Introduction to cancer biology

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CHAPTER 1

Introduction to cancer biology

1. Tumor biology

Cancer is a heterogeneous multifactorial disease and a primary cause of death worldwide. As with normal conditions, various codependent networks, including cellular, tissular, and organismic layers, are involved in the cancerization of normal tissues and even human bodies (systemic disease). Geographically, malignant tumors are formed by three different cancer tissues: the primary tumor, local metastasis, and distant metastasis [1]. Considering a Darwinian view of cancer development, Peter Nowell [2] proposed that colony formation of cancer cells occurred through gradual selection and expansion of the advantageous properties of malignant cells with specific, heritable genetic aberrations. The genome, somatic mutations, and epigenetic modifications are the focus of investigations of the cancer process. In addition, identifying nonsilent somatic mutations in phenotypically normal cells and participating stromal cells, immune cells, and tissue-relevant processes (e.g., angiogenesis) provides ideas for considering a broader study of cancer at tissue and organismic levels [1].

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Historically, the hallmarks of cancer were presented in several studies by Hanahan and Weinberg [3], who organized cancer biology into six major hallmarks: self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Over time, Hanahan and Weinberg [4] updated their views, and 6 years later, Fouad and Aanei [5] updated the picture of cancer hallmarks and presented other cancer-associated hallmarks, such as altered stress response favoring overall survival, the metabolic rewiring and abetting microenvironment, and immune modulation. According to evolutionary mechanisms, Alkhazraji et al. [6] recently re-presented promising hallmarks such as extensive genomic and epigenetic diversification, resistance to cell death, modulation of the modulatory microenvironment, and cellular plasticity. In this chapter, we present tumor biology that covered all the hallmarks studied to date.

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Additionally, we describe novel tumor-associated/derived concepts and components that contribute to validating the hallmarks of tumor biology.

1.1 Cancer hallmarks

1.1.1 Constitutive proliferation

Cell proliferation refers to increases in cell number due to cell growth and division. The proliferation and growth of normal cells are regulated by releasing growth-promoting signals in a controlled manner to provide homeostasis under normal conditions. However, deregulating these signals in cancer cells gives them a survival edge and ensures higher proliferative capacity. The sustained proliferation of cancer cells occurs by binding growth factors/ligands to their cell-surface receptors, which contain intracellular tyrosine kinase domains to promote intracellular signaling pathways that induce cell cycle progression and cell growth. Cancer cell-derived growth factor ligands also bind to the receptors themselves (i.e., autocrine signaling) or to tumor-associated stroma (i.e., paracrine signaling) to sustain growth-promoting signal activation [4].

Elevated frequencies of DNA replication-associated errors and distinct somatic/chromosomal mutation signatures in cancerous cells result in constitutive receptor activation and overexpression, aberrant signaling, and impairment of receptor degradation machinery [5]. The deletion and point mutations that cause *EGFR* (epidermal growth factor receptor) amplification and overexpression cause rapid growth, metastasis, and invasion in highly aggressive lung tumors [7]. Mutationally activated *B-Raf* due to substitution of glutamic acid for valine at amino acid 600 (V^{600E}) impairs B-Raf protein function, thus resulting in excessive activation of the downstream proliferative mitogen-activated protein kinase pathway in melanoma, glioblastoma, and thyroid, lung, and colon cancers [8]. Additionally, defects in negative-feedback mechanism-driven homeostatic regulation due to such mutations in *ras* gene such as oncogenic genes lead to hyper-Ras GTPase activity and enhance proliferative signaling [9]. Promoter methylation in PTEN is considered a loss-of-function mutation that causes amplified phosphoinositide 3-kinase (PI3K) signaling and promotes tumorigenesis in human cancers [10]. Moreover, activated PI3K induces ATP production by stimulating the mechanistic target of rapamycin, a coordinator of cell growth and metabolism that supports cell proliferation. Together, the promotion of cell division rates and inhibition of cell cycle arrest or apoptosis ensures unchecked cancer cell growth and tumorigenesis.

1.1.2 Insensitivity to antigrowth signals

Besides sensitivity to growth-stimulatory signals, cancer cells evade the effects of tumor suppressors that otherwise limit uncontrolled cell proliferation through transducing checkpoint or growth-inhibitory signals or by activating senescence and apoptotic programs. The loss-of-function mutation in inhibitory effectors such as retinoblastoma allows cancer cells to progress to replication with further newly acquired DNA aberrations as well as genomic instability and tumor heterogeneity [11]. Apoptosis inducers such as TP53 protein can halt further cell cycle progression under intracellular stress conditions (e.g., insufficient nucleotide pools, glucose, or oxygenation) or trigger apoptosis while facing irreparable damage of the cellular subsystem (e.g., after chemical exposure, UV irradiation, or oncogene activation) [12]. Therefore, any mutation in p53 gene encoding leads to uncontrolled division and accelerated proliferation.

Once cancer cells proliferate, highly dense populations of cells further reduce cell proliferation due to "contact inhibition." However, this homeostatic mechanism is abrogated during tumorigenesis. *NF2* gene coding merlin protein, as a tumor suppressor, provides contact inhibition through coupling cell surface-adhesion molecules (e.g., E-cadherin) to transmembrane receptor tyrosine kinases (e.g., the epidermal growth factor receptor) [13]. The loss-of-function mutation in the *NF2* gene leads to loss of contact inhibition and triggers a form of human neurofibromatosis [14]. Additionally, LKB1 epithelial polarity protein, as a tumor suppressor, maintains tissue integrity, and its downregulation causes Myc oncogene-induced transformation [15].

1.1.3 Resistance to cell death mechanisms

Usually, cell death through any natural mechanism such as necrosis, apoptosis, necroptosis, and autophagy should work as a barrier to cancer development. Yet pathways for cell death are attenuated or abrogated in those tumors that succeed in progressing to states of high-grade malignancy and resistance to therapy. Apoptosis or programmed cell death is characterized by the activation of caspases, which cleave cellular substrates, and through multistep processes, the dying cells are broken into apoptotic bodies that are taken up by phagocytic cells without triggering inflammation [16]. Tumors evade apoptosis through overexpression of antiapoptotic regulators (i.e., Bcl-2, Bcl-xL) or downregulating proapoptotic factors (i.e., Bax, Bim, Puma) and caspase proteins. Bcl-2 mediates the apoptotic signals from the upstream regulators and downstream effector components

that the chromosomal translocation t [8,14] driving Bcl2 overexpression was cell documented and observed in follicular lymphoma. TP53 tumor suppressor function in response to irreparable DNA damage induces apoptosis that causes loss of TP53 or perturbates the apoptosis-inducing circuitry [4].

Autophagy begins with the engulfment of cytoplasmic materials in the autophagosome, followed by fusion with lysosomes to form the autolysosome. Thereafter, autolysosome-associated catalytic enzymes degrade the cargoes, and by-products are recycled into the cytosol to maintain cellular homeostasis and survival [17]. The intrinsic stress such as hypoxia, nutrient deprivation, pH changes, and extrinsic insults such as chemotherapy and radiotherapy act as inducers of autophagy in cancer cells, further assuring tumor cell survival, treatment resistance, and cancer relapse [18]. On the other hand, the autophagy machinery is linked to apoptosis, and inhibitors of apoptosis similarly inhibit autophagy and thus ensure cancer cell survival. The deletion or loss of beclin (encoding an essential autophagy protein) was indicated in breast, ovarian, and prostate cancer cases and attributed to the role of autophagy in eliminating damaged mitochondria during periods of stress, reducing the burden of reactive oxygen species (ROS) [17].

Apoptotic cells are progressively disassembled and then consumed by its by phagocytic cells. In contrast, necrosis is thought to be independent of the activity of caspase. In the end, necrotic cells become bloated and explode and release their contents, such as proinflammatory signals, which are followed by recruiting the inflammatory cells of the immune system into the surrounding tissue microenvironment. In neoplasia, inflammatory immune cells contribute to cancer progression by promoting angiogenesis, cancer cell proliferation, and invasiveness. Necrotic cell-derived high mobility group 1 (HMGB1) protein and interleukin (IL)-1α induce tumor-promoting inflammation and proliferation of tumor-supportive cells, respectively [19,20]. Moreover, necrotic tumor cell-released potassium suppresses the antitumor immunity CD4 and CD8 T cells [16].

Necroptosis and ferroptosis are two types of regulated necrosis that act as alternative ways to eradicate apoptosis-resistant cancer cells. When apoptosis is blocked, tumor necrosis factor triggers certain cells to undergo regulated necrotic cell death by a caspase-independent process termed necroptosis [16]. One study reported radiation-induced lung tumor cell necroptosis followed by the release of immune-activating HMGB1 from necroptotic cells [21]. While promising, it seems that necroptosis possesses both tumor-suppressive and tumor-supportive effects, and similar to necrosis, necroptotic cells trigger inflammatory responses. Thus, induction

of necroptosis for cancer therapy elevates antitumor immunity responses [16]. Finally, ferroptosis is an iron-dependent form of cell death and occurs through excessive peroxidation of polyunsaturated fatty acid-containing phospholipids in mammalian cell membranes [22]. Therefore, ferroptosis inducers create high expectations for potential cancer therapy strategies based on ferroptosis induction. Ferroptosis is regulated by p53, and thus, any dysregulation in this cooperation gives cancer cells a survival benefit under metabolic stress due to lipid oxidation [22].

1.1.4 Evading replicative-induced mortality

Cancerous cells escape from limited proliferation elucidated by senescence and crisis/apoptosis. Senescence is defined as the process of irreversible exit from the cell cycle and occurs against cellular stress such as nontelomeric DNA damage (e.g., ROS accumulation) and telomeric DNA damage due to shortening of telomeres after exhaustion of replication potential. Cancer cells overwhelm telomere erosion through overexpression or reexpression of the components of the telomerase complex that are capable of protecting and reconstituting the telomeric ends and maintaining sufficient length for further replication [23]. Telomerase is a specialized DNA polymerase that adds telomere repeat segments to the ends of telomeric DNA absent in nonimmortalized cells but significantly reexpressed in cancer cells as spontaneously immortalized cells. Therefore, telomerase activity resists cancer cells against proliferative barriers, including senescence and apoptosis. Moreover, the noncanonical role of telomerase is relevant to its protein subunit, named telomerase reverse transcriptase (TERT) that amplifies proliferative-inducer signaling pathways (e.g., WNT and MYC pathways) [24] and induces activation of the antiapoptotic NF-kB signaling pathway [25]. TERT also suppresses antiproliferative signaling induced by the TGF-β pathway [23] and provides stemness and metastasis through induction of epithelial–mesenchymal transition (EMT)-relevant markers in stemlike cancer cells [26]. Overall, telomerase plays a protective role in the genetic integrity and propagation of a given advantageous cancer cell clone (Fig. 1.1).

1.1.5 Inducing vascularization

Angiogenesis is a biological process through which new blood vessels are shaped from preexisting vasculature. Like normal tissue, tumorigenesis demands the sustained ingrowth of blood vessels to provide oxygen and nutrients and to remove waste products. Angiogenesis occurs through several major, sequential steps: (1) proteolytic enzyme-induced degradation

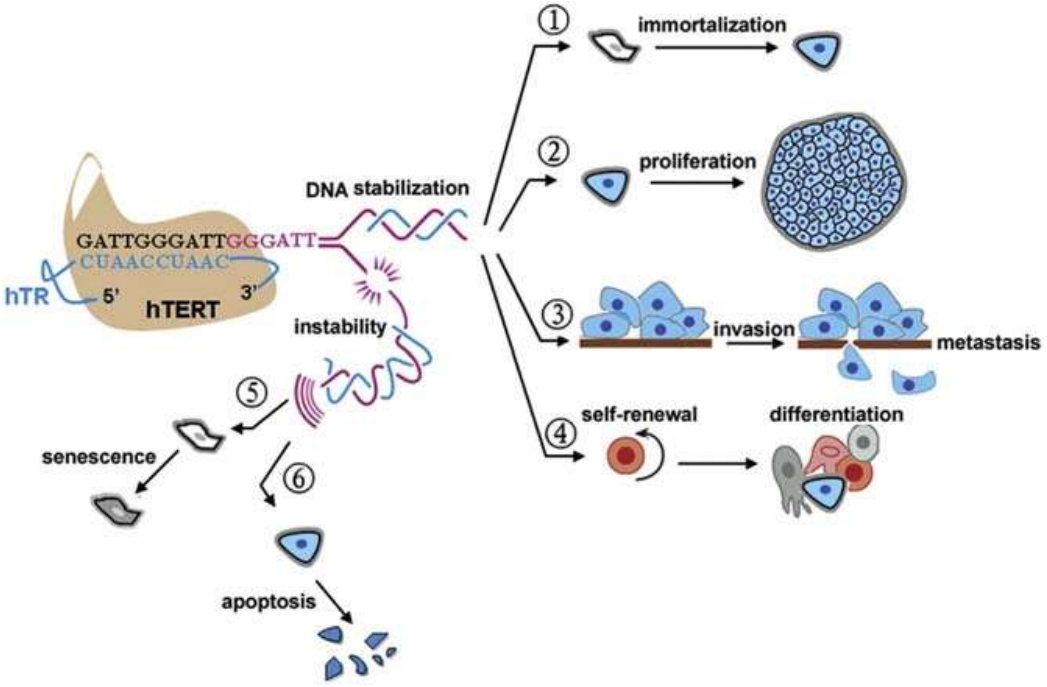

Figure 1.1 Reexpression of TERT provides cancer cell survival through several pathways including (1) immortalizing primary human cells; (2) insuring tumor cell proliferation; (3) inducing invasion and metastasis; and (4) providing stemness and pluripotency; targeting TERT results in telomere loss and (5) nonprevention of stress-induced senescence in normal cells; and (6) tumor cell apoptosis. *(Copy from Lü M-H, Liao Z-L, Zhao X-Y, Fan Y-H, Lin X-L, Fang D-C, et al. hTERT-based therapy: a universal anticancer approach. Oncol Rep 2012;28(6):1945−1952).*

of extracellular matrix (ECM) components surrounding the blood vessels; (2) activation, migration, and proliferation of endothelial cell (ECs); and (3) transformation of ECs into tube-like structures and formation of capillary tubes, followed by the formation of novel basement membranes [28].

Angiogenesis demands the cooperation of several cell types, soluble angiogenic factors, and ECM components and is regulated by pro- and antiangiogenic effectors. Once tumorigenesis occurs, proangiogenic signaling dominates antiangiogenic signaling; this change is termed the "angiogenic switch" [29]. At the molecular level, proangiogenic factors including vascular endothelial growth factor (VEGF), tip cell-produced Delta-like-4 ligand, platelet-derived growth factor-B (PDGF-B), fibroblast growth factor 2 (FGF-2), angiopoietins, matrix metalloproteinase (MMP), ephrins, apelin, and chemokines support angiogenic switching through the transformation of quiescent ECs into ECs proliferative toward new blood vessel formation. For example, stroma- and tumor cell-derived

VEGFs bind and activate VEGF receptor-2 on ECs, which induces EC proliferation and angiogenesis. Tumor cell-derived MMPs induce remodeling of the ECM to facilitate tumor-associated angiogenesis. Myeloid-derived suppressor cells secrete CCL2, CXCL8, CXCL2, and CXCL12 ligands, which bind to their receptors on tumor ECs and increase angiogenesis [18,30]. Tumor-associated fibroblasts and mesenchymal stem cells are present in secret tumor niche VEGF, MMPs, and CXCL12 that can more provide neovascularization [18]. The aforementioned proangiogenic factors are produced by immune cell lymphocytes, neutrophils, and macrophages in tumor niches and influence angiogenesis. Finally, hyperproliferation of tumor cells induces hypoxic conditions due to increased oxygen consumption. Responding to hypoxia, hypoxia-inducible factors (HIFs, HIF-α, and HIF-β) mediate the upregulation of genes encoding VEGF, FGF, and PDGF leading to rapid flipping of the angiogenic switch for promotion of neovascularization and angiogenesis [30].

1.1.6 Tumor invasion and metastasis

Tumor metastasis is a dynamic biophysical process triggered by the dissemination of invasive tumor cells with an unstable genome. They have undergone ECM remodeling, the downregulating of E-cadherin, upregulating of N-cadherin, and transient emerging of the EMT process (Fig. 1.2). Therefore, they lose their polarity and cell−cell/matrix adhesion [32]. Primary tumor cell-secreted MMPs and the proteolytic urokinase-type plasminogen activator system induce ECM remodeling to trigger invasion. Moreover, primary tumor-released extracellular vesicles such as exosomes carrying and displaying invasion-promoting factors that drive metastatic properties induce EMT and ECM remodeling and promote tumor cell resistance to apoptotic signals [33]. After that, invasive cells detach from the primary tumor site and enter the peripheral blood (or intravasation) as circulating tumor cells (CTCs) in both single and cluster forms to migrate toward distant sites to drive metastatic tumor formation [31]. Sometimes, CTC-derived VEGF, MMPs, and IL-8 mediate the extravasation and seeding of CTCs at primary tumors in a "tumor self-seeding" process [31,34,35].

Collective intravasation and migration of CTC clusters (groups of >2 CTCs) demand cell−cell junction formation that is supported by upregulation of stemness and EMT markers and tight junctional proteins such as claudin-11 in single CTCs [31,36]. Compared with single CTCs, heterogenous clusters indicate higher metastatic potential due to their

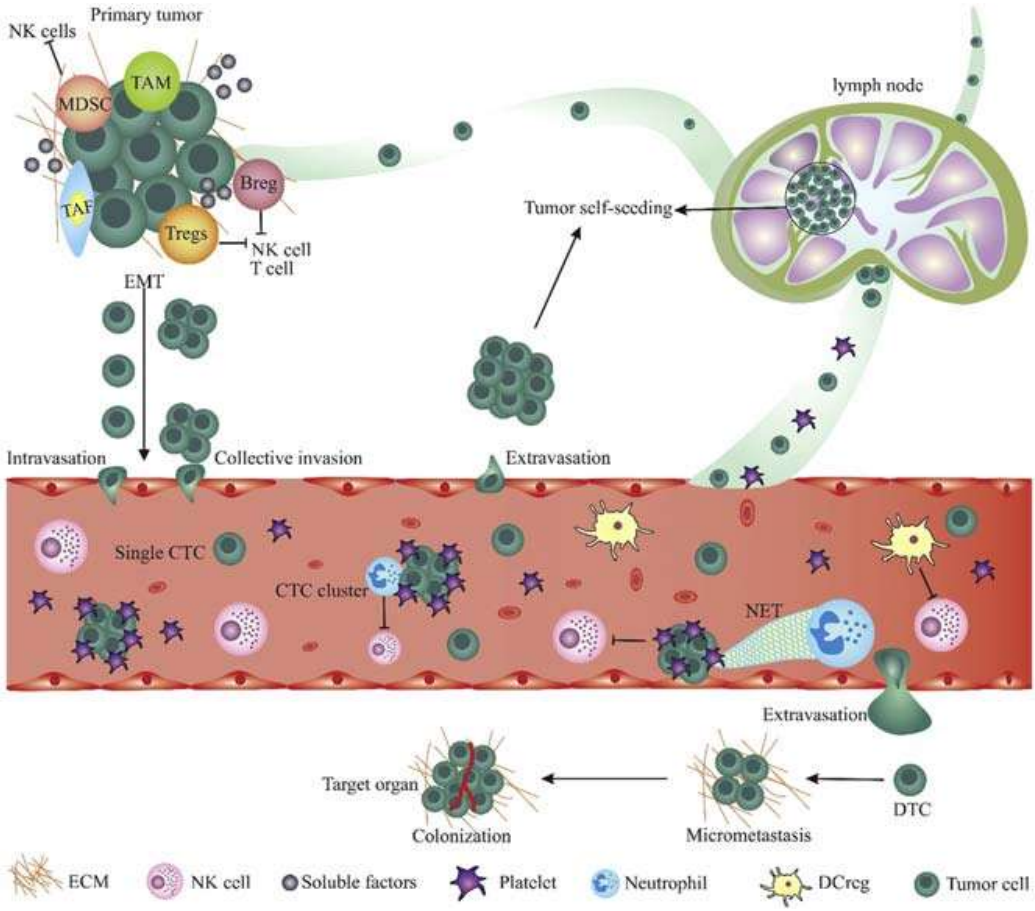

Figure 1.2 Metastasis and immune evasion of CTCs to induce tumor metastasis. Immune-resistant tumor cells detach from the primary tumor under the EMT process and ECM remodeling in both single and cluster forms. CTCs may reenter in local areas and lymph nodes to induce tumor self-seeding or pass intravasation to transfer to distant organs through the bloodstream after extravasation from micrometastasis and macrometastases. Immune-mobilized cells associated with CTC clusters provide protection against shear stress and immune cell cytotoxicity, and at distant sites, they facilitate CTC extraversion. Abbreviations: *Breg*, regulatory B cell; *DCreg*, regulatory dendritic cell; *DTC*, disseminated tumor cell; *ECM*, extracellular matrix; *EMT*, epithelial–mesenchymal transition; *MDSC*, myeloid-derived suppressor cell; *NET*, neutrophil extracellular trap; *TAF*, tumor-associated fibroblast; *TAM*, tumor-associated macrophage. *(Copy from Dianat-Moghadam H, Mahari A, Heidarifard M, Parnianfard N, Pourmousavi-Kh L, Rahbarghazi R, et al. NK cells-directed therapies target circulating tumor cells and metastasis. Cancer Lett 2021;497:41–53).*

colony-forming potential and higher survival against blood pressure and the immune system exerted by stromal and immune cells such as macrophages, fibroblasts, and neutrophils, and platelets [32] (Fig. 1.2).

Low shear stress and size limitations (CTCs of up to 20 μm in diameter vs. capillaries of ~3 to 7 μm), VEGF, exosomes, and MMPs all provide

CTC extravasation through EC and ECM remodeling at distant sites. The mesenchymal–epithelial transition process restores cellular traits of the primary tumor and provides collective migration of clusters to colonize at distant organs and create disseminated tumor cells (DTCs). Organotropism of DTCs must adapt to the premetastatic niche, where they are exposed to interactions with stroma cell types, resident niche cells, exosomes, ECM proteins, and deleterious signals [33]. Finally, DTCs may act as metastasis-initiating cells, generate micrometastatic lesions, and create minimal residual disease. Existing stressful stimuli and inter-DTC stemness markers may remain in dormant states for years or decades until reemerging to form macrometastases and induce metastasis [31,32].

1.1.7 Immunomodulation

The innate and adaptive immune system should eradicate or at least control tumor cell activity. The cross-talk between immune cells and tumor cells reaches a dynamic equilibrium to restrain tumor progression. However, suppressing antitumor immune responses and inducing an immune-suppressive tumor microenvironment (TME) leads to clonal selection and evasion of immune effector-resistant tumor cells [32]. $CD8^+$ cytotoxic T cell (CTL)- and $CD4^+$ helper T (Th)1 cell-produced interferon-γ/cytotoxins are expected to suppress cancer development; however, over-activation of immune cells causes inflammation and promotion of cancers such as those documented for the hepatitis B/C viral-induced inflammatory state and that appear in hepatocellular carcinoma [37]. Tumor-supportive immune cells such as regulatory T cells (Tregs), MDSCs, and M2 macrophages exert tumor immune escape by creating an inflammatory TME, suppressing CTL, and upregulating VEGF, TGF-β, and IL-10, all of which are mediators of antitumor-immune suppression, angiogenesis, and metastasis (Fig. 1.2). VEGF, IL-10, and TGF-β are known as inhibitors of the differentiation of progenitor cells into mature dendritic cells (DCs) [38]. In addition, TGF-β and IL-10 promote immune escape by inducing the differentiation of Th1 to Th2 (immune deviation) [39].

Mutational genetic changes or instability results in the production of heterogeneous tumor antigens that complicates their recognition and elimination by immune cells [40]. Moreover, cancer cells downregulate the major histocompatibility complex on T and NK cells, a receptor crucial for recognizing tumor-associated antigens and initiation of both adaptive (i.e., CTL) and innate (i.e., NK cells) immune responses [32]. Additionally, dormant cancer cells express low levels of immunogenic antigens,