TUMOR IMMUNOLOGY

DR. HOSNY BADRAWY
Tumor immunology is the study of:

1. The antigenic properties of the tumor cells
2. The host immune response to these tumor cells
3. The immunologic consequences to the host of the growth of the malignant cells
4. The means by which the immune system can be modulated to recognize tumor cells and promote tumor eradication
TUMOR IMMUNOLOGY

- Tumor antigens
- Effectors mechanisms in anti-tumor immunity
- Mechanisms of tumor evasion of the immune system
- Immunotherapy for tumors
Causative agents

- Spontaneous
- Chemical carcinogens
- UV and ionizing radiation
- Virus-induced (HepC, EBV, HPV)
- Genetic abnormalities (XP)
- Immunosuppression
Tumors sometime express **mutant proteins** or express proteins that are normally sequestered: **Tumor antigens**

**Diagram:**
- Normal cell presents self peptides bound to MHC molecules.
- A point mutation in a self protein allows binding of a new peptide to MHC molecules.
- A point mutation in a self peptide creates a new epitope for recognition by T cells.

*Fig 14.12 © 2001 Garland Science*
Some tumors are antigenic in the host where they arise because of abnormal expression of self proteins.
How do cancer cells differ from normal?

- Clonal in origin
- Deregulated growth and lifespan
- Altered tissue affinity
- Resistance to control via apoptotic signals
- Change in surface phenotype and markers
- Structural and biochemical changes
- Presence of tumour-specific antigens
Immunosurveillance

• An hypothesis that states that *a physiologic function of the immune system is to recognize and destroy malignantly transformed cells before they grow into tumors.*

• Implies that cells of the immune system recognize something “foreign” on transformed/tumor cells.
Immune Surveillance of Tumors

Normal Cell

Mutation or virus

Transformed (cancerous) but also becomes antigenic

Immune response

Dead

Transformed (cancerous) but escapes from immune response

Mutation

Analogous to a bacterial population being treated with antibiotics such that antibiotic-resistant mutants take-over the population

Is this a common mechanism for tumor progression? Probably not (but there may be some striking exceptions).
Evidence in Support of Immunosurveillance

Immunodeficient individuals are more likely to develop certain types of tumors than immunocompetent individuals.

Clinicopathologic correlations suggest that lymphocytic infiltrates in some tumors (e.g. medullary breast carcinoma, malignant melanoma) are associated with a better prognosis compared to histologically similar tumors without infiltrates.
Histologic evidence indicates that active immune responses occur within tumors or in draining lymph nodes.

There is ample evidence that T and B lymphocytes specific for tumor surface molecules have been activated and expanded in tumor patients.
Immunosuppression leads to increased development of viral-derived tumours (Kaposi / NHL / HPV).

Organ transplant increases malignant melanoma risk. (0.3% general paediatric pop., 4% paediatric transplants)

High TIL presence correlates with improved survival
Since common cancers (e.g. carcinomas of lung, colon, breast, prostate) arise frequently in immunocompetent individuals, immunosurveillance is often not effective.
Evidence for IR to tumours

Animal models showed that pre-treatment of mice with killed tumour material could protect against a subsequent challenge.

T cell ablation or T-cell deficient mice removed this protection.

Transfer of T cells from an immunized mouse could protect a naïve mouse from tumour challenge.
Antigens in tumor cells

I - Unique tumor-specific Ag: are found only in tumor cells and therefore represent an ideal target for an immunologic attack.

II - Tumor associated determinants: are found in tumor cells and also in some normal cells, but qualitative and quantitative differences in Ag expression permit the use of these antigens to distinguish tumor cell from normal cells.
## Antigens involved in tumour recognition

<table>
<thead>
<tr>
<th>Tumour-specific antigens</th>
<th>Testes-specific antigens</th>
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<tbody>
<tr>
<td>• Bcr-abl (CML)</td>
<td>• MAGE 1-3 (melanoma)</td>
</tr>
<tr>
<td>• CDK-4 / β-catenin (melanoma)</td>
<td>• NY-ESO-1 (melanoma)</td>
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<table>
<thead>
<tr>
<th>Differentiation antigens</th>
<th>Tumour associated antigens</th>
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<tbody>
<tr>
<td>• Tyrosinase (TRP-1/2)</td>
<td>• MUC-1 (myeloma etc)</td>
</tr>
<tr>
<td>• Melan-A (melanoma)</td>
<td>• α-fetoprotein (many)</td>
</tr>
<tr>
<td>• Monoclonal Ab (myeloma)</td>
<td>• Her-2/neu (breast)</td>
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• WT-1 (many)  
• myeloblastin (leukaemias)  
• Survivin (many)
TUMOR ANTI GEN S

• Tumor Antigens Recognized by Host T Lymphocytes
• Tumor Antigens Recognized by Antibodies
  – Antibodies produced by host humoral responses
  – Antibodies raised in animals used as diagnostic, therapeutic agents
Examples of Tumor Antigens that Stimulate T Cell Responses

- Viral gene products in virus-associated malignancies.
  - SV40 T antigen (SV40-induced rat tumors)
  - Human papillomavirus E6 and E7 gene products (human cervical carcinoma)
  - Epstein-Barr virus EBNA-1 gene product (Burkitt's, lymphoma and nasopharyngeal carcinoma)
Tumor Antigens Recognized by T Lymphocytes

- Products of mutated normal cellular genes not related to oncogenesis
- Products of oncogenes and mutated tumor suppressor genes
- Products of normally silent genes
- Tumor antigens encoded by genomes of oncogenic viruses
- Tissue-specific differentiation antigens recognized
Tumor Antigens Recognized by Antibodies

- Oncofetal antigens
- Altered glycolipid and glycoprotein antigens
- Tissue specific differentiation antigens
Oncofetal Antigens

• Molecules normally expressed on developing (fetal) but not adult tissues.
• Expression in adult not strictly limited to tumors; low amounts in normal tissues and increased amounts in inflammatory conditions.
• Do not induce protective immune responses.
• Useful as markers that aid in the diagnosis of tumors.
Oncofetal Antigens: Carcinoembryonic antigen (CEA, CD66)

- Heavily glycosylated membrane protein; may function as adhesion molecule.
- Highly expressed in developing gut, liver and pancreas (1st two trimesters).
- Expressed at low levels on granulocytes and gut epithelial cells in adult.
- Highly expressed by carcinomas of colon, pancreas, stomach and breast, with associated elevated serum levels.
- Serum levels also elevated in setting of inflammatory diseases of liver and colon.
Oncofetal Antigens: Alpha-fetoprotein (AFP)

- a-globulin glycoprotein secreted by yolk-sac and liver during fetal life; replaced by albumin in adult life.
- Serum levels elevated in patients with hepatocellular carcinoma, germ-cell tumors, and some gastric and pancreatic tumors.
- Elevated levels also seen in non-neoplastic liver disease (e.g. cirrhosis).
- Serum levels followed to assess tumor burden after treatment of liver or germ-cell tumors.
- Immunohistochemical detection of AFP in sections of tumors may aid in pathologic diagnosis of tumor type.
Altered Glycolipid and Glycoprotein Antigens

- Require multiple enzymes to catalyze sequential addition of carbohydrate groups to protein or lipid cores.
- Due to abnormal expression of these enzymes, many tumors express high levels and/or abnormal forms of surface glycoproteins or glycolipids. (Gangliosides, blood group antigens, mucins.)
- These abnormal cell surface glyco-molecules may contribute to some aspects of the malignant phenotype.
- Xenogenic antibodies have been raised against many of these molecules.
- This class of TAAs is a preferred target for antibody-based cancer-therapy.
Tissue-Specific Tumor Antigens Used in Clinico pathologic Analysis of Tumors

<table>
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<tr>
<th>Tissue</th>
<th>Tumor Type</th>
<th>Antibodies/Proteins</th>
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<tbody>
<tr>
<td>B lymphocytes</td>
<td>B cell leukemias and lymphomas</td>
<td>CD10 (CALLA), Immunoglobulin</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>T cell leukemias and lymphomas</td>
<td>Interleukin-2 receptor (a chain), T cell receptor, CD45R, CD4/CD8</td>
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<tr>
<td>Prostate</td>
<td>Prostatic carcinoma</td>
<td>Prostate-specific antigen, Prostatic acid - phosphatase</td>
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<tr>
<td>Neural crest-derived</td>
<td>Melanomas</td>
<td>S-100</td>
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<tr>
<td>Epithelial cells</td>
<td>Carcinomas</td>
<td>Cytokeratins</td>
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How does the adaptive IR target tumours?

Tumour cell present

Broken up to release antigens

Ab / ADCC / cytokine attack

T_h cells educate other T/B cells

APC recruits T cells able to recognise tumour antigens

CTL recognise and destroy other tumour cells

CTL
Effectors mechanisms against cancer

- Monocyte / macrophage release lytic enzymes and phagocytose necrotic material
- Antibody against tumour antigens
- Induction of tumour-specific CTL and TIL
- Initiation of NK / CTL cytotoxic responses
- Release of cytokines / chemokines (TNFα, IFNs etc) and antiangiogenic factors
Strong evidence that IR controls and eradicates nascent cancer cells

“Immunoediting” eventually produces low antigenicity tumour cells

Pressure from immune system coupled with genomic instability selects for escape
Three Es of Immunoediting

- Elimination
- Equilibrium
- Escape

Genetic instability / tumour heterogeneity
Immunity against tumor

- All components, specific and nonspecific, humoral and cellular affect tumor progression and growth
Immunologic effectors mechanisms potentially operative against tumor cells

**T cells**

T cell response is the most important host response for the control of growth of tumor cells. It is responsible for:

- Direct killing of tumor cells
- Activation of other immunologic cells
- Th cells through direct interaction with APC
  → Secretion of lymphokines to activate other cells

Tc → mostly direct lysis of tumor cells
Direct CTL / NK attack

- CTL
- FasL
- TCR
- Perforin
- Granzyme B
- Fas (CD95)
- Class I + Ag

TUMOUR CELL
Innate IR recognises tumour cell establishment

NK cells and other effectors recruited to site by chemokines, which also target tumour growth directly.

Tumour-specific T cells home to tumour site, along with macrophages and other effectors to eliminate tumour cells.
B cells and antibody dependant killing

antibody to surface Ag eg Her2 neu oncogen protein or to intracellular proteins and could facilitate T cell response by enhancing processing and presentation by APC

Antibodies may act through

- Complement fixation
- Antibody dependant cell mediated cytotoxicity (ADCC)
NK cells

- 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.
- This can be augmented by IL2 and interferon.
- Also, NK cells enhance resistance against metastases.
- Lymphokine activated killer (LAK) which is produced by high doses of IL2.
Recognize lack of normal self class I MHC on some tumors

- May be defense against tumors which have escaped CTL killing
MHC-I recognition by NK cells is due to the surface expression of inhibitory receptors that bind MHC-I.

- Human NK cells express two families of MHC-I binding inhibitory receptors,
  - Killer cell inhibitory receptors (KIR) are type I transmembrane Ig superfamily proteins that bind to classical HLA-A, -B, and -C molecules
  - CD94/NKG2A receptors are heterodimeric type II transmembrane proteins with C-type lectin domains that bind to the non-classical HLA-E
  - Engagement of KIR and CD94/NKG2A inhibitory receptors with MHC-I dominantly engages SHP-1 tyrosine phosphatases and arrests activation signals derived from numerous receptors interacting with cell surfaces, such as CD2, CD16, NKR-P1, integrins, and several recently identified receptors.
Macrophages

- APC
- Stimulate the IR
- Potential effector cells to mediate tumor lysis

Resting macrophages are not cytolytic to tumor cell in vitro but become cytolytic if activated with macrophage activating factor (MAF), MAF secreted by T cell.

Activated macrophages may produce cytotoxic factor that mediate killing as well as bind to and lyse transformed cells.
- Intercellular transfer of lysosomal products, superoxide production. Release of neutral proteinases and secretion of TNF.

Also production of nitric oxide may be the most effector mechanism employed by macrophage.
Potential mechanisms by which tumor cells may escape from immune response

I. Immunoselection of variant cells

This suggested by analysis of the tumor cells present in a lesion which often reveals heterogeneity with respect to morphology and phenotype.

Eg. Melanoma, in which the generation of a T cell response to one melanosomal protein has been associated with the outgrowth of tumors lacking this protein.

The presence of such escape-variant cells is probably due to the inherent genomic instability of transformed cells (mutated oncogene).
II- Antigen modulation

Immune response to a tumor cells selects for the growth of antigen negative cells, antigen loss reflects only a phenotypic change in the tumor cells and if the IR ablated the antigen is reexpressed. Some tumor cells have defective antigen processing machinery, with the results that class I molecule do not get loaded with peptides.
Some tumor cells can release soluble factors that directly suppress immunologic reactivity.
IV- Increase susceptibility to opportunistic infection and can exhibit global depression of T cell response

V- Presences of tumor – specific suppressor T (Ts)
VI- Tumor cells lack many of the essential qualities of professional APCs, such as expression of the costimulatory molecules CD80 and CD86 or production of the activating cytokines IL2 and this may anergize rather than activate T cell.
Escape from immunosurveillance

Lack of Neo-antigens
Escape from immunosurveillance

Lack of class I MHC
Escape from immunosurveillance

Tumors shed their neo-antigens
## Evasion Mechanisms

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<tr>
<th>Low immunogenicity</th>
<th>Antigenic modulation</th>
<th>Tumor-induced immune suppression</th>
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<tbody>
<tr>
<td>No peptide:MHC ligand</td>
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<tr>
<td>No adhesion molecules</td>
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<tr>
<td>No co-stimulatory molecules</td>
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<tr>
<td>Antibody against tumor cell-surface antigens can induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants</td>
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<td>Factors (e.g., TGF-β) secreted by tumor cells inhibit T cells directly</td>
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**Diagram**: Illustrations showing interactions between immune cells and tumors, including T cells, CD8, CD28, LFA-1, TCR, CTL, TH1, and TGF-β.