Carcinoma

Carcinoma is the medical term for the most common type of cancer occurring in humans. It is defined as a cancer that begins in a tissue that lines the inner or outer surfaces of the body, and that generally arises from cells originating in the endodermal or ectodermal germ layer during embryogenesis (Berman, 2004a). More specifically, a carcinoma is tumor tissue derived from putative epithelial cells, having the cytological appearance, histological architecture, or molecular characteristics of epithelial cells (Berman, 2004b) whose genome has become altered or damaged to such an extent that the cells become transformed, and begin to exhibit abnormal malignant properties.

Pathogenesis and Hallmarks of cancer

Cancer occurs when a single progenitor cell accumulates mutations and other changes in the DNA, histones, and other biochemical compounds that make up the cell's genome (Hanahan and Weinberg, 2001). Certain combinations of mutations in the given progenitor cell ultimately result in that cell (also called a cancer stem cell) displaying a number of abnormal, malignant cellular properties that, when taken together, are considered characteristic or hallmarks of cancer (Hanahan and Weinberg, 2001), including:

- the ability to continue to divide perpetually, producing an exponentially (or near-exponentially) increasing number of new malignant cancerous "daughter cells" (uncontrolled mitosis);
- the ability to penetrate normal body surfaces and barriers, and to bore into or through nearby body structures and tissues (local invasiveness);
- the ability to spread to other sites within the body (metastasize) by penetrating or entering into the lymphatic vessels (regional metastasis) and/or the blood vessels (distant metastasis) (Figure A).

If this process of continuous growth, local invasion, and regional and distant metastasis is not halted via a combination of stimulation of immunological defenses and medical treatment interventions, the end result is that the host suffers a continuously increasing burden of tumor cells throughout the body. Eventually, the tumor burden increasingly interferes with normal biochemical functions carried out by the host's organs, and death ultimately ensues. A progenitor carcinoma stem cell can be formed from any of a number
of oncogenic combinations of mutations in a totipotent cell, a multipotent cell, or a mature differentiated cell (Figure A).

Classification and types of carcinomas

Malignant neoplasms are exceptionally heterogeneous entities, reflecting the wide variety, intensity, and potency of various carcinogenic promoters. One commonly used classification scheme classifies these major cancer types on the basis of cell genesis, specifically, their (putative) cell (or cells) of origin (Travis et al., 2004)

1. Epithelial cells > carcinoma
2. Non-hematopoietic mesenchymal cells > sarcoma
3. Hematopoietic cells
   a) bone marrow-derived cells that normally mature in the bloodstream > Leukemia
b) bone marrow-derived cells that normally mature in the lymphatics > Lymphoma

4. Germ cells > Germinoma

Other criteria that play a role in a cancer classification, staging and diagnosis include the degree to which the malignant cells resemble their normal, untransformed counterparts, the appearance of the local tissue and stromal architecture, the anatomical location from which tumors arise and genetic, epigenetic, and molecular features.

Various histological types and variants of carcinoma are:

Adenocarcinoma: (adeno = gland) Refers to a carcinoma featuring microscopic glandular-related tissue cytology, tissue architecture, and/or gland-related molecular products, e.g., mucin.

Squamous cell carcinoma: Refers to a carcinoma with observable features and characteristics indicative of squamous differentiation (intercellular bridges, keratinization, squamous pearls).

Adenosquamous carcinoma: Refers to a mixed tumor containing both adenocarcinoma and squamous cell carcinoma, wherein each of these cell types comprise at least 10% of the tumor volume.

Anaplastic or Undifferentiated carcinoma: Refers to a heterogeneous group of high-grade carcinomas that feature cells lacking distinct histological or cytological evidence of any of the more specifically differentiated neoplasms.

Large cell carcinoma: Composed of large, monotonous rounded or overtly polygonal-shaped cells with abundant cytoplasm.

Small cell carcinoma: Cells are usually round and are less than approximately 3 times the diameter of a resting lymphocyte and little evident cytoplasm. Occasionally, small cell malignancies may themselves have significant components of slightly polygonal and/or spindle-shaped cells (Bermann, 2004b, Travis et al., 2004).

There are a large number of rare subtypes of anaplastic, undifferentiated carcinoma. Some of the more well known include the lesions containing pseudo-sarcomatous components: spindle cell carcinoma (containing elongated cells resembling connective tissue cancers), giant cell carcinoma (containing huge, bizarre, multinucleated cells), and sarcomatoid carcinoma (mixtures of spindle and giant cell carcinoma). Pleomorphic carcinoma contains spindle cell and/or giant cell components, plus at least a 10%
component of cells characteristic of more highly differentiated types (i.e. adenocarcinoma and/or squamous cell carcinoma). Very rarely, tumors may contain individual components resembling both carcinoma and true sarcoma, including carcinosarcoma and pulmonary blastoma (Travis et al, 2004)). Although tumors can arise in almost any tissue, the frequent organ sites of carcinoma are

- **Lung**: Carcinoma comprises >98% of all lung cancers.
- Breast: Nearly all breast cancers are ductal carcinoma.
- Prostate: The most common form of carcinoma of the prostate is adenocarcinoma.
- Colon and rectum: Nearly all malignancies of the colon and rectum are either adenocarcinoma or squamous cell carcinoma.
- Pancreas: Carcinoma is almost always of the adenocarcinoma type and is highly lethal.

Some carcinomas are named for their or the putative cell of origin, (e.g. hepatocellular carcinoma, renal cell carcinoma).

**Cancer and the Immune System**

The origins and progress of cancer immunology has been reviewed in depth, highlighting the development of ideas from Ehrlich and Medawar through to the cancer immune surveillance hypothesis of Burnet and into the era of cellular and molecular immunology (Dunn et al., 2002; Kaufmann, 2008). The immune system works essentially by discriminating self from non-self. Non-self is discriminated from self by fundamental differences in biochemistry, such as the arrangement of carbohydrate residues on glycoproteins or the absence of methylated cytosine residues in DNA. These differences are detected by the numerous pattern receptors, which are a hallmark of the innate immune system. These pattern receptors include the Toll-like receptors (O’Neill, 2008). The activation of innate immunity leads to the efficient priming of adaptive immune responses mediated by B and T cells. These cells carry antigen receptors and, through education and cooperation, can distinguish self from non-self antigen and trigger subsequent events. However, tumour cells are self in origin and their biochemistry and behaviour differs only subtly from their healthy counterparts and thus, requires the detection of altered self. There is now a substantial body of data to show that innate and acquired immune responses to tumours do exist and that a multitude of immune cell types and their associated molecules are involved in detecting and eliminating tumours.
Immunity to infection and tumour immunity share a common ‘dark side’, that of immune evasion. It is a sad fact that, by the time a patient presents with a clinically detectable tumour, the tumour has already successfully evaded cancer immune surveillance mechanisms and is living alongside the immune system. Indeed, the immune system places strong selective pressure on tumours (and pathogens). Ultimately, the rare tumour cells that have mutations in the pathways that allow immune detection, elimination and evasion, the phenomenon of Immunoediting, (Figure B) are the cells that survive, proliferate and kill the patient (Teng et al., 2008). The goal behind many immunotherapeutic strategies is to tip the balance from tumour immune evasion to a productive anti-tumour response.

Figure B: Immune evasion and Inflammation (important components of Immunoediting) as Cancer Hallmarks. (from Hanahan and Weinberg, 2011).

Studies of the role of the cellular immune system in controlling cancer cells, promise to deliver not only fascinating insights into the immune system but also lay the foundation for future cellular immunotherapies. A better understanding of Tumor associated macrophages (TAM) and other myeloid-derived tumor-infiltrating cells as
pivotal players in the tumor microenvironment and as sources of Cancer-related inflammation (CRI) (Montovani et al., 2008) could certainly shed new light on the mechanistic understanding and development of efficient anticancer therapies. The present study was undertaken to understand the interaction of tumor cells of various origins, especially lung, with immune cells like monocytes/macrophages to establish new insights into such crosstalk.