



Cancer Biology: a Primer for Perioperative Clinicians

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Abstract

Purpose of Review Cancer biology is a field that has grown exponentially in the last several decades. Elucidating the mechanisms involved in tumor development, while broadening our understanding, continues to reveal unexplained phenomena. Attempting to understand cancer biology requires a framework from which to start; two landmark reviews from 2000 and 2011 by Hanahan and Weinberg present such a framework. With advances in cancer therapeutics, an appreciation of the underlying tumor biology is necessary to optimally care for patients in the perioperative period.

Keywords Hallmarks of cancer · Cancer biology · Metastasis · Angiogenesis · Apoptosis · Inflammation · Mutations · Tumor microenvironment

Introduction

Better understanding of cancer biology and an interest in the potential role of perioperative factors on tumor microenvironment have resulted in an increasing amount of research literature by perioperative clinicians. The ability to weave that body of knowledge into a relatable tapestry for cancer researchers is facilitated by Douglas Hanahan of The University of California, San Francisco, and Robert A. Weinberg of The Massachusetts Institute of Technology. Their articles, *The Hallmarks of Cancer* [1••] and *Hallmarks of Cancer: The Next Generation* [2••], review major discoveries over many decades of research and synthesize a framework to guide our understanding of cancer biology. An attempt is made herein to present major concepts of cancer biology for perioperative clinicians.

Hallmarks

Tumor development results from changes in the genome of cells. Mutations or alterations of the genome allow for oncogenes to gain function and tumor suppressor genes to lose

function. These mutations can be point mutations (changing one base nucleotide) or whole chromosome alterations. Tumors evolve in a survival of the fittest—taking survival advantages as produced by these mutations. Hanahan and Weinberg proposed six alterations of normal cell physiology involved in cancer formation, the hallmarks of cancer: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Cancers of different types will take varied paths to tumor development—achieving these hallmarks at different stages depending on the inciting genetic event. Also discussed are hallmarks that are emerging from continued research as are characteristics that help enable cancer cells to achieve the various hallmarks. In the treatment of cancer, surgery and the perioperative period produce changes in the biological milieu which favor tumor recurrence and metastasis. The surgical stress response and the pharmacodynamic effects of anesthetics may promote the progression of metastatic disease [3••]. Understanding the way our therapies affect many of these hallmarks of cancer casts a new light on the potential of perioperative physicians to modulate patients' underlying cancer biology.

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Sustaining Proliferative Signaling

Normal cells require a signal (such as growth factors) to move from a resting to a proliferative state. Cancer cells no longer depend on outward signals to divide. They can make their own extracellular growth signals (e.g. PDGF, platelet-derived

growth factor in glioblastomas). Tumor cells may overexpress the receptors that transduce growth factor signals; these receptors often carry *tyrosine kinase* activity inside the cell. Many breast cancers overexpress the HER2/*neu* receptor [4]. Cancer cells can also change the extracellular matrix receptor (integrin) expression; this fundamentally changes the way the cell communicates to the outside environment (potentially telling the cell to become motile, resist apoptosis, or divide). Most complicated is the alteration of the downstream circuitry of growth factors (e.g. ras oncogenes in colon cancer [5] and B-Raf proteins in melanoma [6]).

Of critical importance in cancer biology are the ancillary cells present in tumors. Fibroblasts, endothelial cells, and inflammatory cells are likely to play a significant role in the deregulation of growth. Heterotypic signaling (between cell types) may be more important than the cancer cells, autonomy of growth factor production. During the perioperative period, multiple events influence these ancillary cells to play a prominent role in wound healing. These cells release soluble growth factors. Not only does the body mount a response to the surgical wounds, but complications arising in the postoperative period (e.g. surgical site infections and anastomotic leaks) herald an onslaught of inflammatory cells. The association between chronic inflammation and tumor development is well-recognized [7]. As discussed further below, inflammatory infiltrates during this critical time may contribute to the growth of, as yet undiagnosed, micrometastatic disease or cancer recurrence.

Evading Growth Suppressors

Normal cells maintain quiescence with either growth inhibitors or immobilized inhibitors in the extracellular matrix. The intracellular circuitry is associated with the cell cycle clock, and the majority goes through the retinoblastoma protein (pRb). The retinoblastoma protein is a stop sign. TGF β works along with pRb to keep the cell in a quiescent state. pRb function may be eliminated by virus associated tumors (e.g., cervical cancers and HPV [8]). Cancer cells may downregulate or display dysfunctional TGF β receptors allowing progression through the cell cycle to an active state. This is further confounded by some late stage tumors utilizing TGF β in activating an epithelial-to-mesenchymal transition (EMT) important in tumor invasion and metastasis [9••].

Cancer cells also avoid terminal differentiation. Normal cell circuitry relies on the *Mad-Max* complex of transcription factors to signal differentiation. With the overexpression of the *c-myc* oncogene, cancer cells may avoid differentiation with an overabundance of *Myc-Max* complexes favoring growth. Much of the research on the perioperative period is limited to in vitro studies given the profound multitude and complexity of the variables present in vivo—preoperative comorbidities, anesthetic management, surgical technique, etc. In efforts to understand the recurrence and metastasis of ovarian cancer

patients following surgery, ovarian cancer cells were exposed to volatile anesthetics and increased expression of TGF β as well as other tumor promoting factors were discovered among other factors that contribute to increased migration and metastatic potential [10].

Resisting Cell Death

Normal cells are subjected to programmed cell death known as apoptosis. Acquired resistance to programmed cell death is a hallmark of most tumors. Normal cells have sensors and effectors that govern apoptosis. Sensors detect DNA damage, signaling imbalance, growth factor insufficiency, hypoxia, or lack of extracellular signals (from neighboring cells or matrix). The p53 tumor suppressor protein senses DNA damage and will initiate apoptosis; p53 is functionally inactivated in over half of all cancers. The effectors are caspases, proteins that destroy subcellular organelles and the genome. The intracellular circuitry centers on mitochondria and the release of cytochrome c via proteins of the *bcl-2* family. There are a multitude of experiments showing that alteration of apoptotic machinery in cancer cells drastically increases growth rates.

Autophagy is a normal cell process with sensors and effectors that break down cellular organelles allowing recycling of catabolites for biosynthesis. Experiments suggest that activation of autophagy is another hurdle tumor cells must overcome during development. However, to complicate the picture further, other researchers have discovered that some therapies including radiation and cytotoxic drugs may induce a certain level of autophagy that is protective to cancer cells—a survival response that may allow some cancers to persist beyond traditional therapy, with growth of more resistant clones.

Necrosis may also be under genetic control; the resulting inflammatory infiltrate may be tumor promoting with growth stimulating factors. Strangely, tumors may gain an advantage by tolerating some degree of necrosis. Exposure to volatile agents has been shown to promote resistance to apoptosis in colon cancer and neuroblastoma cell lines via alterations in caveolin-1 regulation and *bcl-2* expression [11, 12]. In contrast, propofol has been found to induce apoptosis in a multitude of studies [13–17]. In comparing anesthetic techniques, retrospective analyses are beginning to realize the potential benefits of propofol-based anesthetics compared to volatile agents [18–19, 20••].

Enabling Replicative Immortality

Normal cells are limited in their ability to divide because of the telomeres, which are present on the ends of chromosomes. After each cell cycle, a short segment of these base pair repeats is clipped. Once depleted, the ends of the chromosomes are not able to be protected resulting in fusions, karyotypic disarray, and eventual cell death. Cancer cells upregulate

telomerase which adds the 6-base pair repeat onto the ends of telomeres extending the replicative potential to immortality.

In the absence of genomic surveillance as a result of mutations, cells may in fact survive telomere shortening with aberrant chromosomal breaks, fusions, deletions, and amplifications—serving to increase the mutability of the genome. With subsequent activation of telomerase in later stage cancers, these new mutations are now protected by elongated telomeres.

Inducing Angiogenesis

Once greater than 100 μm , tumors require delivery of oxygen and nutrients via capillary blood flow for survival; simple diffusion is inadequate. Tumors often initially lack the ability to encourage new blood vessel growth, but in order to grow beyond a certain size, they must attain that ability. Angiogenesis is guided by a balance of stimulatory and inhibitory signals. The prototypical stimulating factor is vascular endothelial growth factor (VEGF) and its receptor on endothelial cells which have *tyrosine kinase* activity. A typical inhibitor is thrombospondin-1. Integrins and adhesion molecules mediating communication between cells and extracellular matrix also play a role with quiescent vessels expressing one class of integrins, while sprouting capillaries express a different class of integrins. The angiogenic ability of tumors appears to be activated at mid stage with the flip of a switch—when the balance is tipped in favor of angiogenic stimulation.

The blood vessels in tumors are not normal; they are aberrant, convoluted, erratic, leaky, distorted, and often enlarged. The switch is turned on to varying degrees in different tumors, with some hypovascularized (e.g., pancreatic ductal adenocarcinoma) and others highly angiogenic (e.g., pancreatic neuroendocrine). Occasionally, the dominant oncogenes (e.g., *ras* and *Myc*) can upregulate angiogenesis—suggesting that one transforming agent may be responsible for more than one hallmark. In other tumors, the angiogenic switch may be produced indirectly by immune inflammatory cells. Considering the perioperative period, the role of opioids in modulating angiogenesis in cancer biology remains debated with a preponderance of studies suggesting a clear pro-tumor angiogenic role yet others suggesting anti-angiogenic [21, 22]. Surgical trauma produces localized areas of ischemia which are known to induce secretion of hypoxia-inducible factor (HIF)—a known stimulator of angiogenesis. Surgical stress as manifested by beta-adrenergic stimulation has also been shown to upregulate VEGF—motivating perioperative physicians to consider therapies that reduce that stress (e.g. beta-blockers and neuraxial anesthesia) [23]. Volatile anesthetics have been found to increase expression of HIFs as well as VEGF [10, 24]. In contrast, propofol was found to inhibit HIF-1 activation in a prostate cancer cell line [24].

Activating Invasion and Metastasis

Primary tumors produce cells that move to distant sites finding new homes—metastases, the cause of 90% of human cancer deaths [25]. Normal cells exist in their microenvironment by tethering to cells and stroma via cellular adhesion molecules (CAMs). In the case of epithelial cells, E-cadherin keeps cells together and fixed on the basement membrane. This interaction not only maintains normal organ structure but conveys antigrowth signals. Losing functionality of CAMs is important in the development of tissue invasion and metastasis (e.g., N-CAM becomes less adhesive in Wilms' tumor and neuroblastoma [26]). Integrin expression is also critical in maintaining normal relationship with the surrounding stroma. Changing integrin expression by cancer cells to favor adherence to degraded stromal elements aids in metastasis. The proteases that degrade stroma are also upregulated with inhibitors of proteases downregulated. Stromal and inflammatory cells are often the source of the proteases aiding in invasion and metastasis.

Invasion and metastasis is a multistep process beginning with local invasion, then intravasation of cancer cells into blood and lymphatic vessels, transit through the system, extravasation into the parenchyma of a distant site, formation of a micronodule, and finally growth into macroscopic tumors. The epithelial-to-mesenchymal transition (EMT) is a process normally found in embryologic development; cancer cells can transiently activate this program to allow for invasion and metastasis. The cells lose adherens junctions, convert to fibroblast-like shapes, express proteases, increase motility, and are more resistant to apoptosis. Interestingly, cells at the margins of cancer may have undergone epithelial-mesenchymal transitioning while cells at the core have not—suggesting distinct microenvironmental stimuli governing different aspects of the tumor.

Crosstalk with stromal cells contributes to invasion and metastasis. Mesenchymal stem cells (MSCs) in the tumor stroma have been found to stimulate invasiveness. Tumor associated macrophages (TAMs) can foster invasion by supplying proteases. It is conceivable that the capability to invade and metastasize is acquired and not the result of any new mutation beyond that required for initial tumor growth.

Once disseminated into a new home, cancer cells may revert to a non-invasive state via the reverse process of mesenchymal-to-epithelial transition (MET) without the presence of the same EMT-inducing signals of the primary tumor. In addition to mesenchymal invasion, collective invasion involves growth into adjacent tissues often without metastasis such as seen in squamous cell carcinomas.

Metastasis involves dissemination of cells into a new environment and then adaptation of these cells to the environment to evolve into a successful colonization. The timing of this process varies widely. Some tumors may actively suppress

the growth of metastasis as evidenced by the explosion of metastasis after the resection of a primary tumor. Other metastases may remain dormant for decades after primary resection before becoming clinically apparent, e.g., breast and melanoma—suggesting a prolonged period of evolution to solve the problem of colonization. Each disseminated cancer cell may need to develop new hallmarks such as angiogenesis to survive in the new microenvironment. It is possible for disseminated cell colonies to disseminate further, even returning to the primary tumor—potentially modifying the genotype and phenotype of the primary tumor. Most solid tumor patients are known to have circulating tumor cells (CTCs); increasing counts of CTCs portend worse prognosis [27, 28]. Perioperative events (surgical manipulation, surgical stress, and anesthetic agents) may boost the level of CTCs during resection—increasing the chances of seeding metastatic cancer cells at distant sites. The concurrent inflammatory and immunosuppressant changes (discussed below) during the perioperative period produce a fertile environment for either CTCs or dormant micrometastases, as mentioned previously. Enzymes synonymous with local invasion are the matrix metalloproteinases (MMPs), degrading the local matrix allowing for tumor cell migration. MMPs have been found to be elevated by tumor associated inflammation, adrenergic stimulation (surgical stress), and exposure to volatile anesthetic agents [10, 23, 29]. Propofol has been shown to downregulate MMP expression [30]. Tissue injury at the time of surgery activates platelets for the purposes of hemostasis and neutrophils for repair, but activated platelets and neutrophils can mask CTCs from the immune system either by cloaking by platelets or trapping by neutrophil extracellular traps (web-like traps in the sinusoids of the liver) [3••]. Organs with high-volume low-flow circulation like the liver and lung make ideal resting spots for cloaked CTCs.

Enabling Characteristics and Emerging Hallmarks

Enabling Characteristic: Genome Instability and Mutation

Human cells have a remarkable ability to maintain genomic integrity with DNA monitoring and repair enzymes. The fact that mutations do arise resulting in cancer argues that cancer genomes must acquire increased mutability in order for tumor progression. Key in this caretaker system is the p53 tumor suppressor gene and its pathway, which is lost in some way in the majority of human cancers. Genomic instability is the means by which cancer cells obtain these other hallmarks. Increased mutability occurs through the breakdown of the genomic maintenance machinery as mentioned above. The responsibilities of this

system include detecting DNA damage, repairing DNA damage, and inactivating mutagenic agents prior to DNA damage. Defects in this system are advantageous to tumors by accelerating the rate of evolution of premalignant cells into cancer cells with favorable genotypes. This enabling characteristic allows cancer cells to acquire hallmark capabilities. Demethylation can activate tumor suppressor genes, restoring anti-tumor activity. Lidocaine has been shown to demethylate DNA breast cancer cells in vitro [31, 32]. In vitro experiments with isoflurane-treated human neuroglioma cells and mice brains revealed DNA damage in part by manipulation of the p53 pathway [33].

Enabling Characteristic: Tumor-Promoting Inflammation

The presence of an inflammatory infiltrate in tumors has long been recognized. More recently, immune cells have been found to display profound tumor-promoting effects. Inflammatory cells have been implicated in aiding tumor cells acquire numerous hallmarks such as sustaining proliferative signaling, inducing angiogenesis, avoiding cell death, and activating invasion and metastasis. Immune cells can also release reactive oxygen species, a known mutagenic agent, which can further mutate cells toward a malignant state. Inflammation during the perioperative period is unavoidable as a result of surgical wounding. However, the degree of inflammation may be proportional to the degree of surgical stress, stimulation, adrenergic stimulation, and/or anesthetic management. Inflammatory cells directly secrete tumor promoting agents such as VEGF and MMPs. As such, COX-2 inhibitors have been advocated as important in perioperative analgesic regimens [34••]. The inflammation present also mediates the immune response (discussed below). Propofol has anti-inflammatory effects including suppression of inflammatory mediators such as PGE₂ [35, 36].

Emerging Hallmark: Reprogramming Energy Metabolism

Most of our cells utilize glycolysis to convert glucose to pyruvate and subsequently oxidative phosphorylation in the mitochondria to generate ATP for cellular energy. Many cancer cells limit their energy metabolism to glycolysis only. Cancer cells compensate for this decreased efficiency of energy production by increasing expression of glucose transporters—as is seen by positron emission tomography (PET) scans. One potential rationale for cancers choosing this pathway is to allow for the diversion of glycolytic pathway metabolites to be used in the biosynthesis of other necessary compounds (e.g., nucleotides and amino acids).

Emerging Hallmark: Evading Immune Destruction

Our immune system functions normally to inhibit the development of tumors. Indeed, cancer cells that are highly immunogenic are culled leaving behind cancer cells that are weakly immunogenic; this process is known as immunoediting. In this way, the tumor is made of cells that are weakly immunogenic and less prone to destruction by the immune system. Cancer cells may also directly inhibit cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells by secreting immunosuppressive agents. The recruitment of other inflammatory cells which are immunosuppressive (e.g., regulatory T cells, T_{regs} , and myeloid-derived suppressor cells, MDSCs) is another way cancer cells can evade immune destruction. The perioperative period is marked by immunosuppression; surgical stress induces adrenal release of glucocorticoids and catecholamines. This results in a reduction in the level and efficacy of cellular mediated immunity, i.e. natural killer (NK) cells and cytotoxic T lymphocytes (CD8+), and a relative increase in tumor promoting cells (T_{reg}) and $T_{\text{H}2}$ cells [34••, 37]. As stated above, inflammatory mediators play a role in the immune response; PGE_2 influences melanoma cells to alter receptors to avoid NK cell destruction [38]. Anesthetic technique directly influences immune cell composition as seen in a randomized trial of breast cancer patients comparing a balanced volatile technique with propofol-paravertebral block; the propofol group had increased levels of NK cells and helper T cells [39]. Propofol has also been shown to preserve NK cell activity compared to volatile anesthetics [40]. Blocking inflammation and adrenergic stimulation with NSAIDs and beta-blockers in patients undergoing breast cancer surgery has been shown to preserve NK cell activity and reduce monocyte (macrophage precursor) production perioperatively [41].

The Tumor Microenvironment

Cross talk with the ancillary cells present in the stroma has been recognized as a crucial component of cancer biology. Cancer stem cells (CSCs) remain elusive in their phenotype and origin but are likely to be closely related to the EMT programming and self-renewal capacity that is important in cancer dissemination. Some evidence points to CSCs as resistant to chemotherapy and may be able to maintain in a prolonged dormant state. Other studies suggest the ability of cancer cells to differentiate into their own stromal cells necessary for support (e.g., endothelial cells and cancer-associated fibroblasts). With increased mutability, intratumoral genetic heterogeneity allows for creation of subpopulations of cells each with separate yet complementary roles important for overall tumor growth.

Cancer-associated fibroblasts represent the preponderant cell type. Fibroblasts secrete components of the extracellular matrix and are likely responsible for the desmoplastic stroma seen in late stage carcinomas. The role of inflammatory cells of the immune system has been discussed above. The balance of the conflicting immune inflammatory response (tumor antagonizing vs promoting) may prove to be important in prognosis and guiding therapy. Endothelial cells in tumors have different expression profiles and cell surface markers compared to normal blood vessels. Pericytes are cells that normally support blood vessels; tumor blood vessels are supported less by pericytes—leading to decreased vascular integrity. Progenitor cells or stem cells of the normal non-cancerous stroma must also be considered a source of the new tumor microenvironment, either by proliferation of stroma cells, differentiation of pre-existing stem cells, or recruitment of bone marrow derived stem cells.

The complex interactions between these cells and tumor cells are dynamic. Both stromal cells and cancer cells change in the progression toward tumor development. New neoplasias recruit stromal cell types into a neoplastic stroma, which in turn further develops the phenotype of the cancer. Continued feedback between cell types eventually allow cancer cells to invade adjacent tissue and disseminate to distant sites. A similar signaling paradigm will subsequently be set up with metastatic cancer cells and the new microenvironment.

Summary

The advantages of targeted therapy include specificity and theoretically less toxicity. However, responses have been found to be transitory as cancer cells may become less dependent on one hallmark (e.g., angiogenesis) and more likely to exhibit another (e.g., direct invasion into normal blood vessels for oxygen and nutrient extraction). This adaptive response has been seen in glioblastomas treated with antiangiogenic agents. Targeting multiple hallmarks and characteristics may be the key to more durable responses to cancer therapy.

Patients on hallmark-specific therapies are encountered far more frequently in the perioperative period. Tyrosine kinase inhibitors, such as erlotinib, sorafenib, and sunitinib, are small molecule drugs that share a mechanism of action on receptors of different function—EGF receptor and VEGF receptor. Immune checkpoint inhibitors, such as ipilimumab and nivolumab, are inhibitory antibodies specific to checkpoint molecules used by cancer cells to trick the immune system into inhibiting a T cell attack. Other common antibodies specific to hallmarks widely used include bevacizumab, specific to VEGF, and cetuximab, specific to EGFR. Understanding the mechanism of action of targeted therapies and the

influence of perioperative factors on cancer biology will be important for perioperative clinicians to optimally care for the surgical patients minimizing complications and possibly improving outcomes.

Compliance with Ethical Standards

Conflict of Interest Jonathan A. Wilks declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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