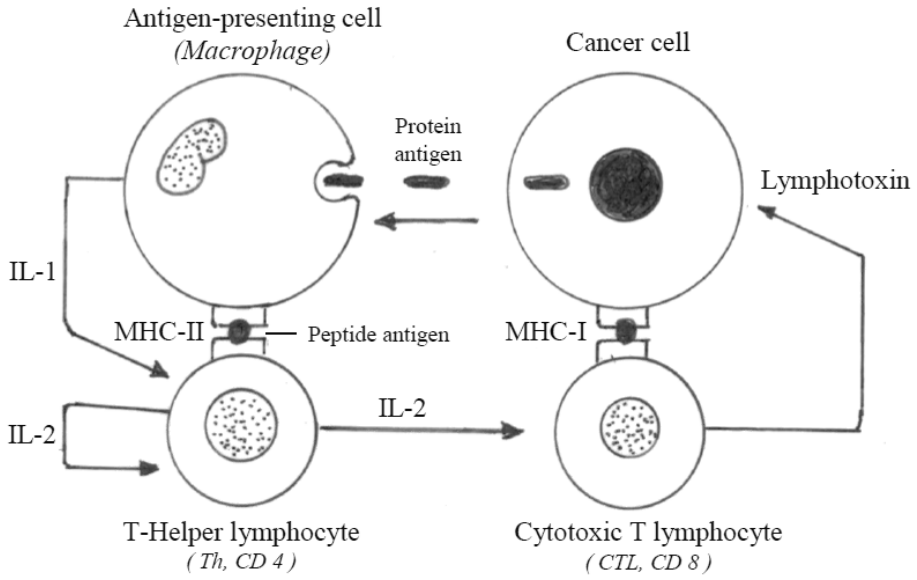

Fig 8-8 *Interactions and cooperation between the macrophage, T-helper lymphocyte and T-cytoxic lymphocyte in cancer cell killing.*

Three examples of cooperation need to be emphasized in regard to cancer cell killing.

(1) ThL-1 and CTL

The T-helper lymphocyte (CD4) after antigenic stimulation, will produce IL-2 which activates cytotoxic lymphocyte (CTL or CD8). The latter will produce lymphotoxins lethal to cancer cells (Fig 8-8).

(2) ThL-2 and B-Lymphocytes

The T-helper lymphocyte (subset ThL-2) after antigenic stimulation will produce cytokines (IL-4 and IL-6) which activates B-lymphocytes. Moreover, B-cells equipped by its MHC – class II molecules, can present peptide antigens to T-helper lymphocytes leading to expression of CD40 Ligand (CD40L) on the surface of T-cells. Binding of CD40-L to CD40 receptors on B-lymphocytes will stimulate their proliferation (clonal expansion) and the synthesis and secretion of antibodies (Fig 8-9).

(3) Plasma Cells and NK/Macrophage (ADCC)

Antibodies produced by plasma cell will bind to surface tumor cell antigens, rendering them more vulnerable to attack by natural killer cells and macrophages (Fig 8-9). This is an example of cooperation between adaptive and innate immunities in cancer cell killing (antibody dependent cellular cytotoxicity, ADCC).

FAILURE OF IMMUNE RESPONSE

It is at present obvious that tumor escape from immunologic rejection is a multifactorial phenomenon, partly due to poor tumor antigenicity, as well as, defects in the immunologic reactions of the host. Moreover, tumor cells can sense immune defenses and react to their advantage (e.g. by secreting inhibitory cytokines such as TGF-β). The following is a list of factors responsible for tumor escape from the immunologic reactions:

1. Weak or absent tumor antigenicity
2. Shedding of antigen
3. Blocking antibodies

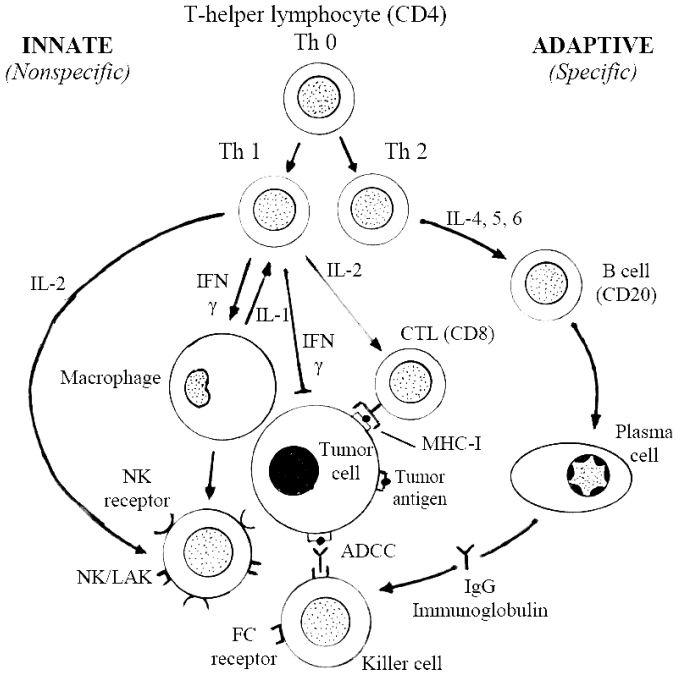

Fig 8-9 *Interactions and cooperation among immune cells in cancer cell killing. Abbreviations: Th=T-helper lymphocyte, IL=interleukin, IFN= interferon, CTL=cytotoxic T-lymphocyte, MHC=major histocompatibility molecule, NK=natural killer cell, LAK=lymphokine activated killer cell, FC=receptor for fraction crystalline end IgG, and ADCC=antibody dependent cellular cytotoxicity*

4. Activation of suppressor T lymphocytes
5. Cytotoxic T inhibitors (e.g. GM-CSF or TGF-beta)
6. MHC deficiency
7. Perivascular binding site barrier preventing entrance of antibodies to the centre of tumor
8. Tumor tissue pressure barrier
9. Intra-tumor heterogeneity
10. Resistance of cancer cells to cytotoxic cytokines.

IMMUNOTHERAPY

Immunotherapy of cancer are classified under two main groups (Yotnda, 2010), namely: active and passive (Table 8-10). In *active immunotherapy*, we make use of the immune system of the patient to fight cancer, whereas, in *passive immunotherapy* we resort to other extrinsic immunologic approaches. The main problem with immunotherapy of human cancer is that the tumor antigens expressed are heterogeneous, inconsistent and poorly-immunogenic. Several ways of confronting this problem are to augment the immune system of the patient by cancer vaccines , in vitro stimulation of effective immune cells of the patient or nonspecific stimulation of innate immunity. An alternative strategy is to resort to exogenous means, such as the administration of cytokines, monoclonal targeted therapy or gene therapy. The following is an outline of the five main methods of immunotherapy in clinical use and trials.

1. Active immunotherapy

a. *Immunoprevention:* Development of vaccines against human oncogenic viruses (e.g. HBV, HPV E6 and E7).
b. *Active specific immunization:* Postoperative vaccination by irradiated tumor cells (colon, melanoma) with adjuvants to minimize recurrence.

2. Adoptive immunotherapy

a. Expand tumor infiltrating lymphocytes (TIL) in vitro by IL-2 stimulation then reinfusion to patient.
b. Expand cytotoxic T lymphocytes (CTL) in vitro by irradiated tumor cells.
c. Sensitize CTL against active peptides of mutant p53 or RAS.

3. Immunomodulation (nonspecific immunostimulation)

a. Interferon-α: Hairy cell leukemia, node-positive melanoma and CML.
b. IL-2: Renal cell carcinoma and melanoma.
c. BCG: Carcinoma in situ (CIS) or superficial cancer of urinary bladder

Table 8-10 Classification of Cancer Immunotherapy

I. Active
Cancer vaccines (preventive or therapeutic)
Nonspecific stimulation of innate immunity
II. Passive
Immune cell transfer (adoptive immunotherapy)
Cytokine therapy
Monoclonal targeted therapy

4. Monoclonal Antibodies

A monoclonal antibody (moAb) is a purified antibody generated against a specific antigen (epitope) or idiotype (Fig 8-10). They are prepared in tissue culture using hybridoma systems of mice origin. Their early clinical use was faced with several problems. Thus, because moAbs are foreign antigens, they can cause antigen-antibody reaction with serious organ damage and inactivation of the antibody.

Over the years, molecular engineering was used to increase both the safety and effectiveness of moAbS. The first of these molecular constructs were chimeric antibodies (IgG molecule which is 75% human and 25% murine), thus reducing its antigenicity. Later, humanized antibodies (95% human and 5% murine) and fully human antibodies were prepared. The terminology of these four antibodies are: murine (-omab), chimeric (-ximab), humanized (-zumab). A list of approved monoclonal antibodies used in targeted therapy is listed in (Table 8-11).

To increase the effectiveness of moAbS, they may be conjugated to a toxin (e.g. diphtheria toxin), radioactive molecules or nanoparticles (e.g. nanogold). Unconjugated antibodies act by either blocking a ligand or a receptor. Another mechanism is to induce cellular apoptosis. Conversely, conjugated antibodies have a wider field effect, affecting the targeted cell, as well as, its neighbors, hence are more effective (Fig 8-11). The radionuclide selection is most often determined by tumor size. Thus, beta-emitters can penetrate a long distance (2 mm for ^{131}iodine and 11 mm for ^{90}yttrium) and hence are used for large tumors (>0.5cm in diameter). Conversely, alpha-emitters (e.g. ^{213}Bismuth) can penetrate a distance of only 84 μm, hence it is used for small collection of tumor cells such as leukemia and malignant ascites.

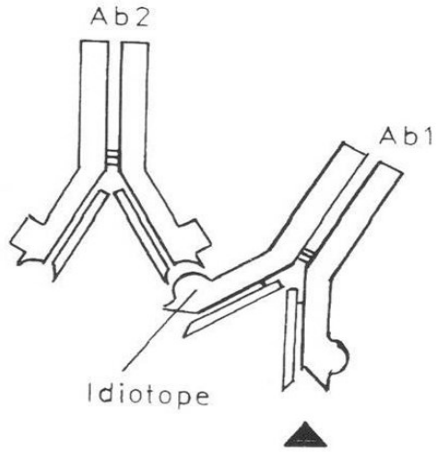

Fig 8-10 *Antibody against antibody or idiotype-anti-idiotype interactions. An antibody (Ab1) recognizes an antigen (solid triangle) is itself acts as an antigen and recognized by another antibody (Ab2). This interaction results in inhibition of target cell. Example of anti-idiotype targeted therapy is Rituxan used in CD20 positive B-cell non-Hodgkin lymphoma.*

Table 8-11 Approved Monoclonal Antibodies Used in Targeted Therapy of Cancer

Antibody	Target	Malignancy
Rituximab (Rituxan) [b]	CD20	B-cell NHL
Tositumomab (Bexxar) [a]	CD20	B-cell NHL
Trastuzumab (Herceptin) [c]	HER-2	Breast
Bevacizumab (Avastin) [c]	VEGF	Colorectal
Cetuximab (Erbitux)[b]	EGFR	Colorectal
Gemtuzumab (Mylotarg) c	CD-33	AML

a - Murine antibody, ^{131}I-conjugate b - Chimeric antibody and c- Humanized antibody

GENE THERAPY

Gene therapy is the transfer and expression of a foreign gene into cancer cell, performed with therapeutic intent. The process involves the replacement of an absent or defective gene (e.g. tumor suppressor gene), the introduction of a toxic gene (e.g. TNF) to induce tumor cell death, or to insert genes which stimulate or enhance the immune response (e.g. IL-2 or IFN).

Two strategies of gene therapy are available, namely the ex vivo and the in vivo modalities. The *ex vivo* approach removes cell from the patients, modifying them with the therapeutic gene, and then reinfusing the altered cells into the patient. The *in vivo* approach, involves the direct injection of the therapeutic gene in a carrier vehicle into the patient.

The methods of *gene delivery* may be viral or non -viral. Viruses (retroviruses or adenoviruses) are considered ideal vectors for gene transfer, and the engineered viruses are not pathogenic because viral replication genes are eliminated (Fig 8-12). Retroviruses are generally preferable since they integrate into host DNA, and hence produce a long-term gene effect. Their disadvantage, however, is their limited size for the therapeutic gene and the requirement of dividing target cells. Non-viral methods of gene delivery include DNA encapsulated in liposomes and particle-mediated gene transfer, but, unfortunately, the expression of genetic material is very poor in these methods. A fundamental problem in gene delivery is that unless all clonogenic tumor cells are transduced, unmodified tumor cells will simply grow.

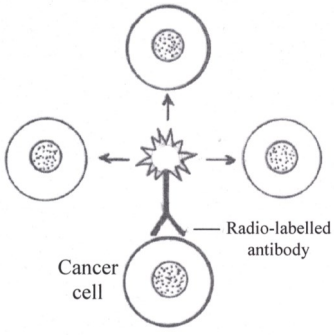

Fig 8-11 *Radioimmunotherapy (RAIT) of Cancer. A monoclonal antibody conjugated with radioisotope will kill not only a target cell, but also its neighboring cells, a phenomenon called cross-fire effect of bystanders.*

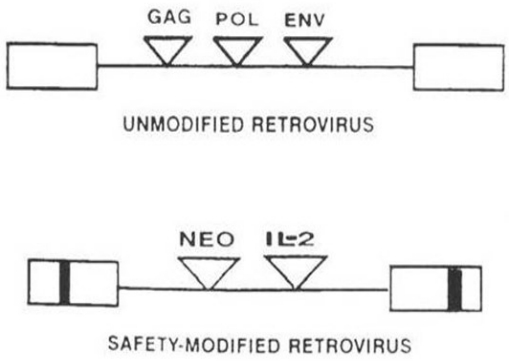

Fig 8-12 *Modification of a retrovirus vector for production of molecular vaccines. Genes responsible of replicative functions (GAG, POL and ENV) are removed and the selected genes (neomycin and interleukin-2) are inserted. The horizontal boxes represent the long terminal repeat sequences, on which the insertion of the virus depends*

The following are 4 examples of gene therapy used in current trials:

1. Modulation of gene expression: anti-sense oligonucleotides against a specific DNA sequence or aberrant RNA.

2. Gene replacement: to correct for a missing tumor suppressor gene by tumor transfection (e.g. p53 or nm23).

3. Chemoprotection: transfer multidrug resistance (MDR) gene to bone marrow stem cells to confer resistance to chemotherapy (Fig 8-13).

4. Suicide vector approach: tumors acquiring thymidine kinase (TK) gene are more susceptible to cytotoxicity of antiviral drugs (e.g. ganciclovir), hence selective tumor cell killing (Fig 8-14). Trials were made on mesothelioma, brain and ovarian cancer.

Considering the generally weak antigenicity of human cancer, immunologic and gene technologies may be combined together to overcome this difficulty. Several approaches are possible, namely: potentiation of the antigen by recombinant viral gene fusion (e.g. vaccinia virus), and tumor- cell or T-cell modification by transfection of an active gene, a toxic gene, or a MHC.

The following are examples of 5 approaches of immunogene therapy.

1. *Gene vaccines:* immunization by genes rather than antigens.

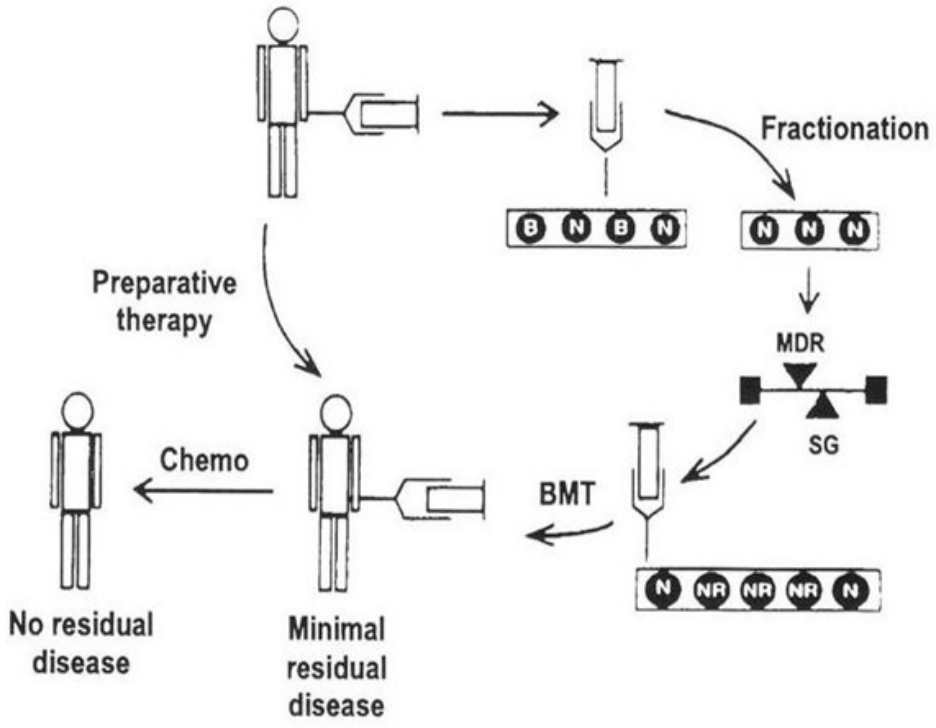

Fig 8-13 *Autologous bone marrow transplantation for advanced breast cancer with chemoprotection of marrow stem cells by MDR gene. This involves fractionation to separate malignant cells (B) from normal stem cells (N), insertion of multidrug resistance gene (MDR) to marrow stem cells which are infused to the patient with intensive chemotherapy. This method has the potential risk of conveying chemoprotection to malignant cells if fractionation is inadequate.*

2. *Recombinant gene fusion:* potentiate the weakly antigenic tumor antigens by the strongly antigenic recombinant vaccinia virus.

3. *Tumor cell modification:* augment tumor antigenicity by adjuvants, e.g., GM-CSF gene, cytokines as IL-2 or IFN, b-2 microglobulin or costimulatory signal B7 (Fig 8-15).

4. *T cell modification:* improve adoptive immunotherapy by transfection of tumor necrosis factor (TNF) gene into CTL.

5. *MHC augmentation:* transfection of human class one major histocompatibility complex (MHC-1) into tumor cells deficient in that antigen by direct injection of liposomes/plasmid DNA complex.

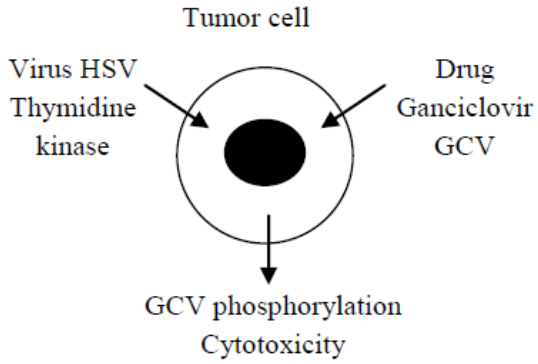

Fig 8-14 *Gene therapy by suicide vector. HSV-thymidine kinase (virus vector) is injected into the tumor, and the drug Ganciclovir given to the patient, which is phosphorylated in the tumor (in vivo engineering) resulting in selective cancer cell killing. This method is handicapped by the poor diffusion of the injected virus vector (a distance of only 5mm).*

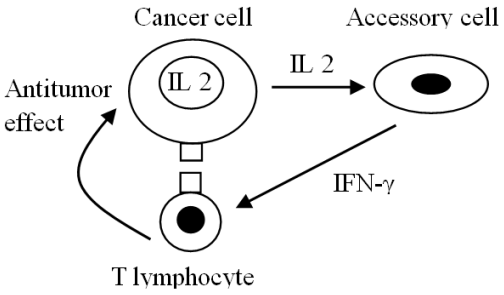

Fig 8-15 *Tumor cell modification by inserting interleukin-2 (IL-2) gene. The locally released IL-2 will activate other accessory stromal cells in the microenvironment to produce other cytokines (e.g. INF-γ) with antitumor effect.*

CONCLUDING REMARKS

The field of cancer immunology was introduced about 3 decades ago. Since that time, it has been applied for use in several clinical settings, with variable degrees of success. It is possible through a critical review of these studies to classify these immunoapplications into three main groups, namely: effective, poorly-effective and ineffective applications.

I-Effective Applications

1. Immunopathology

This is among the most fruitful applications of tumor immunology, with proven diagnostic value (tumor phenotyping), a guide to therapy (predictive markers) and foretell prognosis (prognostic markers). In general, tissue markers are more accurate than serum markers in cancer diagnosis.

2. Preventive Vaccines

Vaccines were developed against oncogenic viruses especially hepatitis B virus (HBV) and human papilloma virus (HPV) aiming at prevention of liver and cervical cancers respectively. In recent reports, the use of HBV vaccine has reduced the infection rate by 90% and reduced the incidence of hepatocellular carcinoma to one third. Similar favorable results were obtained in human papilloma virus vaccines. Thus, the use of bivalent vaccine (against HPV- 6/18) or tetravalent vaccine (against HPV-16/18/6/11) will give protection against infection in 90% and 100% respectively, that lasts for about 6 years.

The development of vaccination against Helicobacter pylori organism is still under investigation in animal models.

3. Immunotherapy

An effective immunotherapeutic agent must significantly increase the long-term survival of patients, at a reasonable cost. Only few agents fulfill this definition, such as:

A. Active immunotherapy: intravesical bacillus calmette-Guerin (BCG) therapy for carcinoma in situ of the urinary bladder. This proved to be superior to intravesical chemotherapy with a cure rate of 50% after 5 years and 30% in 10 years for such high-risk type of cancer. BCG acts through nonspecific stimulation of the innate immunity of the patient.

B. Passive immunotherapy (monoclonal targeted

therapy): examples include: Trastuzumab (Herceptin) in HER-2 positive breast cancer patients, and Rituximab (Rituxan) in CD-20 positive non-Hodgkin lymphoma.

II-Poorly Effective Applications

In this group, the therapeutic outcome is rather limited, with only 5% to 7% long-term survival. Examples of this group are the use of high-dose IL-2 in melanoma and renal cell carcinoma (5% survival) and the use of adoptive T-cell therapy in metastatic melanoma (7% survival).

III-Ineffective Applications

In this group, there is a transient response to therapy, but no long-term survival. This group includes cancer vaccines of all types, antiangiogenic targeted therapy, immune cell transfer and gene therapy. The latter is handicapped by the poor-tumor penetration of the injected gene. Moreover, we do not know, so far, how safe these methods will be.

FUTURE PROSPECTS

There is a tendency to change immunotherapy strategies in the future and improve patient selection. In the past, immunotherapy was given to patients with advanced disease, with disappointing results. Immunotherapy would probably be more effective when applied to patients with minimal residual disease and low tumor burden.

The future combined use of monoclonal antibodies of different mode of action (multitargeted therapy) is expected to complement their effect and improve results of therapy. Conjugated antibodies appear to be more effective than unconjugated antibodies. The recent application of nanotechnology (nanogold-labeled antibodies) may increase the effectiveness of targeted therapy. Thus, in this approach, monoclonal antibodies will selectively localize to tumor cells. Heat will be generated when laser beam is applied, thus allowing a photothermal therapy of a large tumor cell population.

Considering the genetic heterogeneity of malignant tumors, the application of personalized medicine to cancer therapy may lead to future advances. This involves the determination of the gene expression profile of a given tumor or patient, and use this information to guide medical decision making, hence, apply the most effective therapy for individual patients.

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