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Hallmarks of Cancer

Cancer Background

Despite the many recent advances in our understanding and treatment of the disease, cancer is still among the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths worldwide, with cancer being the second leading cause of death in the United States of America.

- About one-third of all people in the US will develop cancer during their lifetimes.
- By 2040, the number of new cancer cases per year is expected to rise to 29.5 million and cancer-related deaths to 16.4 million.

Generally, cancer rates are highest in countries with the longest life expectancy, education level, and living standards, such as the US, Canada, and the UK. However, for some cancer types, such as cervical cancer, the reverse is observed.

Cancer: Causes and Treatments

Cancer is caused by a wide range of environmental factors, leading to DNA damage, hereditary and in utero muta-tions.

- Environmental factors, such as smoking, excessive alcohol consumption, and radiation exposure, contribute to an individual's lifetime risk of developing cancer.
- Inherited genetic mutations play a significant role in around 5 -10%of all cancers.

More than 50 mutations in specific genes have been linked to hereditary cancer syndromes.

Hallmarks of Cancer

The canonical hallmarks of cancer comprise six physical capabilities acquired during the multistep development of human tumors, built on a foundation of genomic instability and inflammation. Research and increased understanding of cancer in the last decade have provided two emerging hallmarks that contribute to establishing the core capabilities-reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of these concepts' widespread applicability increasingly affect the development of new means to treat human cancer.

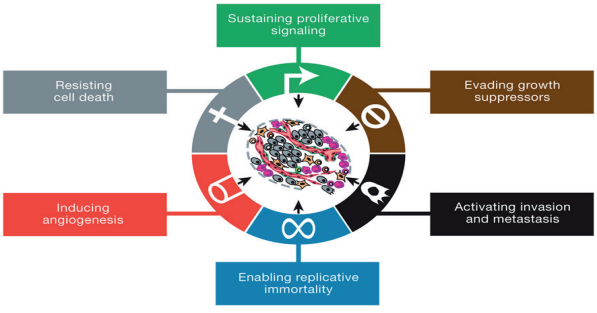

Fig. 1. The Hallmarks of Cancer. Source: Hanahan and Weinberg, 2011

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Sustaining Proliferative Signaling

A fundamental trait of cancer cells is their ability to support chronic proliferation. Healthy tissues carefully regulate the cell growth-and-division cycle, ensuring homeostasis and standard tissue architecture and function. In contrast, cancer cells deregulate these signaling pathways to maintain their survival. Growth factors (GF) that bind to cell-surface receptors containing intracellular tyrosine kinase domains are predominantly affected. This leads to the upregulation of intracellular signaling pathways that regulate cell cycle progression and growth.

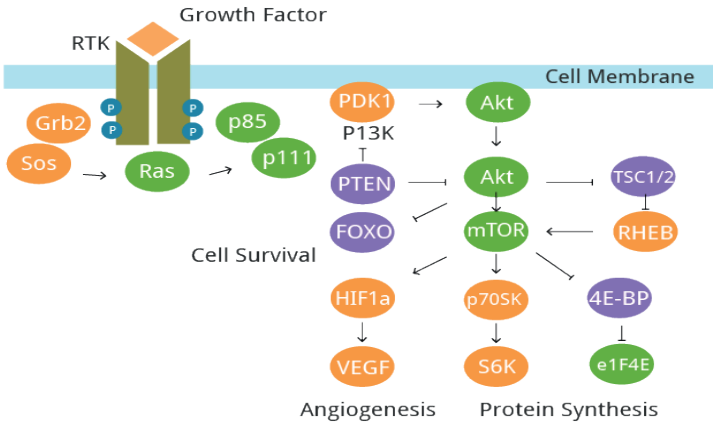

Fig. 2. The deregulation of signaling pathways.

Cancer cells sustain proliferative signaling in several alternative ways:

Evading Growth Suppressors: Numerous tumor suppressors are involved in limiting cell growth and proliferation. They are often discovered through their characteristic inactivation in cancer cells. The two canonical tumor suppressors are the RB (retinoblastoma-associated) and TP53 proteins; they are essential regulators that govern apoptosis, proliferation, and senescence in cells.

Although TP53 and RB are essential regulators of cell-cycle progression, each operates as part of a more extensive network, allowing functional redundancy.

- In-house production of GF ligands and cognate receptors, leading to autocrine proliferative stimulation.
- Cancer cells may stimulate normal cells within the surrounding stroma, subsequently supplying the cancer cells with various growth factors.
- Increased GF receptor expression, rendering cells hyperresponsive.
- Structural alterations in the receptor molecules that increase ligand-independent activation.
- GF independence may arise from constitutive down-stream activation of signalling pathways, negating the need to stimulate these pathways via ligand-mediated receptor activation.
- The RB protein integrates signals from diverse extracellular and intracellular sources, acting as a critical gatekeeper of cell-cycle progression, its absence can result in persistent cell proliferation.
- TP53 receives input from intracellular stressors DNA damage, suboptimal growth conditions and homeostatic imbalances can lead to TP53 halting cell-cycle progression until conditions are favourable, or initiate apoptosis if cellular damage is beyond repair.
- The nuanced effects of activated TP53 are highly context dependent, varying by cell type as well as the severity of cellular stress and DNA damage.

Interestingly, chimeric mice populated with RB null cells do not demonstrate proliferative abnormalities- the only neoplasia observed were pituitary tumors later in life.1 TP53 null mice also develop typically, showing normal cellular and tissue homeostasis, but again develop cancers later in life, such as leukemia's and sarcomas.[2]

Activating Invasion and Metastasis: A well-characterized alteration to aid invasion and metastasis is the loss of E-cadherin by carcinoma cells. E-cadherin aids the assembly of epithelial cell sheets and maintains the cells' quiescence within these sheets by forming adherent junctions with adjacent epithelial cells. The frequently observed downregulation and occasional mutational inactivation of E-cadherin in human carcinomas provided strong support for its role as a viral suppressor of this hallmark capability.[3] Another important driver of cancer metastasis is the loss of Contact inhibition. Contact inhibition ensures healthy, noncancerous cells cease proliferation and growth when they come into contact with each other. This characteristic is lost when cells undergo malignant transformation, leading to uncontrolled proliferation and solid tumor formation.[4]

Contact inhibition can be achieved in a variety of ways:

- One mechanism involves the protein Merlin (coded by the NF2 gene), a tumour suppressor, which when absent results in the hereditary condition neurofibromatosis type 2.
- Merlin regulates contact inhibition via coupling cell-surface adhesion molecules (e.g., E-cadherin) to transmembrane receptor tyrosine kinases (e.g., the EGF receptor). In doing so, Merlin strengthens cadherin-mediated cell-to-cell attachments.
- Sequestering growth factor receptors, Merlin limits the capability of cancer cells to efficiently emit mitogenic signals.
- The second mechanism of contact inhibition requires the LKB1 epithelial polarity protein, involved in epithelial structure organisation and maintaining tissue integrity.
- LKB1 has been shown to negate the mitogenic effects of the Myc oncogene when it is upregulated in organized, quiescent epithelial structures.
- When LKB1 expression is reduced, epithelial integrity is compromised, making epithelial cells more susceptible to Myc-induced transformation.

Expression of other adhesion molecules is notably altered in many carcinomas, with those involved in cytostasis being downregulated. Adhesion molecules generally associated with the cellular movement during embryogenesis and inflammation are predominantly upregulated. For example, N-cadherin, typically expressed in migrating neurons and mesenchymal cells during organogenesis, is upregulated in many invasive cancer cells.[5] Research shows that cell-to-cell contacts formed by dense populations of healthy cells propagated in 2D cell-culture seek to suppress further cell proliferation, presenting as confluent cell monolayers. Conversely, in vitro contact inhibition is absent in numerous cancer types, suggesting that contact inhibition is an in vitro analogous mechanism operating to maintain tissue homeostasis.

Enabling Replicative Immortality: Cancer cells require unlimited replicative potential to form macroscopic tumors, bypassing the Hayflick limit observed in healthy cells while avoiding programmed cell death. Telomeres and telomerase play a crucial role in this hallmark of cancer.

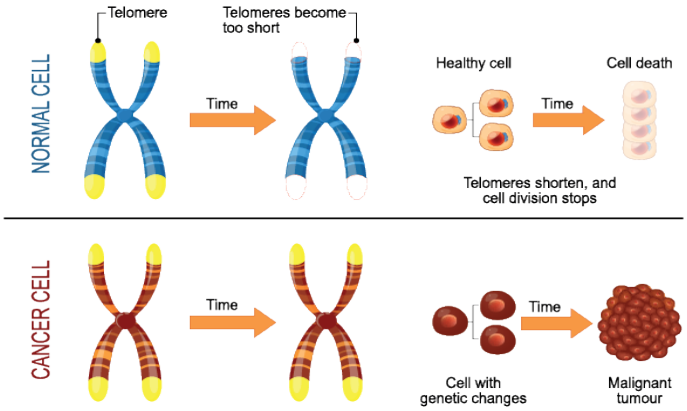

Fig. 3. Telomeres and Cancer.

- Telomere capping of chromosomes is heavily involved in cancer cells developing the capability for unlimited proliferation.
- Telomeres shorten progressively in non-immortalized cells propagated in culture, eventually losing the ability to protect the ends of chromosomes from end-to-end fusions.
- These fusions lead to the formation of dicentric chromosomes, which scramble the cell's karyotype, threatening viability.
- Telomerase is predominantly absent in non-immortalized cells but expressed at functionally significant levels in the vast majority (90%) of spontaneously immortalized cells, such as human cancer cells.
- The presence of telomerase activity is correlated with a resistance to both senescence and apoptosis, which cancer cells must avoid to maintain replicative immortality.

Research suggests that cancer cells often experience telomere loss-induced crisis relatively early during multistep tumor progression due to their inability to express significant telomerase levels. Extensively eroded telomeres have been observed in premalignant growths, along with end-to-end chromosomal fusions, suggesting that cancer cells have passed through a substantial number of successive telomere-shortening cell divisions during their development from healthy cells before the acquisition of telomerase activity.[6]

Inducing Angiogenesis: Cancer cells, like healthy cells, need nutrients and oxygen and the capacity to remove metabolic wastes and carbon dioxide for survival; tumor-associated vasculature formed through angiogenesis caters to these requirements. During tumor development and progression, an "angiogenic switch" is almost always activated and remains on, causing normally quiescent vasculature to form new vessels that help sustain expanding neoplastic growth.[7]

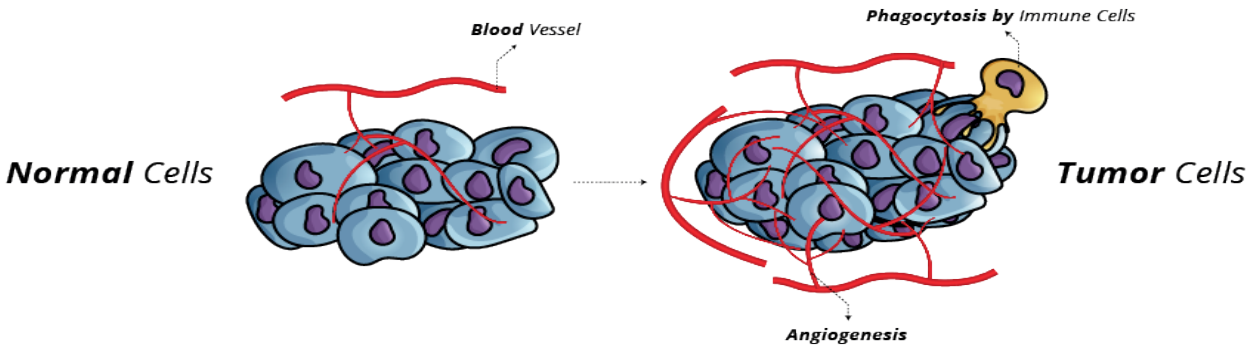

Fig. 4. Cancer Cell Angiogenesis

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The most prominent prototypes of angiogenesis induction and inhibition are vascular endothelial growth factor-A (VEGF-A) and thrombospondin-1 (TSP-1)

The past decade has seen significant focus on angiogenesis. Amid this wealth of new knowledge, other proangiogenic signals, such as members of the fibroblast growth factor (FGF) family, have been implicated in sustaining tumor angiogenesis when their expression is significantly upregulated.8 Historically, angiogenesis was thought only to be relevant for the formation of rapidly growing tumors. However, recent investigation indicates that angiogenesis also plays a fundamental role in the premalignant phase of neoplastic progression.

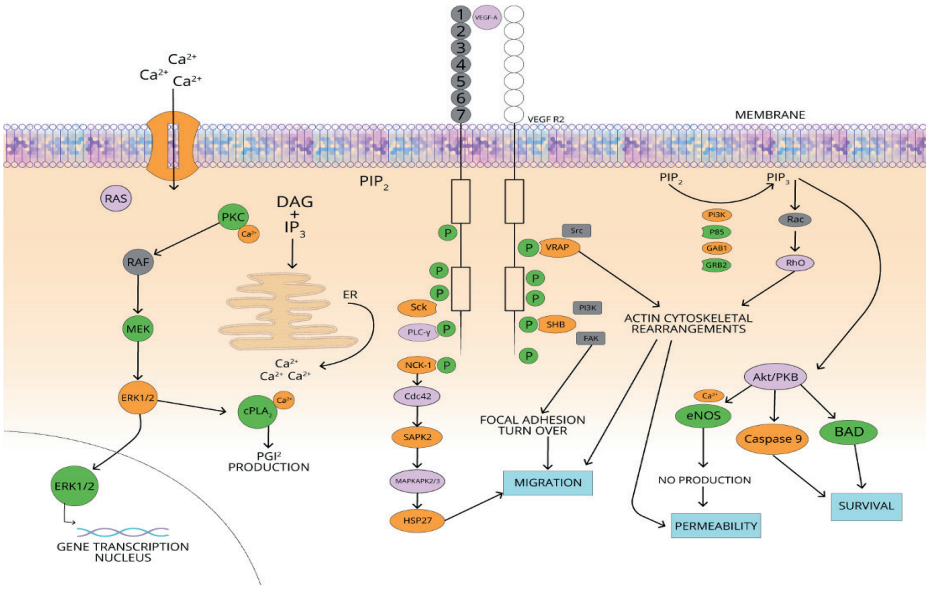

Fig. 5. VEGF Signaling Pathway

- VEGF signaling via the RTKs VEGFR-1–3 is regulated at multiple levels, illustrating its importance in vascular development and maintenance.
- VEGF gene expression is upregulated both by hypoxic conditions and via oncogenic signaling.
- VEGF ligands can be sequestered in the extracellular matrix in latent forms that are subject to release and activation by extracellular matrix-degrading proteases such as MMP-9.
- TSP-1 binds transmembrane receptors displayed by endothelial cells, suppressing the activity of proangiogenic stimuli.
- The blood vessels produced within tumors are typically aberrant, displaying erratic capillary sprouting along with convoluted and excessive vessel branching and distortion.
- Histological analyses of premalignant lesions indicate angiogenesis is induced surprisingly early during the multistage development of invasive cancers both in animal models and in humans.
- Once angiogenesis has been activated, tumours exhibit diverse patterns of neovascularization- pancreatic ductal adenocarcinomas are hypovascularized and may be actively antiangiogenic whereas human renal and pancreatic neuroendocrine carcinomas are densely vascularized.

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Apoptosis

Apoptosis is the process of programmed cell death characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. Apoptosis is considered a vital component of processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death.

Resisting Cell Death: It is well established that programmed cell death via apoptosis serves as a genetic defence mechanism against cancer development. The apoptotic machinery is composed of both upstream regulators and downstream effector components. Regulators are subdivided into two primary circuits:

- The extrinsic program is involved in receiving and processing extracellular death-inducing signals.
- The intrinsic program, responsible for sensing and integrating intracellular signals.

Each program culminates in the activation of a predominantly latent protease (caspases 8 or 9), which proceeds to initiate a cascade of proteolysis involving effector caspases responsible for the execution phase of apoptosis, in which the cell is progressively disassembled and then consumed, both by its neighbors and by phagocytic cells. Currently, the intrinsic apoptotic program is more widely implicated as a barrier to cancer pathogenesis.[9]

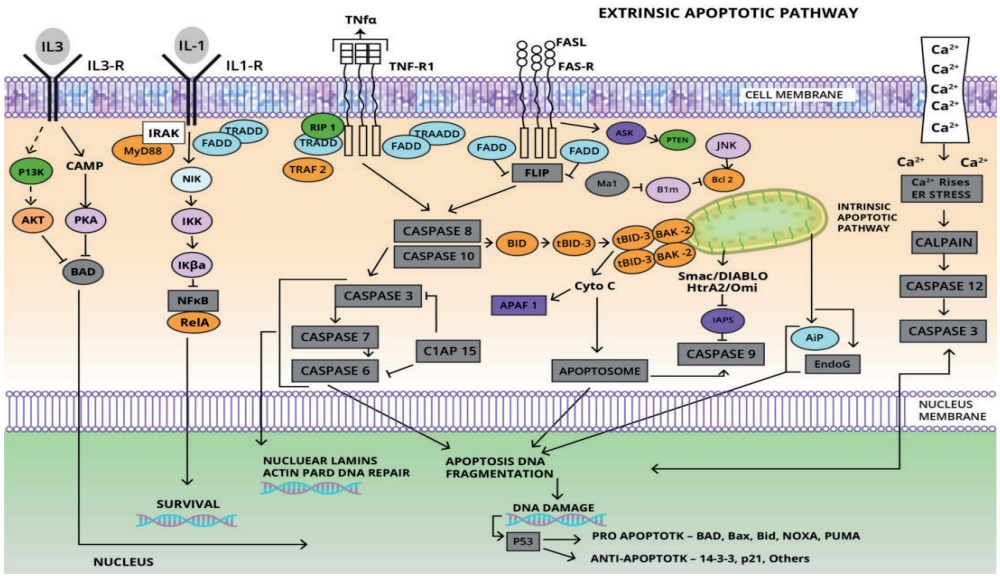

Fig. 6. Apoptosis Pathway

Apoptotic cells undergo morphological changes involving extensive plasma membrane blebbing followed by karyorrhexis. Apoptotic bodies are formed by separation of cell fragments during a process called “budding.” They consist of cytoplasm with tightly packed organelles with or without a nuclear fragment. The organelle integrity remains enclosed within an intact plasma membrane. These bodies are subsequently phagocytosed by macrophages, parenchymal cells, or neoplastic cells and degraded within phagolysosomes. There are three main types of biochemical changes observed in apoptosis:

- Activation of caspases.
- Breakdown of DNA and protein.
- Membrane changes and recognition by phagocytic cells.

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Cancer cells have evolved a variety of strategies to limit or circumvent apoptosis:

- The most common mechanism involves losing the TP53 tumor suppressor function, eliminating a critical damage sensor from the apoptosis-inducing circuitry.
- Cancer cells may increase anti-apoptotic regulator expression, such as Bcl-2, Bcl-xL, or the survival signals Igf1/2 via downregulating pro-apoptotic factors (Bax, Bim, Puma).
- Alternatively, tumors can also short-circuit the extrinsic ligand-induced death pathway to avoid apoptosis.

The variety of apoptosis-avoiding mechanisms presumably reflects the diversity of apoptosis-inducing signals that cancer cell populations encounter during their evolution to the malignant state. In addition to apoptosis, necrosis also plays a role in resisting cell death; cell death by necrosis appears to be under genetic control in some situations, rather than being a random and uncoordinated process.[11 12]

Necrotic cell death releases proinflammatory signals into the surrounding tissue microenvironment, allowing necrotic cells to recruit inflammatory cells. Evidence suggests that immune-inflammatory cells can be actively tumor-promoting in the context of cancer, as these cells can foster angiogenesis, cancer cell proliferation, and invasiveness. Furthermore, necrotic cells can release bioactive regulatory factors, such as IL-1α, which can directly stimulate neighboring viable cells to proliferate, with the potential to facilitate cancer progression.[13]

Emerging Hallmarks and Characteristics

The conceptual progress of cancer hallmarks in the last decade has presented two further hallmarks, the reprogramming of energy metabolism and evading immune destruction. Two pre-requisite characteristics have been defined that enable cancer hallmarks and contribute to disease progression: genomic instability and tumor-promoting inflammation.

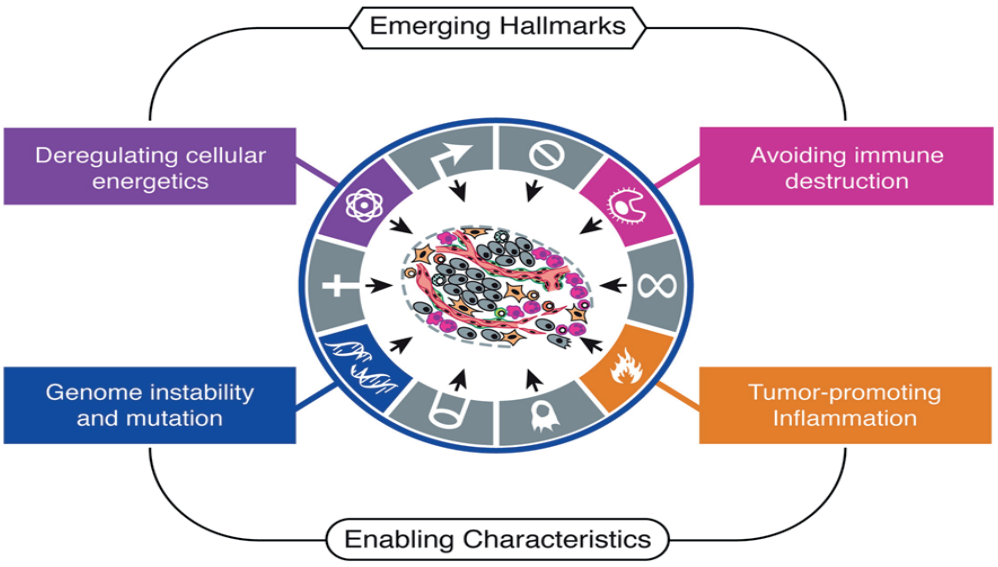

Fig. 7. Emerging Hallmarks and Enabling Characteristics. Source: Hanahan and Weinberg, 2011

Reprogramming Energy Metabolism

The chronic and predominantly unimpeded cell proliferation characteristic of cancer requires both the deregulated control of cell proliferation and energy metabolism adjustments, providing the fuel that enables cell growth and division. Cancer cell metabolism shows unique characteristics compared to normal cells; even in the presence of oxygen, cancer cells can alter their glucose metabolism and regulate their energy production. Cancer cells limit their energy metabolism primarily to glycolysis, resulting in a state coined aerobic glycolysis[14] or the Warburg effect[15]. This reprogramming is achieved by upregulating glucose transporters, notably GLUT1, which substantially increases glucose import into the cytoplasm.[16]

Such reprogramming of energy metabolism may appear counterintuitive, considering that cancer cells must compensate for an 18-fold lower efficiency of ATP production provided by glycolysis relative to normal mitochondrial oxidative phosphorylation. A functional rationale for the glycolytic switch in cancer cells has yet to be found. One hypothesis suggests that increased glycolysis allows the diversion of glycolytic intermediates into various biosynthetic pathways, including those generating nucleosides and amino acids. This, in turn, facilities the biosynthesis of the macromolecules and organelles necessary for assembling new cells. Furthermore, Warburg-like metabolism appears to be present in rapidly dividing embryonic tissues, suggesting a role in supporting the large-scale biosynthetic programs required for active cell proliferation seen in cancer.

Interestingly, some tumors have been found to contain two subpopulations of cancer cells that differ in their energy metabolism pathways. One population consists of aerobic glycolysis-dependant cells that secrete lactate. The second subpopulation preferentially imports and utilizes the lactate produced via the altered glycolytic pathway by neighboring cells their primary energy source, converting the exogenous lactate into pyruvate via Lactate dehydrogenases, which is then shuttled into the TCA cycle.[17]

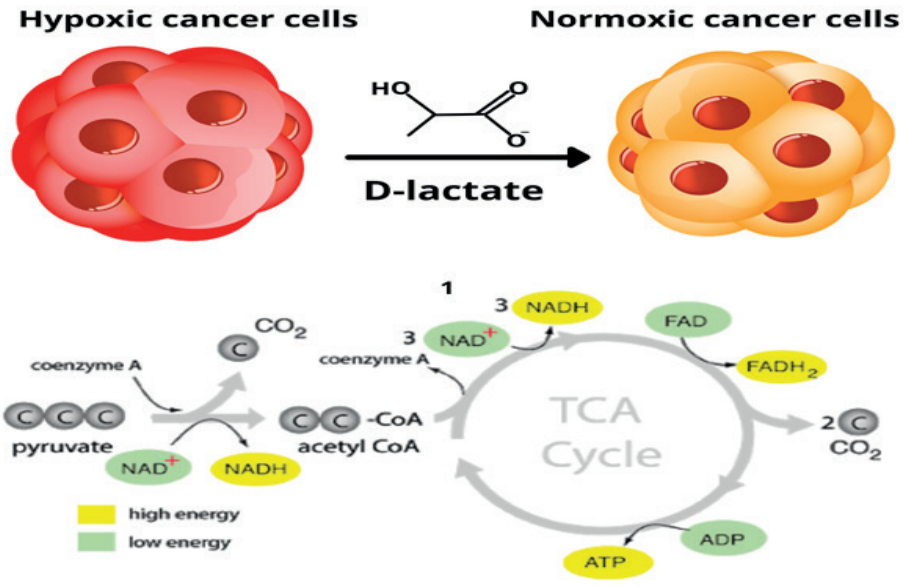

Fig. 8. Two subpopulations of cancer cells.

These two populations function symbiotically: the hypoxic cancer cells rely on glucose for fuel and secrete lactate as waste imported and preferentially used as fuel by their normoxic counterparts[18]. Furthermore, it has been shown that lactate stimulates angiogenesis through activation of the VEGF/VEGFR2 pathway, which may support the metastatic process[19]. Altered energy metabolism is proving to be as widespread in cancer cells as many other cancer-associated traits that have been accepted as hallmarks of cancer.

Evading Immune Destruction

The long-standing theory of immune surveillance proposes that cells and tissues are constantly monitored by an ever-alert immune system which is responsible for recognizing and eliminating cancer cells, preventing tumor development; thus, for tumorigenesis to occur, cancerous cells must avoid detection by the immune system or limit the extent of immunological induced death, thereby evading eradication.

Previous research into carcinogen-induced cancers in genetically engineered immunodeficient mice observed that tumors arose more frequently and grew more rapidly when compared to immunocompetent controls. Functional deficiencies in CD8+ cytotoxic T lymphocytes (CTLs), CD4+ Th1 helper T cells, or natural killer (NK) cells each led to increases in tumor incidence, particularly in mice with combined immunodeficiencies in T cells and NK cells. The results indicated that both the innate and adaptive immune systems contribute significantly to immune surveillance and tumor eradication[20]. Clinical evidence in cancer patients also suggests antitumoral immune responses in some forms of human cancer[21]. Patients with colon and ovarian tumors heavily infiltrated with CTLs and NK cells show a better prognosis than those with reduced circulating killer lymphocytes[22]. Furthermore, some immunosuppressed organ transplant recipients have developed donor-derived cancers, indicating that in the tumor-free donors, the cancer cells were kept in a dormant state by a fully functional immune system[23].

Another hypothesis suggests highly immunogenic cancer cells may evade immune destruction by disabling the immune system's components responsible for eliminating them. Cancerous cells may inactivate infiltrating CTLs and NK cells through the secretion of TGF-β or other immunosuppressive factors[24, 25]. More subtle mechanisms operate by recruiting inflammatory cells that are actively immunosuppressive, including regulatory T cells and myeloid-derived suppressor cells; both can suppress cytotoxic lymphocytes, aid cancer cell survival, and evade destruction by the immune system[26, 27].

Characteristics: Genomic instability and Tumour promoting inflammation.

Cancer cells can regulate inflammatory mechanisms to promote their growth and survival. During a normal response by the immune system, immune cells carry out their designated task of engulfing and destroying foreign invaders. Within the tumor microenvironment, immune cells are corrupted by cancer cells. As a result, the usually anti-tumor immune cells are subverted into tumor-promoting immune cells that secrete pro-survival, pro-migration, and anti-detection factors, enabling tumor growth metastasis. Important molecules and signaling pathways in mediating the immune response to the tumor microenvironment include NF-κB, inflammasome signaling, tumor-infiltrating immune cell markers, and immune checkpoint signaling[28].

NF-κB signaling in cancer and immune cells within the tumor microenvironment has been implicated in the epithelial-to-mesenchymal transition (EMT) of cells, allowing the detachment and migration the tumor mass. Crosstalk between NF-κB signaling in immune-infiltrating cells and cancer cells establishes an environment that promotes tumor growth, invasion, and malignancy[29]. Research has shown that tumors engineer microenvironments to evade immune surveillance and attack, particularly by modulating specific immune checkpoint pathways[30].

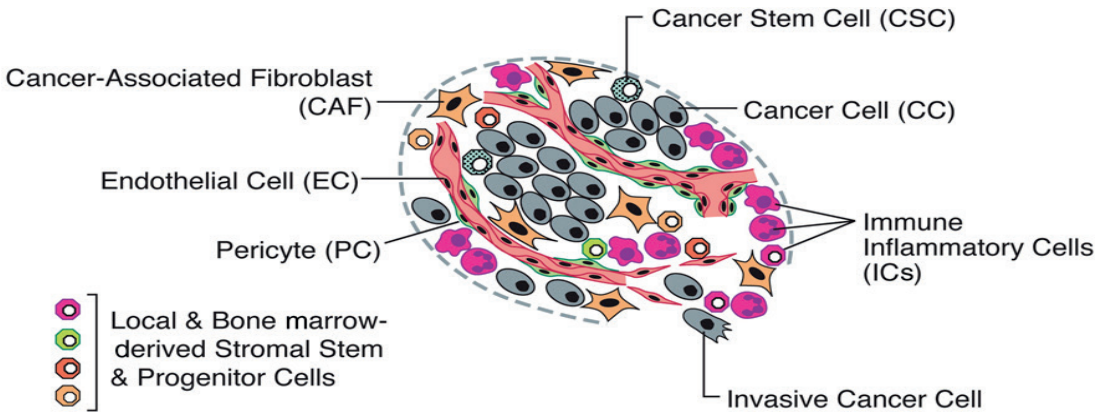

Fig. 9. An assemblage of distinct cell types constitutes most solid tumors.

T cells are the primary effector immune cells, expressing numerous autoinhibitory cell surface receptors, such as lymphocyte-activation gene 3 (LAG-3), programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); modulating cellular dynamics. Within the tumor microenvironment, tumor cells upregulate the ligands to these receptors, enhancing tumor tolerance to immunological assault, enabling evasion and subsequent eradication by the immune system[31].

Pharmacological modulators of these ligand-receptor interactions, known as immune checkpoint therapies, have been intensely researched and deployed as novel immunotherapy agents to treat cancers in recent years. Of particular interest are monoclonal antibodies against PD-1 and CTLA-4. Given these immune checkpoint therapies' early success in activating anti-tumor immune responses, creating immunotherapies targeting other co-inhibitory and co-stimulatory receptors and their ligands in an order appears to be a compelling therapeutic strategy[32].

Genomic instability is a well-known characteristic of most cancers. From sustaining proliferative signaling to avoiding cell death, genome instability generates the genetic abnormalities required for multiple hallmark functions. Either microsatellite instability or chromosomal abnormalities predominantly cause hereditary cancers; the basis for this underlying genomic instability is due to mutations in DNA repair genes. In contrast, The pattern of mutations in sporadic human cancers indicates that the selective pressure for tumor suppressor p53 (TP53) mutations is linked to DNA damage rather than p14ARF activation. Genomic instability in sporadic human cancers has also been linked to oncogene-induced DNA damage[33].

Conclusion

The hallmarks of cancer comprise of both well-established and numerous emerging biological capabilities acquired during the multistep development of human tumors. These hallmarks constitute an organizing principle for rationalizing the complexities of cancer development and progression. From sustaining proliferative signaling to avoiding cell death, genome instability generates the genetic abnormalities required for multiple hallmark functions. The Conceptual progress of the hallmarks of cancer in the last decade has presented two further hallmarks, the reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.

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