Cancer Drug Discovery

Science and History

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Kyu-Won Kim
College of Pharmacy
Seoul National University
Seoul
Korea (Republic of)

Hee-Jun Wee
College of Pharmacy
Seoul National University
Seoul
Korea (Republic of)

Jae Kyung Roh
Department of Internal Medicine
Yonsei University College of Medicine
Seoul
Korea (Republic of)

Chan Kim
Department of Internal Medicine
CHA Bundang Medical Center
Seongnam
Korea (Republic of)

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Preface

This book was written with the aim to provide a comprehensive and multifaceted overview of the history of the development of anticancer drugs and to present future directions for the development of new anticancer drugs. First, this book examines the scientific progress in biological science periodically and the influence such progress had in cancer research. Furthermore, this book outlines the development process of anticancer drugs with a focus on the characteristic drug groups of each era, in relation with the advancements in the relevant fields of chemistry and biological science and also presents a brief mechanism of the drugs. After examining the side effects of each anticancer drug and the treatments for alleviating the effects, this book finally sums up the limitations of the current anticancer drugs and seeks new directions for the development of anticancer drugs.

During the last 60 years, research in biological science has centered on the cell, and cellular molecules, with an emphasis on the activities and functions of various genes. Accordingly, cancer research has also focused on cancer cells; the differences between normal cells and cancer cells, including their genetic variations, were discovered and corresponding molecule-targeted anticancer drugs developed.

The development process of anticancer drugs indicates that leukemia, which can be easily observed through the microscope, served as the model during the early days of cancer research and that the rapid proliferation of the leukemia cells was accepted as the general characteristic of cancer cells. As a result, development of anticancer drugs that have anti-proliferative effects began, starting with the alkylating agent in 1946, based on the unity assumption that all cancer cells characteristically grows abnormally. The search for a standard treatment for all cancers was launched through the development of such cytotoxic anticancer drugs.

Alkylating agents, which are one of the first types of anticancer drugs developed during this process, inhibit persistent cell proliferation, which is the representative feature of cancers, by causing DNA damage, and was developed especially during the 1940s to the early 1970s. The second type, antimetabolites, have been developed since the late 1940s and display structural mimicry with precursors of DNA synthesis, thus inhibiting cell proliferation by inhibiting activities of various enzymes contributing to DNA replication. In addition, as a result of a large-scale drug screen-

ing that began in 1954, plant alkaloids and anticancer antibiotics were developed from the 1960s and continued to be developed until the 1990s. Anticancer drug screenings on chemical molecules also proceeded at the same time, leading to the development of various chemical anticancer drugs from the mid-1960s which continued to be developed until the mid-2000s. These drugs form the third type of anticancer drugs. The fourth type of anticancer drugs, consisting of immunotherapy and miscellaneous anticancer drugs, were developed in the mid-1960s, proceeded to be developed from the 1980s to the 1990s and are still consistently being developed. Immunotherapy anticancer drugs, which activate the immune system to eliminate cancer cells, include cytokines such as interferons, humanized antibodies, and dendritic cells, while asparaginase and others were developed as miscellaneous type of anticancer drugs. Before the molecule-targeted anticancer drugs were developed, the fifth type of anticancer drugs, hormonal cancer drugs were developed for treating several cancers based on the understanding of the biological characteristics of cancers. Hormonal anticancer drugs for treating testosterone- or estrogen-dependent cancers such as diethylstilbestrol or tamoxifen were developed from the 1940s and are continued to be used today. Beginning from the 1990s, new types of molecule-targeted anticancer drugs were rapidly developed, forming the sixth type of anticancer drugs. Molecule-targeted anticancer drugs are products of in-depth biological research on cancers that was intensified from the 1980s. In other words, molecular mechanisms of tumorigenesis and malignancy were better understood by extensive research which used molecular biology as its major research technologies. In particular, various factors that play important roles in various types of cancers were discovered, facilitating the development of new drugs targeting the discovered factors. These molecule-targeted anticancer drugs are forming a major anticancer drug group starting from the 2000s.

Accordingly, this book presents an overview of the scientific discoveries and history of the development of anticancer drugs in the following order. Chapter 1 summarizes the characteristics of cancer in accordance to the development of science. This chapter describes the characteristics of the cancer cells based on the research that focused exclusively on cancer cells, similarly to biological science which mainly focuses on cells. Moreover, this chapter provided characteristics of cancer which interacts with its surrounding microenvironment. In particular, this chapter provides a systematic explanation of cancer in relation with the vascular system, lymphatic system, and immune system, which also relates to the new research prospects presented in the final chapter of this book. Chapter 2 examined the relation between the development of biological science since the advent of the cell theory in 1838 with the corresponding history of cancer research and development of anticancer drugs and summarized the relation through a chronological table. Chapter 3 provided images that explain a historical background of cancer chemotherapy and describe chronologically the developmental history of screening systems of anticancer drugs. Chapters 4–9 classified the characteristics and effects of approximately 160 anticancer drugs, which used the screening system described in Chapter 3 for development, into 6 groups and provided a comprehensive account of the development process and history of each group. Chapter 10 provided details on the side

effects of the clinical use of the anticancer drugs introduced in Chapters 4–9, along with the drugs that can alleviate such side effects. Finally, in Chapter 11, this book provided new anticancer drugs that will be researched and developed, based on research focusing on the difference between cancer cells and normal cells which has been conducted since the 1980s. This book also suggested a cell network research for a next research methodology, based on the perspective that cancer is related with various systemic characteristics of the human body. In other words, this book emphasizes that the research on cell network of the tissue level is necessary.

This book, in short, is a review of the past and current research conducted on anticancer drugs and a proposal for a new direction of cancer research for the future. I would like to express my gratitude to Professor Jae Kyung Roh, Dr. Hee-Jun Wee, and Dr. Chan Kim for joining me as co-authors to write this book. I also thank my graduate students at the research center who helped me with the images and tables included in this book. I also extend my gratitude to Professor Seishi Murakami at the Cancer Research Institute of Kanazawa University, Japan, who has always been a source of advice and encouragement throughout the past 35 years of research on cancer. Lastly, I thank Dr. Jeong Hun Kim at Seoul National University Hospital who helped me throughout my personal ailment. This book would not have been published without their help.

Seoul, Korea Kyu-Won Kim
January, 2016

Contents

Contributors

Kyu-Won Kim

1976	College of Pharmacy, Seoul National University, Seoul, Korea B.S.
1985	University of Minnesota, Minneapolis, U.S.A. Ph.D.

Professional Training:

2000–Present	Professor College of Pharmacy, Seoul National University, Korea
2001–Present	Full member The Korean Academy of Science and Technology
2011–2012	Vice-chairman The Korean Cancer Association
1987–2000	Assistant Professor, Associate Professor, Professor Department of Molecular Biology Pusan National University, Korea
1985–1987	Postdoctoral Fellow Department of Cancer Genetics Dana-Farber Cancer Institute, Harvard Medical School, USA

Awards and Honors:

2005	Ho-Am Prize in medicine, Ho-Am Foundation
2003	The Highest Award for Korea Science, the President of Korea

Jae Kyung Roh

1973	Yonsei University, College of Medicine, Seoul, Korea M.D.
1990	Yonsei University, Graduate School, Seoul, Korea Ph.D.

Professional Training:

2014–Present	Professor Emeritus Yonsei Cancer Center, Yonsei University College of Medicine Honorary Director Cheil Hospital Women's Cancer Center, Seoul, Korea
1981–2014	Assistant Professor, Professor in Medicine Division of Medical Oncology, Yonsei Cancer Center
2008–2011	Chairman National Bioethics Committee, Korea
2006–2008	Chairman Board of Directors, The Korean Cancer Association
2005–2011	Vice President(Health Division) The Korean Federation of Science & Technology Societies(KOFST)
2000–2010	Director Cancer Metastasis Research Center, Yonsei University College of Medicine
1983–1986	Fellow in Medical Oncology Vincent T. Lombardi Cancer Research Center, Georgetown University, School of Medicine, Washington, D.C., USA

Awards and Honors:

2014	ROK Order of Service Merit (4th Class) Green Stripes

Hee-Jun Wee

1989	Pusan National University, Pusan, Korea B.S.
2003	Kyoto University, Kyoto, Japan Ph.D.

Professional Training:

2010–Present	Research Assistant Professor College of Pharmacy, Seoul National University, Korea
2006–2010	Research Assistant Professor Department of Biochemistry, School of Medicine, Chungbuk National University, South Korea
2003–2006	Research Fellow Institute of Molecular and Cell Biology, Singapore

Chan Kim

2005	Yonsei University College of Medicine, Seoul, Korea M.D.
2013	Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Korea Ph.D.

Professional Training:

2015–Present	Assistant Professor Medical Oncology, CHA Bundang Medical Center, CHA University, Seongnam, Korea
2014–2015	Clinical Fellow Yonsei Cancer Center, Severance Hospital, Seoul, Korea
2013–2014	Postdoctoral Fellow Laboratory of Vascular Biology and Stem Cells, KAIST, Daejeon, Korea
2006–2010	Residency in Internal Medicine Severance Hospital, Seoul, Korea
2005–2006	Rotating Internship Severance Hospital, Seoul, Korea

Part I
A Scientific Overview on Cancer

Chapter 1
Advancements in Life Sciences and Characteristic Features of Cancer Cells

Advances in modern life sciences have primarily focused on cellular research because of the "Cell Theory" (Schleiden and Schwann 1838), which defines the cell as the basic unit of all organisms. Since cells are the common structural unit of a variety of organisms including animals and plants, it was hypothesized that complex life phenomena of multicellular organisms could be understood by studying individual cells. Molecular-level research began in 1953, when the double helix structure of DNA—the genetic material that transmits cellular characteristics to the next generation—was elucidated by Watson and Crick. Subsequently, advances in the understanding of the functions and mechanisms of cells were made rapidly.

As molecular-level research of DNA, RNA, and proteins uncovered the mysteries of life, Monod claimed that life phenomena at the molecular level were similar in all organisms.

> What is true for *E. coli* must also be true for elephants. – J. Monod (1954)

The aforementioned statement implies that studies on unicellular *E. coli* can aid our understanding of a larger and more complex organism such as an elephant. This rationale is based on the hypothesis that the cell is the basic unit of all life forms and hence, the life phenomena of a unicellular organism are identical to those of a multicellular organism. Therefore, it was thought that the complex life phenomena of the metaphorical elephant as well as humans, our main interest, could be understood by studying them at the cellular level. Furthermore, such research could improve our understanding of fatal human diseases and consequently therapies could be offered.

This argument has been the unwavering foundation of life science research for the last 60 years. Therefore, this viewpoint has also dominated cancer research, the most studied area in life sciences to date. Consequently, wide-ranging and complex molecular mechanisms underlying cancer have been well characterized. Herein, we briefly examine the characteristics of cancer as elucidated by this approach and describe the history of the development of anticancer drugs based on these characteristics. We also discuss whether the understanding of cancer at the molecular level should be our ultimate goal.

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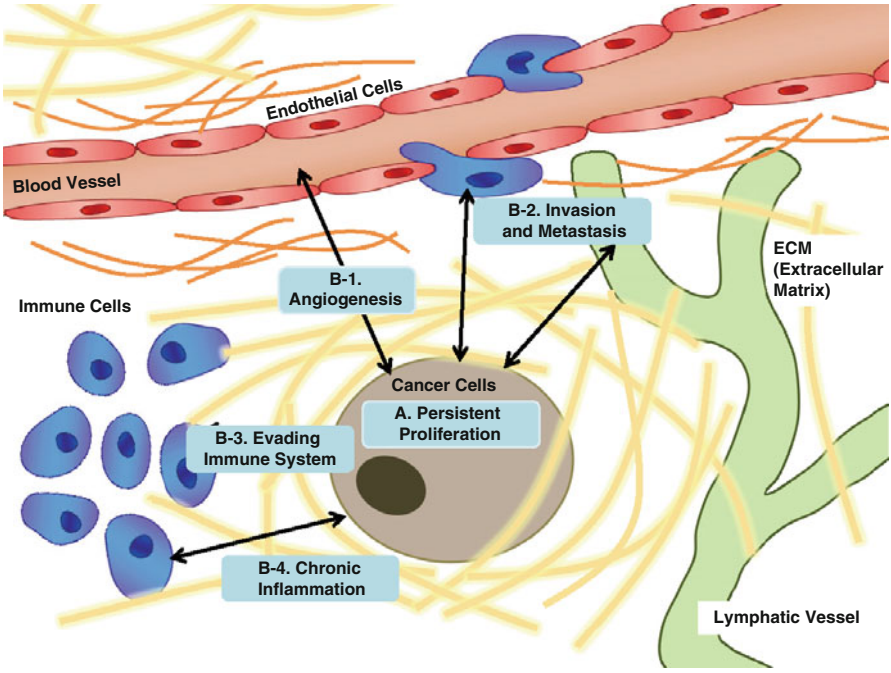


Fig. 1.1 Representative characteristics of malignant cancer. (**a**) Characteristics of cancer cells. (**b**) Properties of cancer cells are regulated by their interaction with surrounding stromal cells and a tumor microenvironment

Moreover, we discuss the characteristics of malignant cancer; these can be broadly classified into two categories, as presented in Fig. 1.1. The first category focuses on the characteristics of cancer cells, and is directly related to their continuous growth. The continuous proliferative capability of cancer cells is a result of changes perpetuated by genetic mutations in signal transduction pathways associated with cell division.

The second category of characteristics depends upon the interactions between cancer cells, neighboring cells, and the microenvironment. These characteristics include induction of angiogenesis by stimulating neighboring blood vessels, invasion of cancer cells into surrounding tissues, metastasis through the vascular and lymphatic systems, avoidance of immune cell-mediated cytotoxicity, and tumor-induced inflammatory reactions in the proximate immune cells.

Most of the currently available cytotoxic chemotherapeutics inhibit the continuous proliferation of cancer cells, and anticancer drugs with molecular targets that are under development focus on this particular feature of cancer cell. In the following section, we first briefly describe the results of research on cancer cell characteristics.

1.1 Characteristics of Cancer Cells

The representative characteristic of cancer cells is abnormal continuous growth. Among the ten hallmarks of cancer cells proposed by Hanahan and Weinberg in 2011 [1], sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, and replicative immortality are directly related to the sustained proliferation of cancer cells. In addition, since "deregulating cellular energetics" and "genome instability and mutation" are also related to the continuous growth of cancer cells, six out of the ten hallmarks are associated with abnormal growth. Therefore, the ability of cancer cells to proliferate continuously is the defining characteristic of cancer, and drugs targeting this property can be used as anticancer drugs.

The results of all the research to date on the continuous growth of cancer cells have been summarized below. Unlike normal cells, cancer cells continuously proliferate due to growth factors responsible for the proliferation and persistent activation of cell surface receptors (particularly receptor tyrosine kinases). Cancer cells continuously produce growth factors, thereby stimulating themselves and neighboring normal cells. In addition, they enhance the responses of growth factor receptors by upregulating cancer cell surface receptors and allowing receptors to function without growth factors, resulting in persistent activation of proliferation-related signal transduction processes. Activation of a persistent proliferation signal is also induced by activating mutations in downstream mediators, such as B-Raf and phosphoinositide 3-kinase (PI3-kinase). Mutations in the phosphatase and tensin homolog (PTEN) phosphatase and mammalian target of rapamycin (mTOR) kinase, which are involved in feedback regulation of cell proliferation, also contribute to the persistent proliferation of cancer cells [2] (Fig. 1.2).

Another mechanism that perpetuates the proliferation of cancer cells is the inactivation of antiproliferative factors. Factors that inhibit cell proliferation are known as tumor suppressors and mainly include the retinoblastoma (Rb) and p53 proteins [3]. These proteins are responsible for initiating cell proliferation and activating senescence as well as apoptosis. Therefore, loss of function of these proteins causes persistent cell division (Fig. 1.3).

"Contact inhibition" is another mechanism that inhibits cell proliferation, which ordinarily involves the Merlin protein encoded by the neurofibromatosis type 2 (NF2) gene [4]. Cancer cells are thought to be resistant to this particular antiproliferative mechanism (Fig. 1.4).

Additionally, evasion of apoptosis can result in the continuous proliferation of cancer cells. Apoptosis is regulated by intracellular and extracellular mechanisms; the Fas ligand/Fas receptors initiate the extracellular mechanism, while caspase 8 and 9 are involved in the intracellular mechanism. The intracellular mechanism is involved more closely in the development of cancer. Apoptosis is regulated by interactions between antiapoptotic (e.g., Bcl-2, Bcl-XL) and proapoptotic (e.g., Bax, Bim, Puma) regulators [5]. The tumor suppressor p53 induces apoptosis when DNA

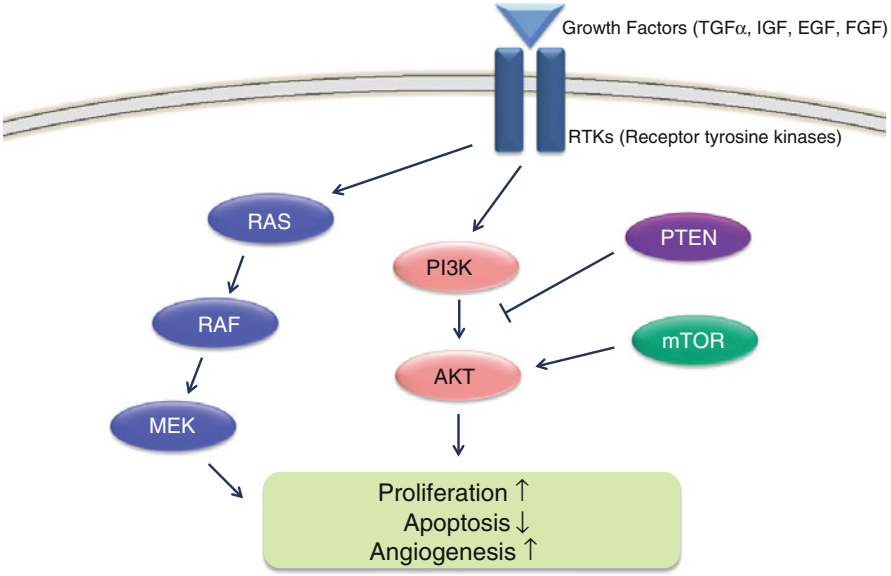


Fig. 1.2 Signal transduction pathways promote carcinogenesis. Two activated PI3K/AKT pathways in cancer cells prevent apoptosis and allow the cell cycle to progress without arresting at the G_0 restriction point, promoting cell division and proliferation. In addition, the RAS/RAF/MEK pathways are activated in cancer cells. This promotes carcinogenesis by activating cell division, preventing apoptosis, and inducing angiogenesis. Furthermore, the mTOR kinase in cancer cells activates AKT, promoting cell division and proliferation, while the PTEN phosphatase, which blocks the PI3K/AKT pathways, is suppressed. As a result, apoptosis is inhibited and abnormal cell proliferation occurs

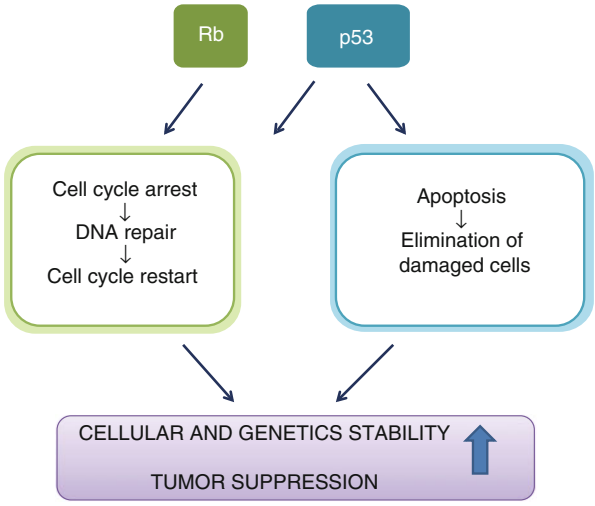


Fig. 1.3 Tumor suppression functions of Rb and p53. Rb is responsible for halting the cell cycle at the G_0 restriction point to prevent cell cycle progression in cells with DNA damage. Rb is phosphorylated when the damaged DNA is repaired, losing its ability to arrest the cell cycle, and the cell cycle resumes. p53 induces apoptosis in cells with DNA damage so that damaged cells are removed efficiently. Thus, Rb and p53 contribute to genetic stability by preventing mutations due to DNA damage and inhibiting the development of tumor cells

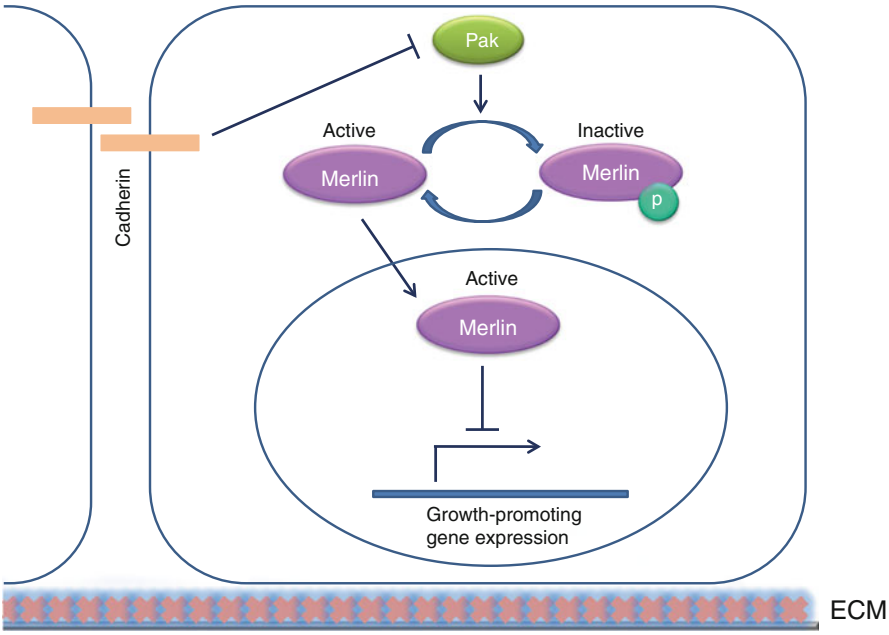


Fig. 1.4 Merlin is a tumor suppressor involved in "contact inhibition." Normal cells stop growing when they encounter neighboring cells, and cell division is inhibited. Merlin is responsible for this phenomenon called "contact inhibition." In normal cells, p21-activated kinase (PAK) activity is inhibited by cell contact, along with Merlin activation. Activated Merlin translocates to the nucleus and prevents cell division by suppressing the expression of mitogenic genes. However, abnormal proliferation can occur in cancer cells because they become resistant to contact inhibition

is damaged and an abnormal chromosome is formed. Therefore, resistance to or evasion of apoptosis in tumor cells is closely related to the dysfunction of the p53 protein, and an increase in antiapoptotic regulators (Bcl-2, Bcl-XL). Inversely, a decrease in proapoptotic regulators (Bax, Bim, Puma) can prevent apoptosis in tumor cells (Fig. 1.5).

For sustained proliferation, chromosomes have to replicate continuously and unlike normal cells, cancer cells are able to do this. Presumably, cancer cells obtain this capability through a "crisis phase" after overcoming senescence. Telomeres and telomerase activity that facilitates the addition of repeat sequences to telomeres are closely involved in this process. Increased telomerase activity or a special recombination mechanism allows cancer cells to maintain a telomere length sufficient for evading senescence or apoptosis [6]. Besides maintaining telomere length, telomerase influences cell proliferation by amplifying the Wnt pathway, and increasing DNA damage repair and RNA synthesis (Fig. 1.6).

For continuous cancer cell proliferation, abnormal expression of cell division genes is required. Abnormal expression can result from chromosomal instability and mutagenesis. Chromosomal instability is closely related to telomere damage and can cause the amplification or loss of a chromosome. An increase in mutational

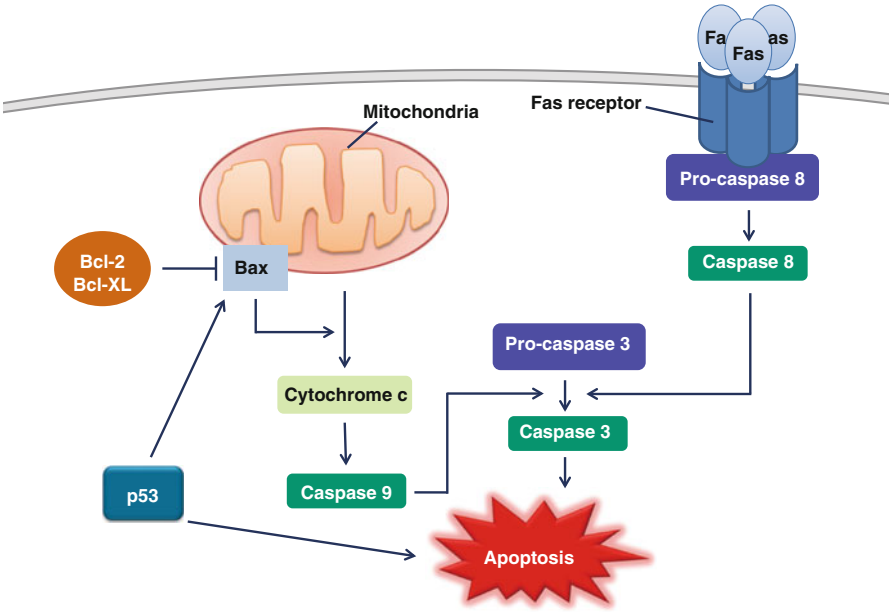


Fig. 1.5 Signal transduction in apoptosis. Apoptosis is induced by both extracellular and intracellular pathways. The Fas ligand/Fas receptor is involved in the extracellular pathway; procaspase 8 is activated to caspase 8 by Fas. The activated caspase 8 and caspase 9 which is activated by cytochrome c activate procaspase 3 to caspase 3. Activated caspase 3 in turn induces apoptosis. The intracellular mechanism is regulated by the interaction between antiapoptotic regulators and proapoptotic regulators. Apoptosis occurs as antiapoptotic regulators (Bcl-2, Bcl-XL) decrease and proapoptotic regulators (Bax, Bim, Puma, etc.) increase. Apoptosis is also induced by p53. However, the apoptosis pathways are inactivated in cancer cells, making continuous proliferation possible

load is associated with an increased sensitivity to mutagens, defective DNA repair mechanisms, or loss of the ability to remove cells harboring mutations. Chromosomal instability is increased by defective chromosome maintenance and repair, which results in frequent mutations [7]. This in turn, enables continuous cancer cell division and induces gene expression necessary for carcinogenesis (Fig. 1.7).

In addition, an energy mechanism known as the "Warburg effect" allows cancer cells to generate ATP by aerobic glycolysis even in the presence of oxygen. Because aerobic glycolysis has a very low ATP synthesis rate compared to normal mitochondrial oxidative phosphorylation, glucose uptake via the glucose transporter increases dramatically in cancer cells, allowing adequate ATP synthesis [8]. Aerobic glycolysis activates oncogenes such as RAS and MYC, which promote continuous cell division by supplying essential amino acids and nucleic acids, and enable the survival of cancer cells by increasing glycolysis in hypoxic conditions. Furthermore, aerobic glycolysis acidifies the microenvironment of cancer cells and promotes degradation of the extracellular matrix (ECM), making invasion and metastasis easier (Fig. 1.8).

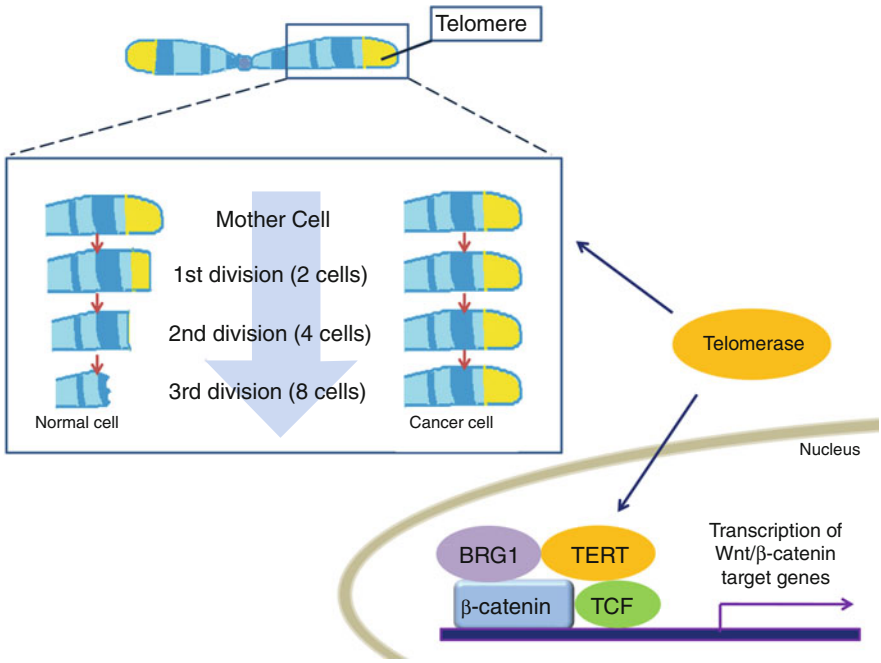


Fig. 1.6 Telomerase activation in cancer cells. Telomeres are the ends of chromosomes where the TTAGGG sequence is repeated. This sequence prevents chromosomal damage and recombination between chromosomes. Telomeres gradually shorten in each cell division and both chromosomes and telomeres are damaged after a certain number of cell division, eventually stopping cell division. All cells have the telomerase gene, which synthesizes telomeres. However, it is inactive in most normal cells and active in about 90% of cancer cells. Because this enzyme maintains telomeres in cancer cells, they are immortal and have the ability to divide continuously. In addition, telomerase promotes cell proliferation by activating the Wnt pathway

1.2 Characteristic Interactions of Cancer Cells with Neighboring Cells and the Tumor Microenvironment

1.2.1 Stromal Cells

In the last 10 years, research has shown that cancer tissue is as complex as normal tissue, which includes a variety of cells. Thus, studying individual cancer cells according to the existing reductive viewpoint has limitations. As shown in Fig. 1.9, cancer cells manifest malignancy by interacting with not only diverse neighboring cell types, but also the ECM and due to various environmental factors such as O_2 and pH [9].

Among the ten hallmarks of cancer proposed by Hanahan and Weinberg in 2011 [1], apart from the six mentioned above, the remaining four hallmarks (inducing angiogenesis, activation of invasion & metastasis, avoidance of immune destruction,

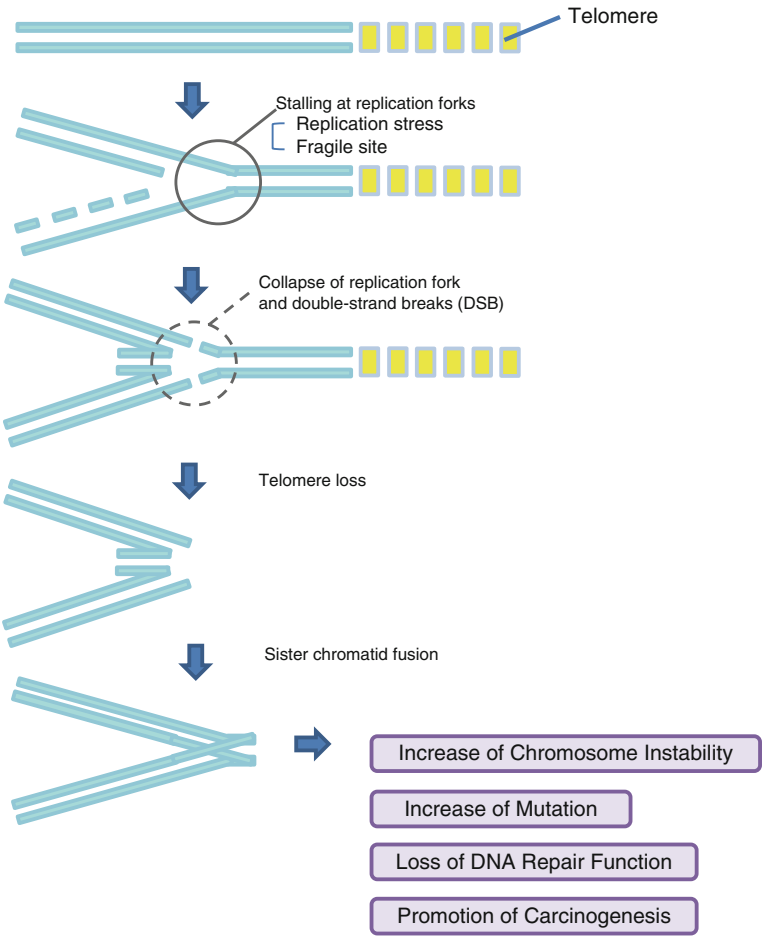


Fig. 1.7 Chromosomal instability increases due to telomere damage. In vigorously dividing cancer cells, double-strand breaks (DSBs) occur at fragile sites when the replication fork stalls and collapses due to replication stress. Distal ends are lost when broken strands are rejoined by non-homologous end joining (NHEJ). As telomeres are lost, chromosomal instability and the incidence of mutations increases. When chromosome repair ability is lost, carcinogenesis is promoted

and tumor-promoting inflammation) are manifested through interactions with neighboring cells and the tumor microenvironment.

Neighboring cells include endothelial cells and pericytes which are involved in angiogenesis. These cells create new blood vessels that transport oxygen and nutrients essential for cancer cell proliferation. Intratumoral blood vessels are formed by the "angiogenic switch," and endothelial cells constituting these tumor blood vessels are expected to be distinct from normal endothelial cells. This is because tumor blood vessels are different from normal blood vessels in many ways such as abnormal vessel structure and hyperpermeability [10] (Fig. 1.10).

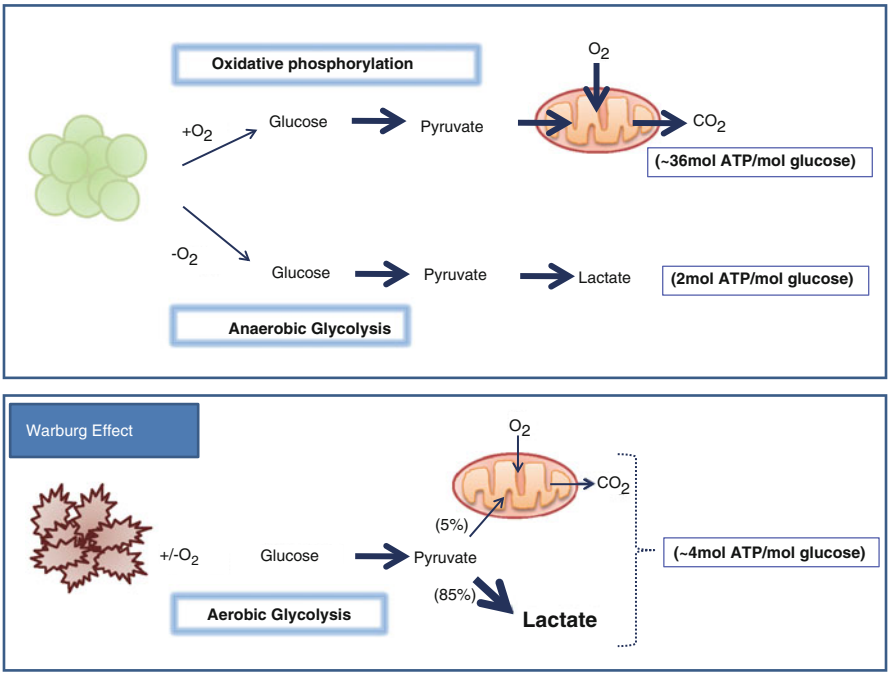


Fig. 1.8 The Warburg effect in cancer cells. In the presence of oxygen, differentiated normal cells convert glucose into pyruvate, after which a large amount of ATP is generated on complete oxidization by oxidative phosphorylation in the mitochondria. Oxygen is essential for this process because it acts as an electron donor in the glucose oxidization process. Under conditions of limited oxygen, cells produce lactate from pyruvate in a process other than oxidative phosphorylation. This process is called anaerobic glycolysis, resulting in the generation of only a small amount of ATP and the lactate produced this way goes through the glycolysis process. Warburg observed that cancer cells converted most of glucose into lactate even in the presence of oxygen. This phenomenon is called the "Warburg effect." Since this reaction takes place in the presence of oxygen, it is called aerobic glycolysis. Although only a small amount of ATP is produced, cancer cells can continuously produce the energy, amino acids, and nucleic acids needed for cell division through this reaction because the glucose uptake capability of cancer cells increases. In addition, cancer cells can continuously divide even under anaerobic or hypoxic conditions because glycolysis is constantly active due to the increased glucose uptake capability

Finger-shaped pericytes surrounding endothelial cells secrete angiopoietin-1 (Ang-1) or vascular endothelial growth factor (VEGF) to synthesize the basement membrane in collaboration with endothelial cells, playing an important role in angiogenesis and vessel maintenance. Therefore, if the pericytes do not cover the endothelial cells properly, intravasation of tumor cells occurs more readily.

Besides blood vessels, lymphatic vessels are also involved in metastasis. Although intratumoral lymphatic vessels are impaired and dysfunctional, functional lymphatic vessels grow in the periphery of tumors and may be involved in metastasis of cancerous cells to the lymph nodes [11] (Fig. 1.11).

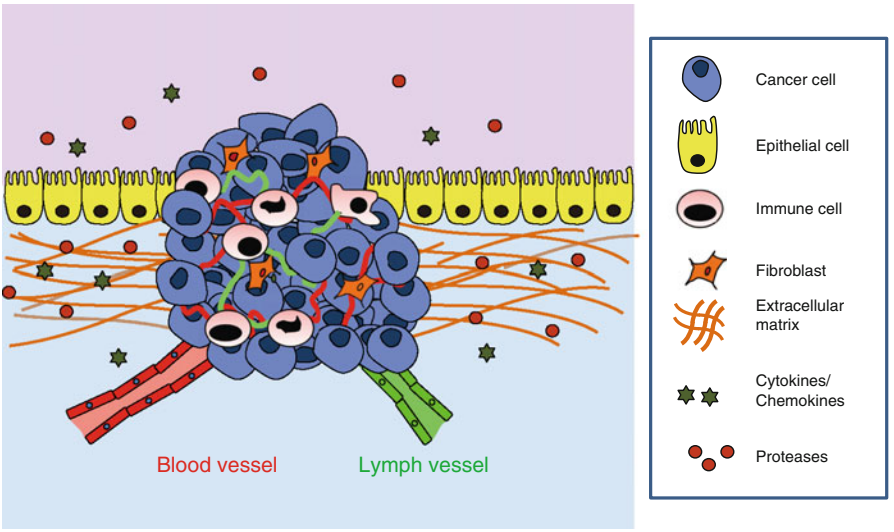
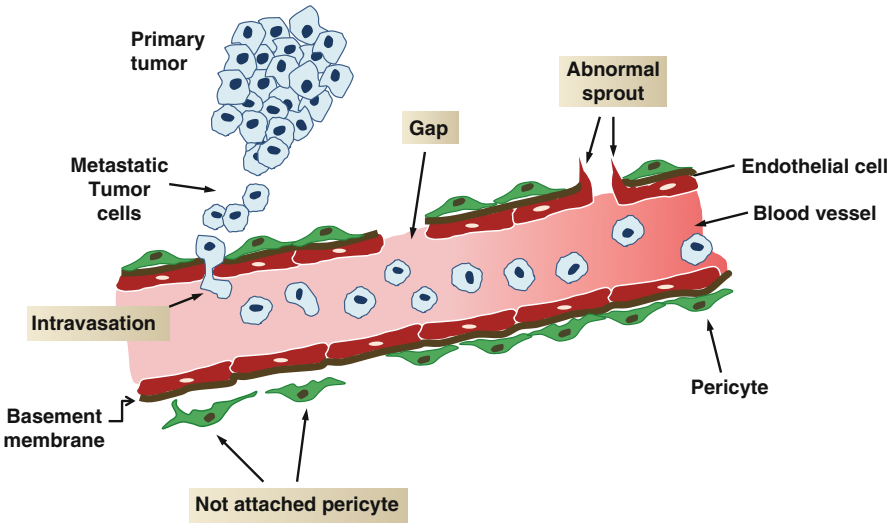


Fig. 1.9 Tumor microenvironment and diverse cell components. Tumor microenvironment refers to the diverse cellular environment of the tumor and consists of endothelial cells, pericytes, immune cells, ECM, fibroblasts, lymphatic vessels, other cell types, and signaling molecules. Through interactions with surrounding stromal cells and microenvironmental factors, tumor cells undergo carcinogenesis and eventually become metastatic. The characteristics properties of cancer cells including angiogenesis, invasion and metastasis, and tumor-promoting inflammation emerge from interactions with the tumor microenvironment as various signaling substances and enzymes are secreted from surrounding cells



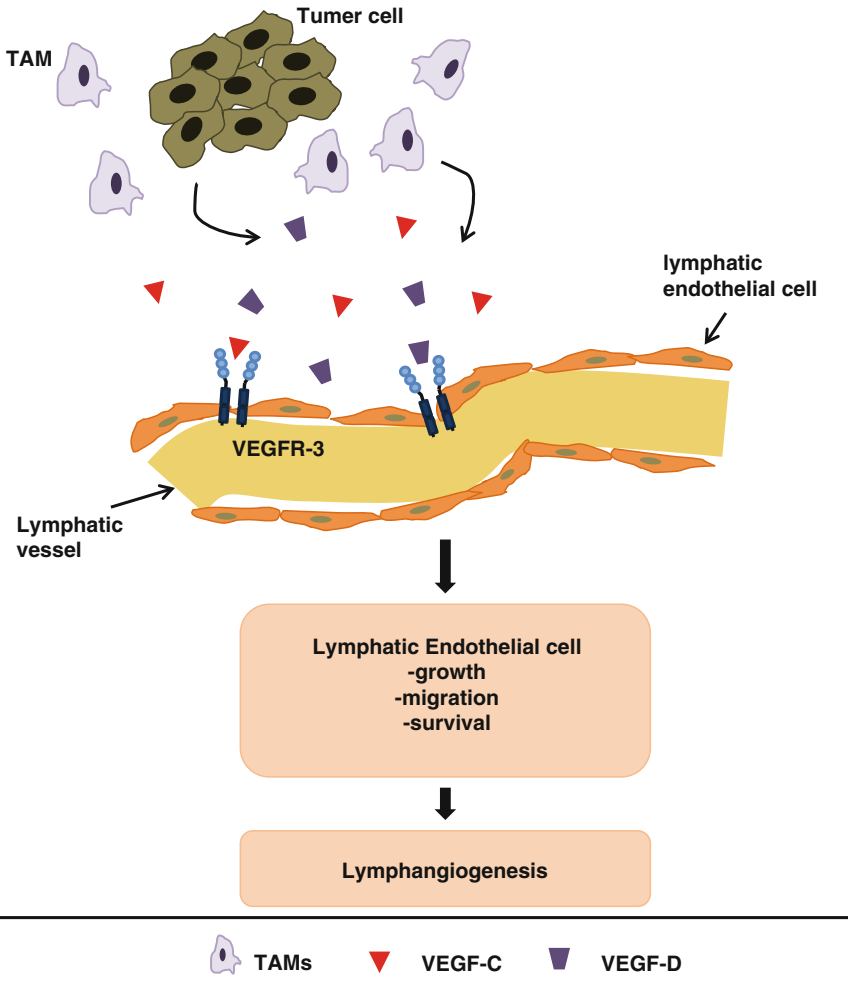


Fig. 1.11 Lymphangiogenesis and metastasis. New lymphatic vessels are generated around a tumor, through which cancer cells metastasize (lymphatic metastasis). Lymphangiogenesis requires lymphangiogenic factors such as VEGF-C and VEGF-D. Cancer cells and tumor-associated macrophages (TAMs) secrete VEGF-C and VEGF-D, which bind to VEGF receptor-3 (VEGFR-3), expressed on the surface of lymphatic vessels. As a result, the growth, migration, and survival of lymphatic endothelial cells increases and lymphangiogenesis is induced

Fig. 1.10 Endothelial cells and pericytes in tumors. Intratumoral blood vessels consisting of endothelial cells and pericytes surrounding endothelial cells are involved in angiogenesis. They supply oxygen and nutrients for the proliferation of cancer cells. Intratumoral blood vessels display abnormal structural and functional characteristics, differentiating them from normal blood vessels. That is, tumor blood vessels have irregular shapes and sizes, and are loosely connected. Furthermore, they are defective in the endothelial cell layer due to abnormal branching, which creates gaps between cells. As these tumor blood vessels are immature and hyperpermeable, their function is also disturbed. Therefore, cancer cells can easily intravasate through blood vessels and metastasize easily

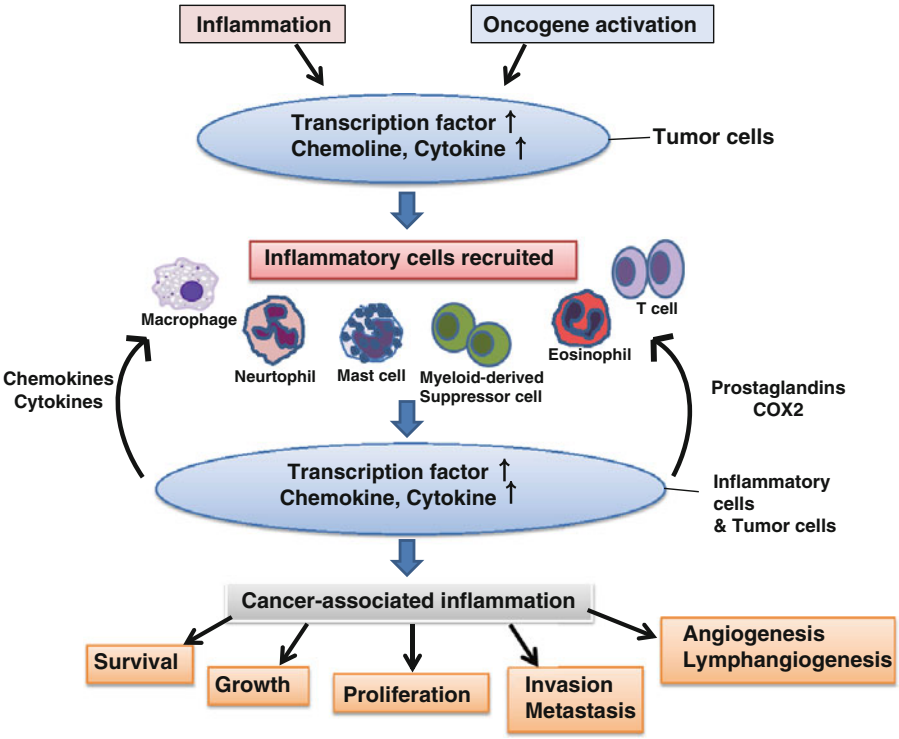


Fig. 1.12 Induction of inflammatory response in carcinogenesis. Transcription factors such as nuclear factor (NF)-kB, signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor-1α (HIF-1α) are activated in tumor cells by stimulation of external pathways such as inflammation and infection, or internal pathways such as activation of oncogenes and secretion of inflammation regulatory factors such as cytokines, chemokines, and cyclooxygenase 2 (COX2). These secretory factors recruit a variety of cells such as macrophages, neutrophils, mast cells, myeloid-derived suppressor cells, T cells, and eosinophils to cancer cells. When transcription factors such as NF-kB, STAT3, and HIF-1α are activated in immune and cancer cells, more cytokines, chemokines, and prostaglandins are produced, which in turn activates immune cells to induce carcinogenic processes such as cell survival, growth, proliferation, angiogenesis, lymphangiogenesis, and invasion and metastasis

Immune cells in the tumor microenvironment play a role in tumor-promoting inflammation. These include T lymphocytes, B lymphocytes, macrophages, mast cells, and neutrophils. These inflammatory cells amplify inflammatory responses by secreting growth factors like epidermal growth factor (EGF), VEGF, fibroblast growth factor 2 (FGF2), as well as chemokines and cytokines [12]. They also induce angiogenesis and upregulate production of ECM-degrading enzymes. Thus, they play an important role in tumorigenesis, invasion, and metastasis of tumor cells. These inflammatory cells include both terminally differentiated cells and undifferentiated progenitors (Fig. 1.12).

Other cells in the tumor microenvironment include fibroblasts, which have tumor-promoting functions such as the proliferation of cancer cells, angiogenesis, invasion, and metastasis [13] (Fig. 1.13).

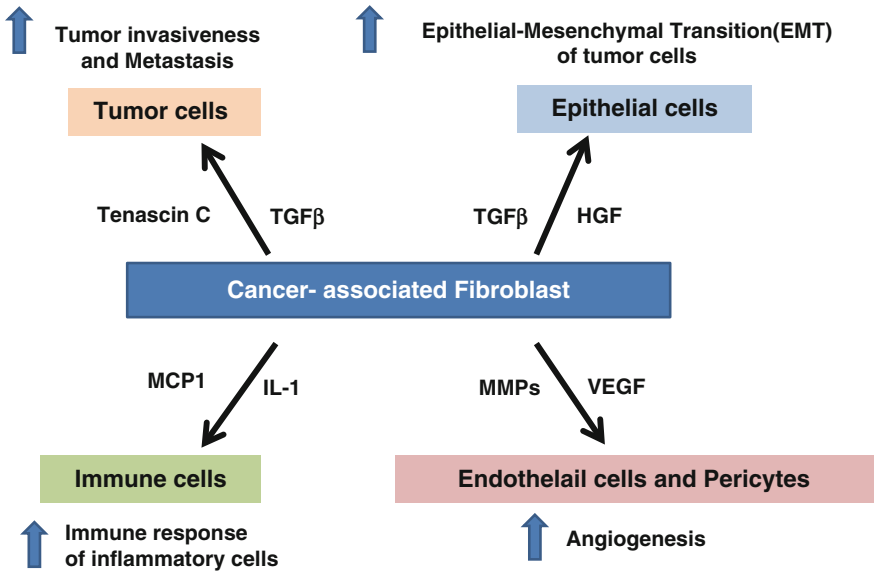


Fig. 1.13 Activated fibroblasts are involved in carcinogenesis. Fibroblasts surrounding tumor cells are frequently in an activated state and are called cancer-associated fibroblasts (CAFs). These fibroblasts secrete a variety of factors including growth factors and chemokines near tumor cells and affect tumor cells, immune cells, endothelial cells, pericytes, and epithelial cells, thereby playing an important role in carcinogenic processes such as progression and proliferation of cancer, angiogenesis, and metastasis. For example, tenascin C, an ECM protein secreted by fibroblasts, induces an ECM-like environment, which induces the invasion of tumor cells that secrete additional tumorigenic factors, eventually promoting tumor progression. By secreting cytokines and interleukins such as monocyte chemotactic protein 1 (MCP1) and interleukin-1, fibroblasts recruit immune cells to the inflammation site and induce immune cell-mediated inflammatory responses. Furthermore, by secreting matrix metalloproteinases (MMPs) and VEGF, fibroblasts assist endothelial cells and pericytes in inducing angiogenesis. By secreting potential tumor growth factors such as transforming growth factor-β (TGF-β) and hepatocyte growth factor (HGF) around epithelial cells, fibroblasts induce EMT in tumor cells and stimulate the proliferation and metastasis of tumor cells

In addition, myofibroblasts are found in wounds and chronically inflamed areas, and can induce fibrosis especially in the lung, kidney, and liver where chronic inflammation can occur.

Recently, cancer stem cells (CSCs) have been discovered in the tumor microenvironment. The origin of solid tumors from CSCs is not well understood. However, it is possible that CSCs develop due to mutations in normal stem cells and undifferentiated cells, or during EMT [14]. CSCs exhibit resistance to anticancer drugs and are activated when cancer relapses after a long latent period. They can also convert to fibroblasts or similar cells through EMT, or become endothelial-like cells through a differentiation process. Therefore, the diversity of tumor cells increases because of CSCs, producing a population of cells that vigorously promotes the progression of cancer (Fig. 1.14).