Basis of Carcinogenesis

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Abstract

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This chapter is dedicated to normal cell biology and how cells become malignant.

Keywords

Genome · Genotype · Phenotype · Telomerase · Hallmarks of cancer · Tumor cell environement · Angiogenesis · Immune process

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History

The name "cancer" comes from the Greek word "Karkinos".

A legend tells us that during the second battle of Hercules, the goddess Era put before him a hydra named Karkinos who seized one of Hercules's legs with one of its coils. He defended himself by decapitating the nine heads of this enormous water serpent. On dying, the hydra created the Cancer constellation in the sky.

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In a second legend, attributed to the Greek physician Paul d'Egine (in the seventh century after JC), the term cancer refers to the idea that once a crab has grabbed an organ, it will not release it.

Historically, we can see that cancer as a disease has a long existence. The skeleton of a prehistorical man from the Iron Age and Egyptians mummies shows signs of cancer. Furthermore, Mesopotamian, Indian, and Persian writings talk about cancer.

In the fifth century before JC, Herodote described the breast tumour of Atossa, Cyrus's daughter and wife of Darius. Hippocrates (460–370 before JC) defines carcinome as being an invasive tumour leading to an inevitable death; he describes skin, breast, stomach, and cervix cancers. Celsus, a Roman physician, defines the stages of the disease according to its growth: cacoethes (early-stage tumour), which is considered as pernicious, malign, carcinoma without ulceration, and carcinoma with an exuberant lesion. He also defines the treatments according to the evolution of the disease: excision, cauterization, and ointments. Galien (130–201 after JC) describes cancer as a tumour, due to excessive mood, a disorder of the black bile for which treatments comprised specific diets, purges, drugs, bleedings, and of course lesion's excision. These treatments have been in use for the last 1500 years.

We also know that, being the disease of the cell, it has always existed even in plants and animals.

Over the past 30 years, we have made tremendous advances in understanding the role of genes in normal cell function and structure but also on how genetic modifications are implicated in the development and evolution of malignancies.

Firstly, it is important to know that a cell can be altered through several factors: environmental, lifestyle, personal, and hereditary factors. The main risk factor for cancer is age.

To begin with let us start with the description of a normal cell.

Normal Cell Biology

The Cell

The cell is the fundamental unit of life, and it is estimated that the human body contains about 100 trillion cells of different types. Every group of cells has a specialised function with a specific structure according to its function. For example, a nerve cell contains structures transmitting neural impulses, while lymphocytes B cells have a structure that is capable of producing antibodies.

Human cells are composed of a plasma membrane, the cytoplasm, and the nucleus. The *plasma membrane* envelopes the cell and regulates the movement of substances in and out of the cell. The *cytoplasm* is a fluidlike substance, enclosed by the plasma membrane, in which organelles or "little organs" are suspended. The *nucleus* is the largest organelle and is located in the centre of the cell. The majority of cells in human body are eukaryotic cells meaning that they contain one nucleus. Mature red blood cells are an exception since they have no nucleus.

The nucleus contains *DNA* (deoxyribonucleic acid) which is a structural component of chromosome.

The majority of human cells possess 46 *chromosomes* (22 pair of autosomes plus one pair of gonosome or sexual chromosomes [XX for women, XY for men]). Diploid cells contain two sets of homologous chromosomes and two copies of each gene, whereas haploid cells, like gamete or sex cell, contain only one set of chromosomes.

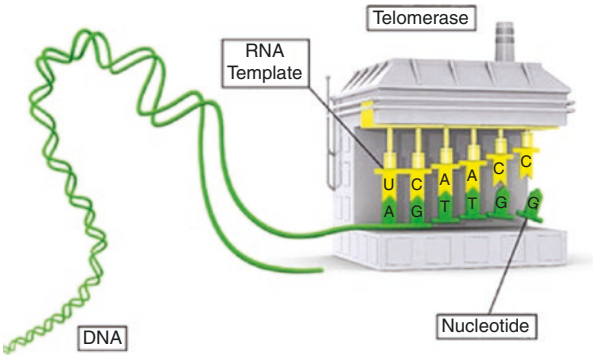
Each of our 46 chromosome comprises two long and tightly coiled strands of *DNA* twisted together to form a DNA double helix that contains all the genetic information for an individual, called the genotype. DNA is made up of four different bases or nucleotides: adenine (A), thymine (T), cytosine (C), and guanine (G). These nucleotides are present in DNA in base pairs (A-T or C-G), with the order of these base pairs differing from one DNA molecule to the next. Each nucleotide is composed of a phosphoric acid and sugar (deoxyribose) backbone, with an associated nitrogenous base (A, T, C, or G). In DNA, these nucleotides are linked together in recurrent sequences.

Genes are sections of DNA and are the core units of heredity defined by the sequence of bases/nucleotides. Each gene can contain a chain of as many as 1000 pairs of nucleotides. The length of DNA sequences are described according to the number of units of base pairs (bp) or thousands of base pair or kilobase pairs (kp) [1]. Genes are present in a cell in two copies or alleles, one maternal and the other paternal.

The Telomeres

The telomeres are the terminal portions of chromosome and sustain its stability. Telomeres shorten with each cell division and thus contribute to cell senescence (the ageing of cells).

The Telomerase



A telomerase is an enzyme in eukaryotic organisms that adds a structure to the endings of each telomere during DNA replication to maintain the length of the chromosome. It is produced from an RNA template with the repeating sequence TTAGGG (*T, thymine; A, adenine; G, guanine). It is present during embryogenesis, in germinal and haematopoietic cells. It is absent in other adult tissues. It is important to note that in most cancer cells, telomerase activity is observed, which explains why the proliferation capacity of cancer cells appears to be unlimited.

The Genome

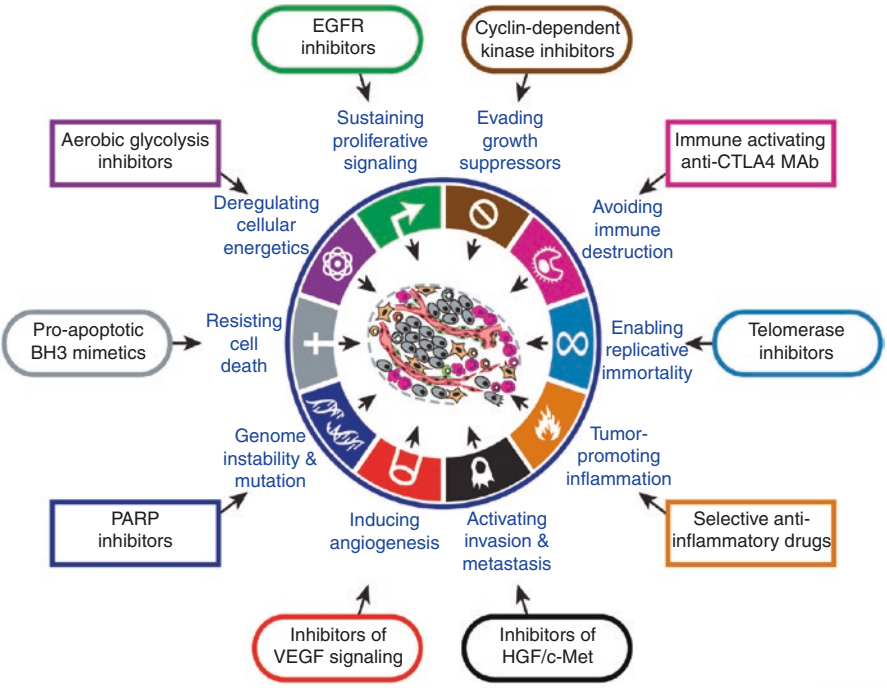
It is the complete set of instructions contained in all our chromosomes; it is also referred to as the "master blueprint" of the human body. It is estimated that only 10% of the genome contains the protein-coding sequences in exons, whereas 90% of the genome is made of noncoding sequences called introns [2].

The transmission of genetic information from one cell generation to another occurs through a base-pairing reaction: the nitrogenous base A pairs with T and G pairs with C. This specific pairing ensures that the new strand of DNA is an exact copy of the original and reduces the risk of errors. This mechanism of DNA replication is highly accurate with the possibility of removing the incorrect nucleotides. However, genetic mistakes or *mutations* can occur and can have very important consequences for cell functioning. Mutations are known to be implicated in several complex diseases such as autoimmune diseases, neurodegenerative disorders, and especially cancer.

Hallmarks of Cancer

Nowadays, progress in human biology and especially human genetics have led to a better comprehension of the sequence of steps that transforms a normal cell to one that is cancerous.

Hanahan and Weinberg [3] described that "the hallmarks of cancer comprise ten biological capabilities acquired during the multistep development of human tumors. (…)



They include sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, promoting tumour inflammation, activating invasion and metastasis, inducing angiogenesis, allowing genome instability and mutation, resisting cell death and deregulating cellular energetics" (Cf. Fig. 1.1).

Generally, a cell will be expulsed when detected abnormal by the organism. A cancer cell has acquired specific characteristics, including the capacity to multiply in an anarchical way and to appear to be immortal. Cancer cells also inhibit the immune system so that it will not be recognized as abnormal. Furthermore, it resists apoptosis/normal cell death and senescence (ageing of the cell): the physiological process leading to a slow degradation of the body's functions. The cancerous cell continues to multiply in an autonomous way due to growth factors and interacts with the extracellular environment called the stroma. Its growth permits it to penetrate the epithelial barrier and invade organs in the proximity. A cancerous cell also has the ability to create blood vessels ensuring that it will receive the nutriments required and allowing the cancer to disseminate via the blood and lymphatic system to others organs of the body.

Before we go into more detail concerning cancer, it is essential that we review normal cell biology in order to understand the genetic basis of cancer pathogenesis [4].

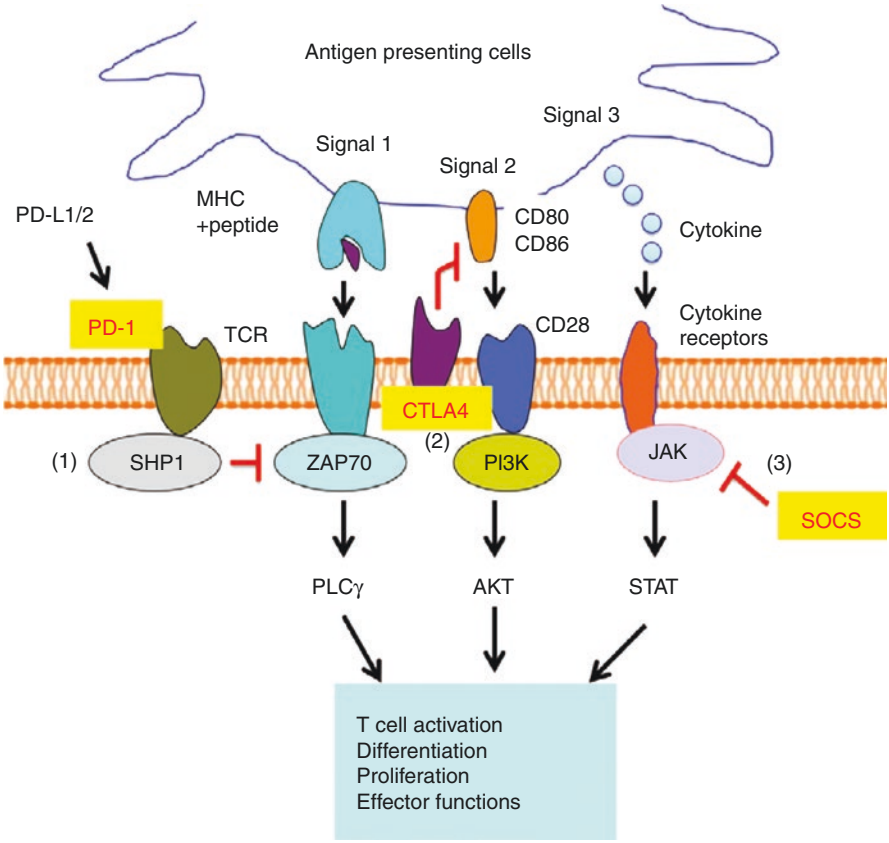


Fig. 1.1 T cell immune checkpoints for antitumour immunity. There are three major T cell activation signals, signal 1, signal 2, and signal 3. Signal 1 is MHC-antigen-peptide complex-TCR signal that activates tyrosine kinases including ZAP70. Signal 2 is the co-stimulatory signals from CD28, in which mostly PI3 kinase is involved. Signal 3 is the cytokine receptor signals that activate the JAK/STAT pathway. T cell activation by TCR, co-simulators, and cytokines is blocked by (1) PD-1, (2) CTLA4, and (3) SOCS (Chikuma et al. [15], p. 6)

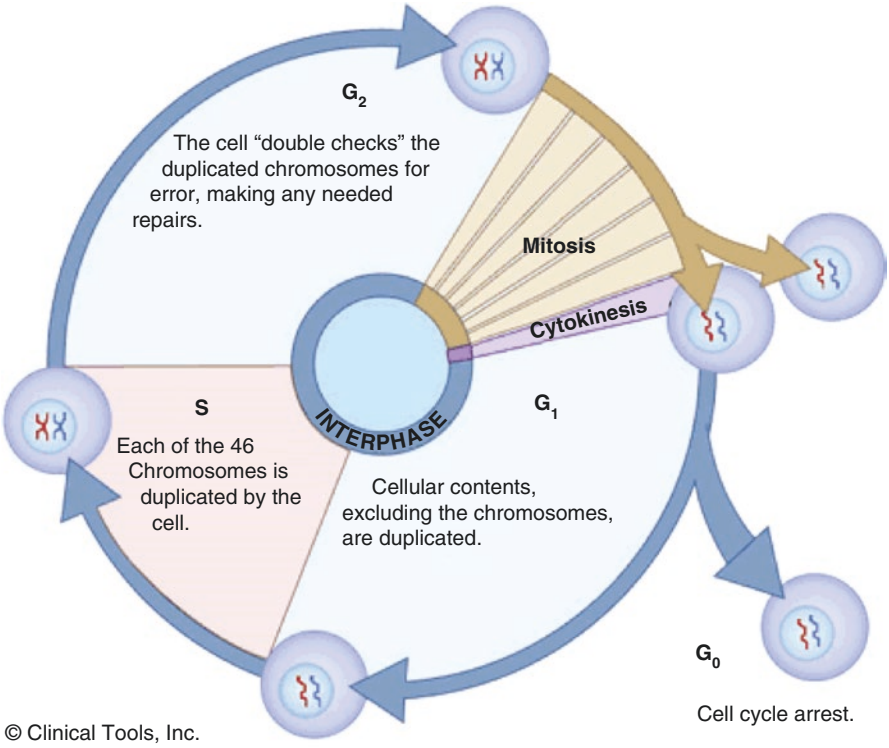
Gene expression has been referred to as the "central dogma" of molecular biology and genetics. Each gene encodes and provides the cell with information to produce a specific protein. Generally, genes and the protein they encode have the same name, e.g. the *p53* gene encodes for the p53 protein. The protein synthesis process comprises two steps: *transcription* and *translation*.

During transcription, RNA copies the specific information contained in the DNA in the cell nucleus. The appropriate section of double-stranded DNA separates thus exposing the sequence of nucleotides. With the base pairs exposed, these DNA nucleotides pair with *RNA* nucleotides present in the nucleus. This pairing generates the messenger RNA (*mRNA*). This mRNA contains the code from the DNA necessary to produce a protein. The mRNA exits the nucleus into the cytoplasm to start

translation, the second step of protein synthesis. During the translation, ribosomes present in the cell are brought into contact with the mRNA using *tRNA* (transfer RNA), as well as, ribosomal RNA and enzymes to produce a sequence of amino acids forming a protein (Sallas, Beth / S2L2 a&b – Cell Cycle, https://goo.gl/images/kB5M13).

In normal tissue, the number of new cells is equivalent to the number of dying cells. This equilibrium is maintained through cell proliferation and regulation. Cell growth and the transfer of genome from one cell to its progeny are guided by genetic expression. If an error or mutation in the genetic expression occurs, it can alter the growth and the reproduction of the cell and may eventually lead to cell death. These errors and mutations are implicated in several diseases, such as cancer, autoimmune diseases, neurodegenerative disorders, and viral infections.

Cell Cycle



The cell cycle is a multistep process leading to the duplication of the cell's contents forming two identical cells. This mechanism is essential in human cells since it serves to replace the cells that have been lost by "general wear and tear" or have died. Each cell proliferates and grows to reach a programmed size and extent (e.g. a nervous cell), then matures, and eventually dies. To maintain the same number of cells in the body, an adult human has to manufacture millions of new cells each second.

The aim of the cell cycle is to produce two genetically identical daughters' cells by copying DNA from the parent cell. This process equally divides the chromosomes between the two daughter cells and duplicates the cytoplasm from the parent cell. The cell cycle comprises four phases:

- G1 (Gap 1)
- S (synthesis)
- G2 (Gap 2)
- M (mitosis)

G1 is the beginning of the cycle and is the phase in which the cell prepares all the necessary components for division. In phase S (synthesis), the DNA replicates by doubling of the DNA and forming chromatin forming two identical sets of chromosomes (chromatids). In G2, the cell grows before the final phase mitosis or cell division.

The Cell Cycle Control System

The four phases are regulated by two molecular controls:

1. Cascade of cyclin (cell cycle proteins), cyclin-dependent kinases (CDKs), and CDK inhibitors
2. Checkpoints that monitor the molecular activities of each phase and delay the progression to the next phase if a problem is detected. These checkpoints have an essential role: they avoid the accumulation of genetic mistakes during the cell cycle.

Prior to these phases, the cell is in a quiescent period, either it has finished its differentiation or it is in a nonreproductive mode. Mitogens, nutrients, and growth factors can stimulate a cell to move from this quiescent mode to the G1 phase of the cell cycle.

What Is Cancer?

Cancer is the dysregulation or loss of equilibrium in the control of the cell cycle. This results in the proliferation of cells that can be localized to an organ and a region or can spread throughout the body.

The mechanism of this transformation that results in changes in the genes involves three groups of genes: the (proto)oncogenes, the tumour suppressor genes,

and the DNA repairing genes. It is estimated that we have around 342 genes associated with somatic mutations and 70 genes associated with germline mutations [5].

DNA is believed to consist of approximately 30,000 genes, among which about 30 are proto-oncogenes and 300 are tumour suppressor genes.

The proto-oncogene is the result of a modification or overexpression of a normal gene. It is involved in the cell division and activates an excessive proliferation of cells: the first step in oncogenesis. One mutation is sufficient to activate this process.

Research on oncogenes has permitted a better understanding of the reasons why some individuals are more predisposed to develop a cancer. The explanation is that they are more susceptible to convert their oncogenes into proto-oncogenes.

Tumour suppressor genes are negative regulators of cell proliferation. They inhibit mechanisms leading to oncogenesis or activate mechanisms that inhibit oncogenesis. During oncogenesis, tumour suppressor genes are not activated.

An initial mutation transforms a normal cell into a cancerous cell; while a second mutation inevitably leads to cancerogenesis.

The gatekeeper gene Rb which inhibits cell growth is an example of a tumour suppressor gene, and the gene TP53 is a gene protecting the cell against aggressions.

More and more publications suggest that genes are mutable and can evolve in a negative or positive manner. Changes in lifestyle may have a real impact on behaviour and may deeply impact genetic patrimony

Genotype and Phenotype

The genotype is the inherited genes (patrimony), and the phenotype is actually the expression of the genotype. The phenotype includes physical appearance, biochemical processes that take place in the body, and the genetic determined behaviour.

The relationship between genotype and phenotype is mediated by environmental inputs on gene expression, trait development, and phenotypic integration.

One of the characteristic of cancer cells is their phenotypic plasticity, the fact that they are able to change state according to environmental fluctuations [6].

Today cancer is studied more from the perspective of dysregulated pathways rather than as a disease resulting from individual gene mutation. In fact, with a pathway-centred view, we acknowledge different genomic profiles from different cancer patients with the hypothesis that mutated genes from the same pathway are likely to produce similar disease phenotypes. A pathway-centred approach helps finding genotypic causes of diseases, classifying disease subtypes, and identifying drugs [7].

Metabolism and Cancer Cell

In this section we will discuss cancer cell metabolism and how this differs from that of healthy cells. Different components are involved in this process.

The Role of Glucose: Warburg Effect

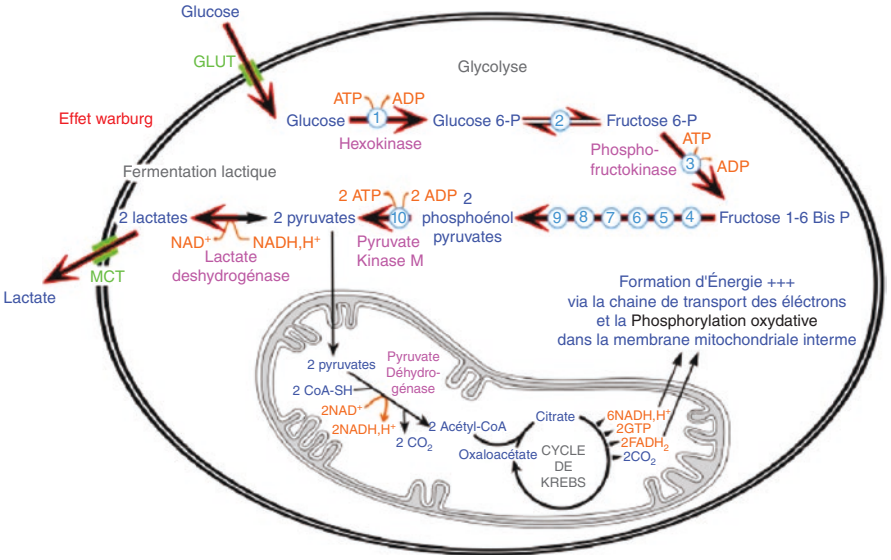
Otto Warburg in the early 1930s described the process by which cancer cells obtain their energy, essentially from glucose through glycolysis.

In the presence of oxygen, most differentiated (healthy) cells change glucose into pyruvate in the cytoplasm and then into carbon dioxide. Through this reaction, a maximum of ATP (adenosine triphosphate) is produced and that of lactate is limited. This reaction is only possible in the presence of oxygen and is referred to as aerobic glycolysis.

In a cell the energy is produced in the mitochondria where lipids are changed into glucose. Glucose is fundamental; in addition to ATP, it also provides the metabolic intermediates required for anabolic reactions. Glucose and glutamine are two essential energy sources.

By comparing healthy liver cells with tumour liver cells, Warburg noticed that tumour cells needed more glucose. By measuring the level of oxygen, he observed that compared to healthy cells, tumour cells consumed less oxygen, metabolized ten times more glucose, and produce more lactic acid, the by-product of glycolysis.

According to Warburg's theory, an irreversible change of the respiratory process in the mitochondria results in cell death. However, some cells like tumour cells can adapt their metabolism to an anaerobic one, thus needing substantially less oxygen to growth. Consequently, the cell morphology changes and growth becomes anarchical.

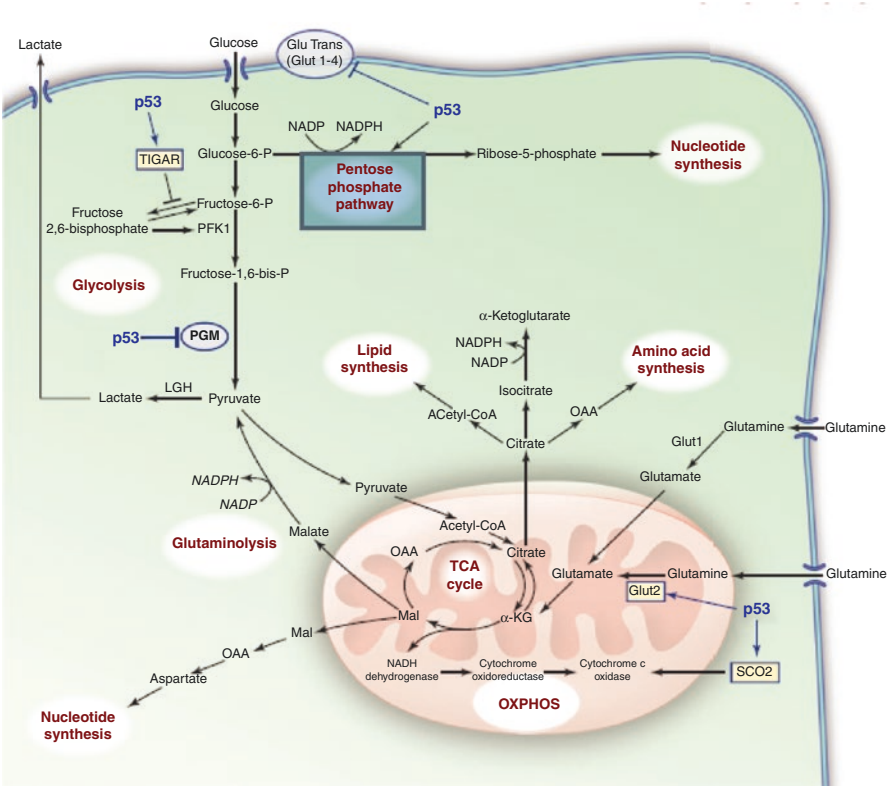


The theory developed by Warburg could only be completely validated with the development of molecular biology and its discoveries. Today, substantial evidence for this theory exists which is referred to as the "Warburg effect".

Further research has shown that mitochondria are able to function in tumour cells. Finally, Warburg did not discover why healthy cells become malignant, but he did identify one of the most important characteristics of tumour cells. His research provided important insights, crucial for understanding complex metabolic diseases.

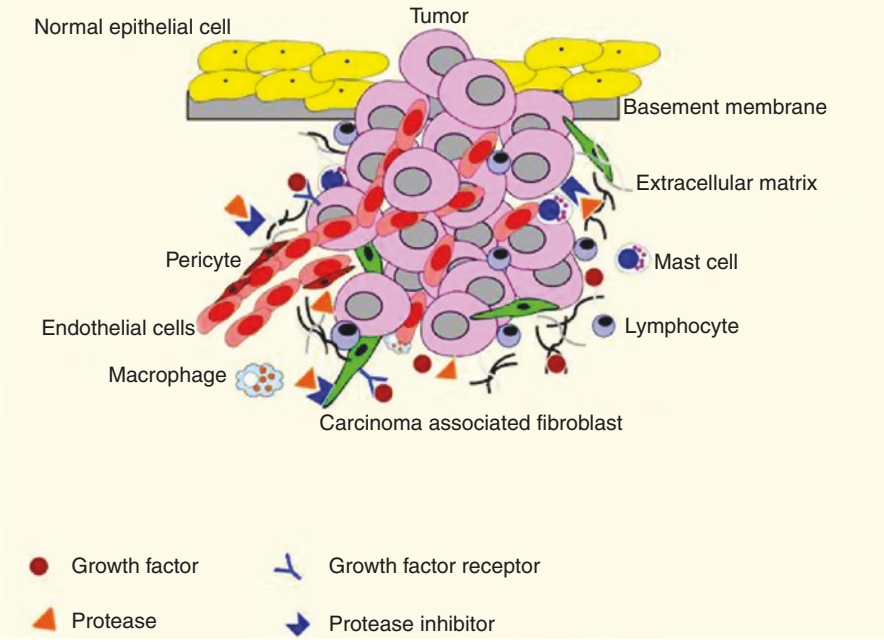
Levine and Puzio-Kuter identified different intermediates implicated in cell growth and division. They also showed that oncogenes and tumour suppressor genes regulated key cancer-producing pathways [8].

The metabolism of the cancer cell may have an impact on the therapeutic target. Indeed, we can see that the energy production is fundamental for growth, proliferation, and cell survival. The energy production by the cell is a source of oxidation which might influence the mutation process by changing the bases of the DNA and damage the lipid membrane. Obesity and diabetes increase the risk of cancer, while calorie restriction reduces it. As an example, a large animal with a low metabolic level (In body mass) has a lower risk of developing cancer.



Tumour Cell Environment

Cancer development results not only from the dysregulation of cells but also from complex interactions between the tumour tissue and the peri-tumoural stroma [9].



The stroma consists of a compilation of cells, including fibroblasts/myofibroblasts, glial, epithelial, fat, immune, vascular, smooth muscle, and immune cells along with the extracellular matrix (ECM) and extracellular molecules. The cells constituting the stroma are not malignant, but their direct or indirect interaction with cancer cells may alter their functioning and their phenotype.

In normal tissue, fibroblasts play a very important role and produce the noncellular scaffolds, the extracellular matrix (ECM), and contribute to the basement membrane production by secreting collagen and laminin. The cellular/tumoural environment is not static and is continually being remodelled. Fibroblasts serve as scaffolds and secrete increased levels of ECM proteins, growth factors, and chemotactic factors. Thereby, they coordinate the influx of inflammatory cells and vascular progenitor cells, as well as supply the scaffold for cell growth and proliferation [10].

In the tumour microenvironment, fibroblasts are the main component of the tumour stroma. In some cancer, there are more fibroblast cells than cancer cells. Fibroblasts within tumours have an activated phenotype and behave like fibroblasts in wound healing. Cancer-associated fibroblasts (CAFs) are functionally and phenotypically distinct from normal fibroblasts (in the same tissue). CAFs are distinctly different from physiologically activated fibroblasts in that they are always in action: neither reverting to their original normal phenotype nor undergo apoptosis (programmed cell death) and elimination.

This abnormal interplay between tumour and stroma cells, combined with active molecular signal transfers, drives the cancer stroma phenotype and may result in permanent alterations in cell function. Growth factors and chemokine produced by fibroblasts and immune cells are damaged, thus stimulating tumour cell growth and recruitment of precursor cells, which themselves respond with abnormal growth and proliferate. Malformed tumour vessels contribute to tumour hypoxia, acidosis, and increased interstitial fluid pressures.

This interplay between the tumour cells and the microenvironment has and continues to be an area of considerable interest for the development of targeted therapies.

Angiogenesis

Angiogenesis is the process by which a new vascular tree is formed from an existing one. This vascularisation supplies cells with oxygen and nutrition and removes carbon dioxide and waste products.

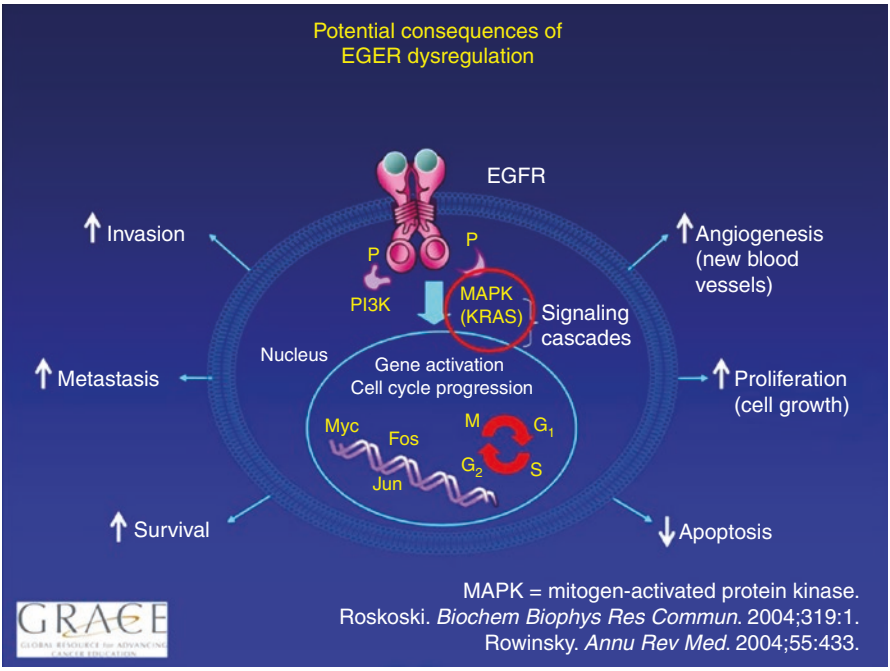
Capillaries are needed in all tissues for exchange diffusion of nutrients and metabolites. Changes in metabolic activity lead to proportional changes in angiogenesis and, hence, proportional changes in capillarity. Oxygen plays a pivotal role in this regulation. Haemodynamic factors are critical for survival of vascular networks and for structural adaptations of vessel walls.

Interestingly, scientists were investigating angiogenesis even before the dawn of the twenty-first century. In 2669 BC, Chinese medicine considered that the heart controlled the blood. In 1550 BC, vessel tumours were described in Ebers Papyrus. Hippocrates of Cos (460–370 BC) observed that the building of tumour was associated with swollen blood vessels around the tumour giving the impression of the claws of a crab. He thus named this type of tumour, karkinos and karkinoma. Later in ca. 200 AD, Galen of Pergamum, a Greek physician in the Roman Empire, described blood vessels related to tumour growth. Islamic medicine between ca. 1000 and 1300 AD, especially Avicenna, brought new knowledge of the cardiovascular system. During the renaissance period, the understanding of anatomy and vascular the system developed [11].

John Hunter, anatomist and surgeon in the eighteenth century was the first to bring insight in angiogenesis. Despite never citing the word angiogenesis in his work “the treatise” published in 1784, he was the first to describe the formation of new vessels during wound healing. More recently Judah Folkman (1933–2008), considered by many as the modern father of angiogenesis partly because of his pioneering studies, showed that tumour growth is angiogenesis-dependent.

Tumour cells need active angiogenesis to be able to growth. In tumour cells, there is an overexpression of angiogenic molecules (VEGF and FGF) and a reduction of the anti-angiogenesis factor expression. Tumours send signal, such as VEGF, that drives the proliferation of neighbouring blood vessels.

*VEGF: vascular endothelial growth factor
*FGF: fibroblast growth factor


Potential consequences of
EGER dysregulation
EGFR
Invasion
Angiogenesis
(new blood
vessels)
P
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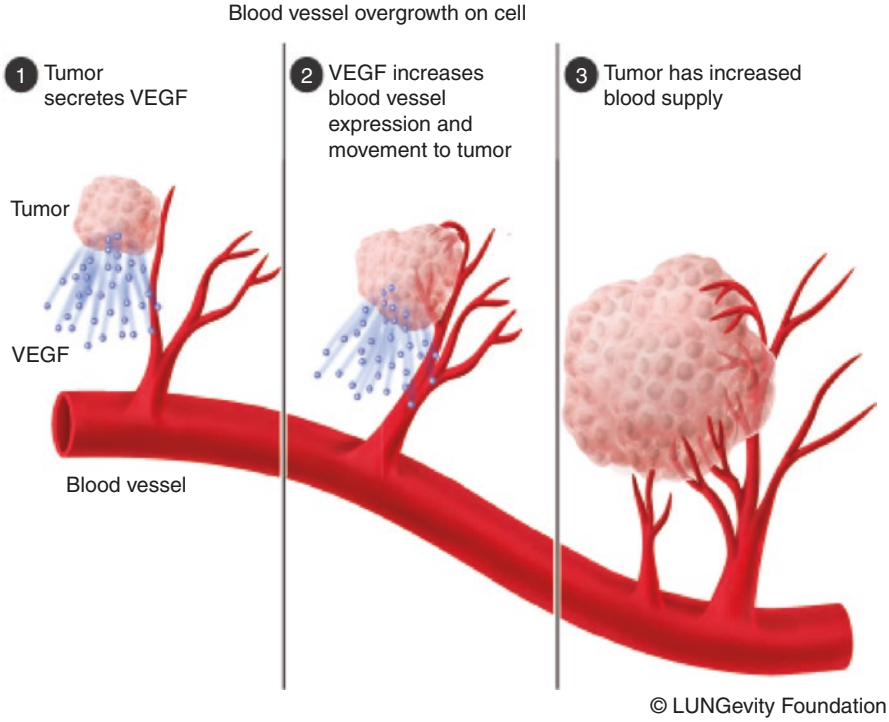
PI3K
MAPK
(KRAS)
Signaling
cascades
Nucleus
Gene activation
Cell cycle progression
Metastasis
Proliferation
(cell growth)
Myc
Fos
Jun
M
G1
G2
S
Survival
Apoptosis
MAPK = mitogen-activated protein kinase.
Roskoski. Biochem Biophys Res Commun. 2004;319:1.
Rowinsky. Annu Rev Med. 2004;55:433.


Blood vessel overgrowth on cell
1 Tumor
secretes VEGF
2 VEGF increases
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expression and
movement to tumor
3 Tumor has increased
blood supply
Tumor
VEGF
Blood vessel
© LUNGevity Foundation

The recognition that the control of angiogenesis could be of therapeutic value has stimulated research over the past 40 years. On one side, stimulation of angiogenesis can be therapeutic in ischemic heart disease, peripheral arterial disease, and wound healing. On the other side, decreasing or inhibiting angiogenesis can be therapeutic in cancer, ophthalmic conditions, rheumatoid arthritis, and other diseases.

A recent publication [12] shows how the branched peptide NT4 reduces angiogenesis and the invasiveness of tumour cells.

Anticoagulants (heparin derivatives) have an inhibitory role on tumour cells and procoagulants (thrombin), rather an activator role of proliferation, migration, and invasion. In the last few years, the relation between the peptide NT4 and heparan sulphate proteoglycans (HSPGs) has been extensively investigated. HSPGs are composed of a core protein, an O-glycosylated with a glycosaminoglycan (GAG). HSPGs are able to interact with a variety of proteins, such as those in the extracellular matrix (ECM): macromolecules; growth factors, such as fibroblast growth factors (FGFs); chemokines; morphogens; enzymes; heparin-binding epidermal growth factor-like growth factor (HBEFG); platelet-derived growth factor (PDGF); and many others. Most of the proteins that engage with HSPGs have a heparin-binding site that interacts with the sulphated GAG chains of HSPGs. NT4 binds to HSPGs and selectively targets cancer cells and tissues.

So, this peptide provides evidence of interplay with tumour invasion pathway and should continue to be used in studies related to links between coagulation and tumour progression involving HSPGs (Bracci et al. [12], p. 5).

Immune Process

Cancer should be considered, by our immune system, as an aggressor and therefore should be recognized as an intruder and be destroyed. However, cancer cells through different mechanisms escape detection by our immune system.

The tumour microenvironment (TME) that contains stromal cells and immune cells shapes cancer development and impact the response to tumour therapy (Hanahan and Weinberg [3]; Palucka and Coussens [13]). Intratumoural immune cells include lymphocytes, such as T, B, and natural killer (NK) cells, as well as a variety of myeloid cells (granulocytes, monocytes, macrophages, and dendritic cells).

T cells require glucose for proliferation and survival. Naïve or quiescent T cells require extrinsic cytokine stimulation to maintain glucose uptake for normal functions. Activated T cells require substantially more energy to grow, proliferate, and perform effector functions required of an activated lymphocyte. Energy production in the activated T cell may initially rely on AMPK activity for maximal ATP production and later, rely on changes in Glut1 expression, glucose uptake, and aerobic glycolysis. Without enough energy, activated T cells undergo apoptosis [14].

On one hand, T cells are activated through antigen recognition by the T cell receptor (TCR) and co-stimulatory signals such as CD28. On the other hand, the

inhibitory signals for T cell activation (i.e., immune checkpoints) are very important to maintain self-tolerance and prevent autoimmunity and an excessive immune responses.

Under self-tolerance, we understand the absence of an immune response directed against a person's own tissue's antigens.

We should make the distinction between central tolerance and peripheral tolerance depending on where the state is originally induced, in the thymus and bone marrow (central) or in other tissues (lymph node [peripheral]). The mechanisms by which these forms of tolerance are established are distinct but the resulting effect is similar.

For antitumour therapy, Th1 cells that produce interleukin-2 (IL-2) and interferon-c (IFNc) play an activating role, while CD4+ regulatory T cells (Tregs) suppress antitumour immunity.

So, immune checkpoints are inhibitory pathways connected to the immune system that are crucial for maintaining self-tolerance.

The two immune checkpoint receptors that have been most actively studied in the context of clinical cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4, also known as CD152) and programmed cell death protein 1 (PD1, also known as CD279), are both inhibitory receptors.

The T lymphocyte recognizes the tumour cell through the binding of its receptor to its antigen; the contact of PD-1 with PD-L1 prevents the T lymphocyte from recognizing the tumour cell as an invader/foreign cell which results in immune tolerance.

The clinical efficacies of antibodies that block either of these receptors provide evidence that antitumour immunity can be enhanced by inhibiting immune checkpoints. The expression and activation of immune checkpoint proteins are important immune resistance mechanisms of tumours. A number of other immune checkpoints are promising targets for therapeutic blockade based on preclinical experiments with inhibitors for many of these currently under development.

In addition to TCR and co-stimulatory signals, T cell activation requires a third signal: signals from the cytokine receptors (Fig. 1.1) [15]. For example, IL-2 is necessary for the proliferation of T cells, and IL-12 and IFNc are important for Th1 differentiation and CTL activation.

SHP1 Phosphatase

ZAP70: A protein normally expressed near the surface membrane of T cells and natural killer cells. It is part of the T cell receptor and plays a critical role in T cell signalling. It is a member of the protein-tyrosine kinase family.

PI3K: A type of enzyme that transmits signals in cells and that helps control cell growth. Some tumours have higher-than-normal levels of PI3K.

CD80-CD86: Cluster of differentiation (CD) 80 and 86 are proteins found on dendritic cells, activated B cells, and monocytes that provide a co-stimulatory signal necessary for T cell activation and survival. It is the ligand for two different

proteins on the T cell surface: CD28 (for autoregulation and intercellular association) and CTLA-4 (for attenuation of regulation and cellular disassociation).

JAK: Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway.

(SOCS) suppressors of cytokine signalling are major negative regulators of the JAK/STAT pathway.

The immune checkpoints like CTLA4 or PD-1/PL-L1 are those which have been studied most to be use as therapy. The inhibitors of PD-1 and PD-L1 prevent the binding of the receptor with the corresponding antigen allowing the T lymphocyte to recognize the tumour cell with subsequent destruction by the immune system.

In this first chapter, we can see how complex a single cell is. New discoveries, with more and more precise technology, will more than likely uncover an even more complex system with new pathway that can be targeted for cancer treatments.

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