Limitations of the somatic mutation theory of cancer

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Objectives

• The somatic mutation theory and the tissue organisation field theory of carcinogenesis.
• Application in clinical practice
Sutton-Boveri theory, 1929

• For the last half century, the approach about the origin of cancer has focused almost exclusively on only one theory, the somatic mutation theory (SMT).

• This theory was first enunciated in 1914 by Theodor Boveri in his book entitled The Origin of Malignant Tumors (Boveri T. The Origin of Malignant Tumors. Williams & Wilkins; Baltimore, MD: 1929)
Later research on the origin of cancer confirmed the origin of malignancy to occur because of permanent changes in the chromatin, known to contain the heritable material.

a. Cancer is derived from a single somatic cell that has accumulated multiple DNA mutations.

b. Cancer is a disease of cell proliferation caused by mutations in genes that control proliferation and the cell cycle.

c. Cancer is a clonal, cell-based disease.
20\textsuperscript{th} century research

- **Identification of DNA as the genetic material** (Avery et al, Studies on the chemical nature of the substance inducing transformation of pneumococcal types. J Exp Med. 1944)

- **Description of the chemical structure of the DNA** (Watson JD, Crick FHC. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. Nature. 1953; Franklin R, Gosling RG. Molecular configuration in sodium thymonucleate. Nature. 1953)

\textit{Cancer is due to DNA mutations}
D.W. Smithers, 1962

• In an exceptional, critical and cogent paper entitled “An attack on cytology” by D. W. Smithers, published in The Lancet in 1962, objections were made to the cell-based view of carcinogenesis (Smithers DW. Cancer: an attack of cytologyism. Lancet. 1962)

• Criticism to the Somatic Mutation Theory persists today with a call for cancer to be studied as a problem of tissues disorganization (Kreeger & Lauffenburger Cancer systems biology: a network modeling perspective. Carcinogenesis 2013)
A cell-based or a tissue-based perspective in developmental and cancer biology?

Cell-based

• The reductionist view in biology: the cell is the “unit” of the organism, and as such changes observed at tissue level must be found at the cellular level.

• Molecular changes in the DNA of a founder cell will make a cell unable to control its proliferation and this, in turn, will result in the formation of a
A cell-based or a tissue-based perspective in developmental and cancer biology?

**Tissue based**

- A single cell isolated in the absence of the other tissue, fails to originate the tissues that would result from cellular reciprocal interactions.
- Carcinogenesis is a reversible process, whereby normal tissues (or their components) in contact with neoplastic tissues may normalize the latter (Sonnenschein & Soto Theories of carcinogenesis: an emerging perspective. Semin Cancer Biol. 2008)
A tissue-based perspective

• Brash & Cairns (2009) stated “The prime mystery in carcinogenesis remains the very first step, because it is hard to imagine how the numerous genetic changes found in cancer cells could have been produced in any cell as the result of a single exposure to a DNA-damaging agent, or why months or years should have to elapse before the effect of these changes is observed” (Brash & Cairns The mysterious steps in carcinogenesis. Br J Cancer. 2009)

• Cellular and extracellular components (e.g. matrix) are co-determinants of the neoplastic phenotype (Giussani et al, Tumor-extracellular matrix interactions: Identification of tools associated with breast cancer progression. Seminars in Cancer Biology 2015)
The microenvironment

- Tumours as complex tissues in which mutant cancer cells have conscripted and subverted normal cell types to serve as active collaborators (Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000)

The microenvironment

1. Primary tumor growth (benign)
2. Invasion of neighboring tissue (malignant)
3. Intravasation
4. Interaction with blood components and travel in bloodstream
5. Extravasation at distant site
6. Proliferation at secondary organ
7. Angiogenesis to sustain growth
8. Metastasis of metastases
Cellular heterogeneity in the tumour and the microenvironment

• The tumour microenvironment and its related cell types contribute to malignant transformation.

• The cellular milieu influences the interactions within the tumour and surrounding microenvironment, including immune-cell interplay.
• The upper left panel depicts many elements reported in association with tumour promoting microenvironments.

• The upper right panel illustrates an indolent tumour microenvironment.
Tumour promoting microenvironments.

Characteristics:

- paracrine signaling axes between tumour cells, stromal cells, vascular cells and immune cells
- neo-angiogenesis with porous/leaky vascular ECM
- reactive stroma
- ECM remodelling
- tumour cell invasion and intravasation.
- Tumour promoting immune-cell phenotypes
Indolent tumour microenvironment

Characteristics:
• innate immune-cell mediated tumour cell killing
• cellular and humoral adaptive immune-cell anti-tumour responses
• normal vasculature with pericyte coverage and intact basement membrane
• quiescent stroma
• parallel collagen orientation
• In solid epithelial tumours, invading cells must first cross the basement membrane (BM). The BM is a natural barrier between the epithelium and the stroma, a network of extracellular matrix (ECM) populated by a number of other cell types that surrounds the tissue. Metastasizing cells migrate through the stroma to reach blood or lymph vessels, where they can be carried to other organs.
Barcellos-Hoff & Ravani experiment, 2000

- The mammary gland stroma of mice was first irritated to affect their extracellular matrix composition and increase cytokine production and receptors involved in cell-to-cell interactions.

- Immortalized but non-tumorigenic mammary epithelial Comma-D cells were inoculated into the cleared-fat pads of those mice. The inoculated Comma-D cells originated tumours mostly in the irradiated mice when compared with the non-irradiated mice (Barcellos-Hoff MH, Ravani SA. Irradiated mammary gland stroma promotes the expression of tumorigenic potential by unirradiated epithelial cells. Cancer Res. 2000)
The tumour microenvironment contains a wide variety of inflammatory and immune cells, cytokines, and chemokines that have pro- and anti-tumorigenic activity, the balance of which likely dictates clinical outcome (Shurin et al, 2008)
Monocytes can differentiate towards macrophages M1 or M2.

Macrophages can inhibit or promote all aspects of tumour development depending on the composition of the tumour microenvironment (Quaill & Joyce Microenvironmental regulation of tumor progression and metastasis Nat Med. 2013)

- M2 (pro-cancerous phenotype) are proangiogenic/tissue-remodelling.
- M1 (anti-cancerous phenotype) express high levels of cytokines involved in anti-tumour and anti-microbial activity (i.e., TNF-α, IL-1, IL-6)

*Tumour-associated macrophages (TAMs) have an M2 phenotype*
### Diagram Overview

The diagram illustrates the roles of M1 and M2 macrophages in the immune response.

#### M1 Macrophages
- **Defense against bacteria**
  - Bacteria
- **Tumor suppression**
  - Tumor cell
- **Immuno-stimulation**
  - T cell

#### M2 Macrophages
- **Tissue repair and angiogenesis**
  - Damaged tissue
- **Tumor promotion**
  - Tumor cell
- **Down-regulation of M1 and adaptive immunity**
  - Inflammatory site

#### Key Factors
- **GM-CSF**
- **M-CSF**
- **IL-4, IL-13, IL-10**
- **Corticosteroids**
- **IL-1ra**
- **CCL18, CCL22**
Where are TAMs (2) located?

- TAMs are preferentially localized in tumour hypoxic regions. They promote an overexpression of proangiogenic molecules (ie. VEGF, PDGF) by HIF-1 activation.

- TAMs are the major source of cytokine production in the tumour microenvironment.
Tumour regression

• Repolarisation of TAM towards M1 phenotype characterises an immune-competent microenvironment that favours tumour regression.

• In vitro study has been shown that Baicalin initiated TAM reprogramming to M1-like macrophage in HCC cells resulting in reduced proliferation and motility (Tan et al, Autophagy-induced RelB/p52 activation mediates tumour-associated macrophage repolarisation and suppression of hepatocellular carcinoma by natural compound baicalin. Cell Death and Disease 2015)
Maffini et al, 2005

• Studies have demonstrated a normalization of epithelial tumour cells that reverted to form normal mammary gland ducts when injected into normal mammary gland stroma (Maffini et al. Stromal regulation of neoplastic development: age-dependent normalization of neoplastic mammary cells by mammary stroma. Am J Pathol. 2005)

• Tumour cells normalise and or normal cells become malignant when placed in a different tissue microenvironment (Whiteside TL. The tumour microenvironment and its role in promoting tumour growth. Oncogene 2008)
Spontaneous remissions

• A review of past reports demonstrates that regression is usually associated with acute infections, fever, and immuno-stimulation (MacAdam DH. Spontaneous Regression: Cancer and the Immune System, Xlibris, 2003)

• Current primary cancer management procedures neither harness the benefits of patients’ own immune system nor stimulate it to achieve tumour regression. In fact, it opposes its natural role (Jessey, Immunity over inability: The spontaneous regression of cancer, Journal of Natural Science Biology and Medicine, 2011)
Spontaneous regression of neuroblastoma

• This childhood neoplasm is probably the one with the highest documented rate of spontaneous regression (Brodeur, Neuroblastoma: biological insights into a clinical enigma. Nat Rev Cancer. 2003)

• The regressions of these cancers include even those classified as stage 4S, which metastasize in the liver, skin, and/or bone marrow (Haas et al. Complete pathologic maturation and regression of stage IVS neuroblastoma without treatment. Cancer. 1988)

• Cell and tissue differentiation and apoptosis are central to the regression process.
Regression of hormone-sensitive tumours and their metastases

• Breast and prostate tumors are not autonomous given that these tumors regress after gonadectomy or chemical hormonal ablation
Tissue organisation field theory

• The “normalization” of tumour cells, a phenomenon consistently observed in various experimental models, is readily explained by understanding the role of the tissue and cancer microenvironment.

• The need for a new outlook on carcinogenesis, predicated by Smithers (Smithers DW. Cancer: an attack of cytologism. Lancet. 1962) over 50 years ago and recently called for by Brash and Cairns (Brash & Cairns, The mysterious steps in carcinogenesis. Br J Cancer. 2009) could be further justified on both theoretical and pragmatic grounds.
Thank you

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