Cancer Biology and Its Treatment Modalities: A Brief Historical Perspective

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Abstract

For thousands of years, tremendous amount of research has been carried out to understand one of the leading causes of death – cancer. Being known for its complexity, researchers have put tremendous efforts in acquiring every bit of knowledge that is required to understand the distinct aspects of tumor biology, progression, invasion, and metastasis. These include understanding the tumor physiology, developing different detection techniques, as well as identifying the genetic roots of the disease. This in turn would help in unraveling the signaling circuitry that regulates intercommunication within the tumor microenvironment. The main objective of this chapter is to provide a comprehensive overview of the different historic events that have taken place in the field of cancer research. Besides, it also briefly describes the different hallmarks of cancer that have been put forth to elaborate the different mechanisms adapted by cancer cells for their survival and progression.

Keywords

Cancer · Tumor biology · Detection · Signaling · History · Hallmarks of cancer

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1.1 Introduction

Cells are most commonly defined as the *basic building blocks* or *fundamental units* of life. They are known to form discrete functional packages in an organized pattern to build up an entire organism. For the proper maintenance of homeostasis, cells are constantly involved in sending and receiving tremendous amount of information among each other through the means of chemical signaling molecules. This form of communication governs and coordinates all the basic activities of a cell – including cell growth and development, tissue repair, strengthening of immunity, removal of toxic components, as well as balancing the mediums of cell death pathways. Any form of variation in these signaling interactions may lead to erroneous interpretation of the cellular information processing, thus hampering the homeostasis and leading to different forms of diseased states.

Cancer is one such highly complex disease that arises due to dysregulation of various signal transduction networks, which overall govern the molecular communications and major cellular processes. Under normal circumstances, individual cells or group of cells undergo expansion in response to distinct regulatory signals that govern their ability to progress through different stages of cell cycle and perform their primary function within the provisional microenvironment. However, in case of cancer, specific genetic mutations affect the functioning of signaling molecules and in turn give rise to a loss of control over critical cellular functions. Any fault in the processing of a particular aspect of the multistep and well-connected signaling pathway may result in impairment of the entire signaling network and eventually lead a normal cell to acquire cancer phenotype.

Being one of the leading causes of deaths globally, significant advances have been made in understanding tumor biology, tissue invasion, and metastasis. With decades of research undertaken to comprehend distinct arenas of cancer biology – from understanding the tumor physiology to developing different detection techniques and from identifying the genetic roots to deciphering the signaling circuitry that controls the intercommunication between various cells within the tumors – research in this field has significantly evolved. This chapter elaborates the 4000-year history of cancer and how the story has unfolded over the period of time, giving us more in-depth insights into the realm of cancer biology and expanding the horizons of avenues in cancer treatment.

1.2 Historical Perspective

Cancer has been known to the human race for over a long period of time, starting way beyond the introduction of its Greek terminology “karkinos” by the well-known Greek physician Hippocrates in 460 BC. The oldest records for human bone and breast cancers have been found in the ancient Egyptian mummies dating back to 1600–1500 BC (Sudhakar 2009). In the past 250 years, there have been a huge number of researches undertaken to comprehend the core of cancer biology, the signaling pathways involved, and the advancements in the treatment regimens.

In 1775, Sir Percivall Pott, an English surgeon and one of the founders of orthopedics, successfully established the relationship between exposure to chimney soot and the incidence of squamous cell carcinoma of the scrotum among chimney sweepers (National Cancer Institute 2015). He was the first scientist to report the effect of environmental exposure on the development of cancer (Fig. 1.1). In 1863, German researcher Rudolf Virchow identified an increase in the number of leukocytes in the blood specimens of cancer patients. He coined the term "leukemia" to describe this condition and proposed a link between inflammation and cancer. Further, in 1886, a Brazilian ophthalmologist Hilário de Gouvêa studied a case of childhood retinoblastoma and provided the first-ever documented evidence explaining the link between cancer and its inheritance. In 1895, Wilhelm Conrad Röntgen discovered the X-rays, and subsequently, in 1896, Emil Grubbe experimented with the use of X-rays in the treatment of cancer. With the discovery of radioactivity by Marie and Pierre Curie in 1898, the use of radium in radiation therapy for cancer treatment also began in few years. In 1902, Theodor Boveri proposed that alterations at the chromosomal level in a single cell may lead to activation of cellular pathways promoting uncontrolled cell division that subsequently led to cancerous tumor formation. Further, Paul Ehrlich in 1909 put forth the "immune surveillance" hypothesis, which suggested that the immune system usually suppresses tumor formation and, thus, provided the first fundamental principle of chemotherapy.

The beginning of the nineteenth century involved identification of the etiologic agents responsible for causing cancer. In 1911, Dr. Peyton Rous, a young American pathologist, discovered that the supernatant from tumor cells of Plymouth Rock hen contained a transmissible virus that was an etiologic agent causing spindle-cell sarcoma. Although he was the pioneer in identifying that some cancers are caused by infectious agents, this discovery gained importance only in the late 1950s. Further, Temin and Rubin demonstrated that a number of additional viruses could induce transformation in tissue culture cells and tumors in appropriate animal models (Frank 2011). This discovery expanded research into oncogenic retroviruses, which were known for their ability to direct DNA synthesis from an RNA genome through a polymerase commonly termed as *reverse transcriptase*. Studies on the replication of these oncogenic viruses, mechanisms by which their viral oncogenes integrated into the host genome, and subsequent expression of these oncogenes that induced malignant transformation were gaining popularity in the scientific community. This fetched Rous the Nobel Prize in 1966 for identifying the mode of malignant transformation by a virus that was named "Rous sarcoma virus (RSV)" in his honor. Besides, George Papanicolaou developed the *Pap smear test* in 1928 for the detection of cervical cancer in a precancerous state (National Cancer Institute 2015). The subsequent clinical trial was launched in 1952 and was known as "the largest clinical trial of secondary prevention in the history of cancer," as it provided significant advancement in the detection of cancerous cells till today.

The era of the 1940s marked three decades of intense growth in the field of cancer treatment. In 1941, Charles Huggins discovered that the removal of testicles caused reduction of testosterone levels and the subsequent administration of estrogens promoted the regression of prostate tumors. Thus, hormonal therapy came into

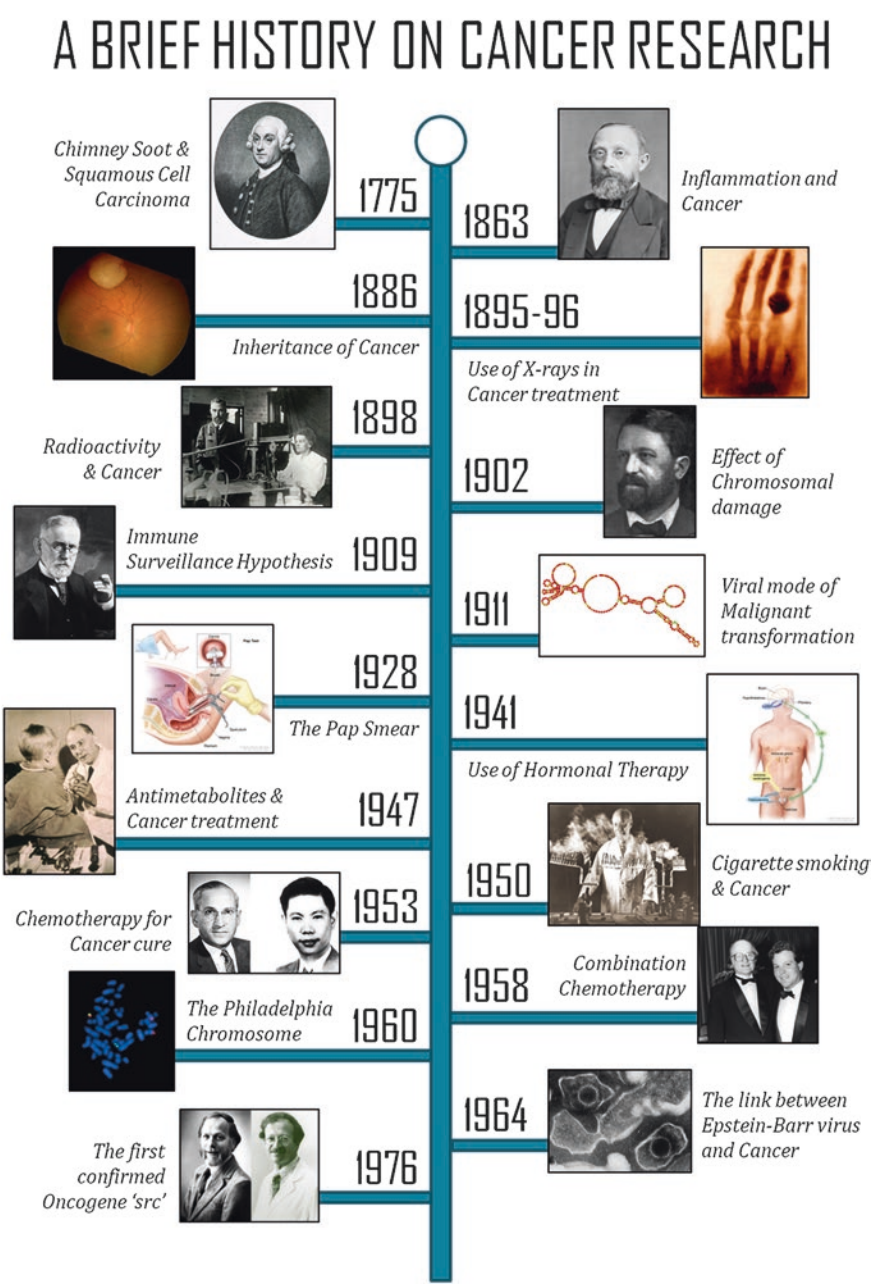

Fig. 1.1 A brief history of cancer research. This timeline illustrates the important events that have taken place in the field of cancer biology. (Images taken from (National Cancer Institute 2015) and Google images)

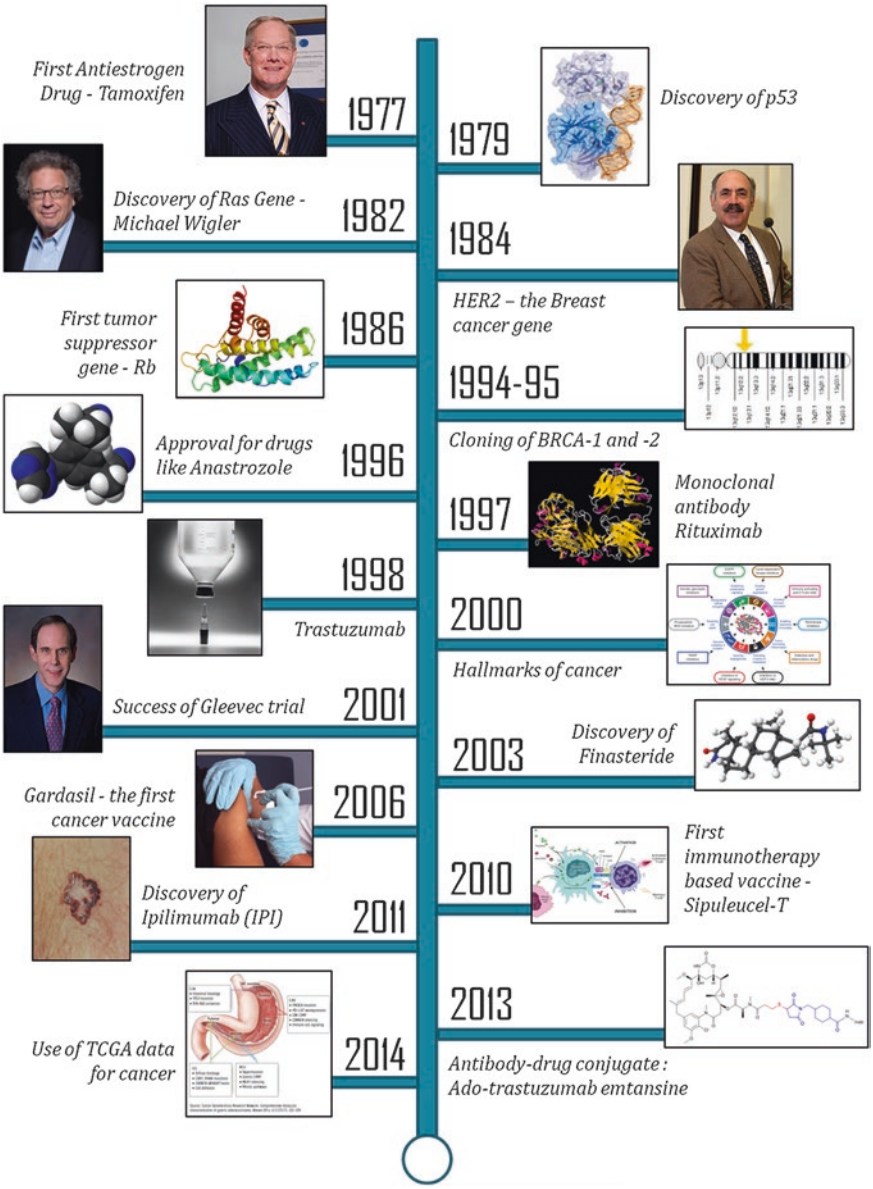

Fig. 1.1 (continued)

mainstream application for prostate cancer treatment. In 1947, Sidney Farber, a world-renowned pediatric pathologist, demonstrated that folic acid stimulated leukemic cell growth, while treatment with the antimetabolite drug aminopterin induced remissions of acute leukemia in children (Benner 2015). Although the antimetabolite drugs were known to be structurally similar to the biomolecules required for cellular processes such as DNA synthesis, they induce cell death by blocking these important processes. In 1950, Ernst Wynder, Evarts Graham, and Richard Doll identified cigarette smoking to be an important factor responsible for the development of lung cancer. With the use of the drug methotrexate for chemotherapy treatment of a patient with choriocarcinoma (a rare cancer of the reproductive tissue that mainly affects females), Roy Hertz and Min Chiu Li achieved the first complete cure of a human solid tumor in 1953. Subsequently in 1958, it was shown that combination chemotherapy with the drugs 6-mercaptopurine and methotrexate not only could induce partial as well as complete remissions but also prolonged the survival rates in patients with acute leukemia. Developed by Emil Frei and Emil Freireich, the combination therapy became more famous through the VAMP protocol trial (vincristine, amethopterin, mercaptopurine, prednisone) that was used to identify the different mechanisms by which each drug provides better treatment for cancer. In the case of chronic myelogenous leukemia (CML), Peter Nowell and David Hungerford in 1960 identified an unusually small chromosome (known as the Philadelphia chromosome) in the cancer cells of 95% patients. In 1964, the Epstein-Barr virus (EBV) was identified for the first time to be the etiologic agent for a number of human cancers, including nasopharyngeal carcinoma, Hodgkin lymphoma, and some gastric (stomach) cancers.

In 1969, the term "oncogene" was coined from the Greek word "onkos" meaning mass or load, and it describes the potential of a particular gene to cause cancer. Consequently, the first confirmed cellular oncogene "src" was discovered in 1976 by Dominique Stehelin, Harold Varmus, J. Michael Bishop, and Peter Vogt. Using an oncogenic retrovirus, they demonstrated that the DNA of normal chicken cells contained a gene related to the oncogene of avian sarcoma virus. The oncogene in the virus did not represent a true viral gene but was a normal cellular gene, which the virus had acquired during replication in the host cell and thereafter carried along. In this way, they identified the growth-controlling oncogenes in normal cells, and this finding led Bishop and Varmus to win the Nobel Prize in 1989. Another commendable discovery showed that the src-encoded protein displays an intrinsic protein tyrosine kinase (PTK) activity (Hunter and Sefton 1980).

Besides the discovery of viral mode of transformation, the start of the 1970s provided three competing theories about carcinogenesis. They were based on causes that resulted in transformation of normal cells into cancerous forms and were identified as viral, environmental, and biological (malfunctioning genes). Although none of the theories could alone stand to present the full story of cancer, each of these theories could eventually be proven correct in individual cases. In 1971, Dr. Judah Folkman proposed that angiogenesis plays a critical role in cancer development and that preventing this process can inhibit tumor growth by starving the tumor of vital nutrients (Emory University). In 1977, the US Food and Drug Administration (FDA)

approved the first antiestrogen drug – tamoxifen. The drug belonged to a class of selective estrogen receptor modulators, or SERMs, and was approved for breast cancer therapy. The year 1979 marks the landmark discovery of the most widely studied and commonly mutated gene in human cancer, the TP53 gene (also called p53). The protein product (p53 protein) was found to be a tumor suppressor, as it controlled cell proliferation and suppressed tumor growth. Further, in 1982, three different labs (Mariano Barbacid and Stuart Aaronson at the NIH, Robert Weinberg at MIT, and Michael Wigler at Cold Spring Harbor Laboratory) isolated the same gene called *RAS* from cancer cells. This viral gene encodes for 21 kDa (p21) proteins that belong to a class of small GTPases and have been found to be involved in cellular signal transduction. Thus, over-activation or expression of mutationally active form of the Ras protein was found to cause a number of cancers. In 1984, a new oncogene named "neu" was discovered in rats, and the human counterpart of this gene, HER2, was found to be overexpressed in the more aggressive form (~20%–25%) of breast cancers, known as HER2-positive breast cancers. Subsequently, in the year 1986, Stephen H. Friend with his team isolated the first tumor suppressor gene – "Rb gene" – that was associated with an inherited (familial) form of cancer called retinoblastoma. With respect to breast and ovarian cancers in women, it was known that specific inherited mutations in the tumor suppressor gene "BRCA" increased the risks of these cancers as well as several other cancers in both men and women. Therefore, for more in-depth functional analysis, the tumor suppressor genes BRCA1 and BRCA2 were cloned in 1994 and 1995, respectively.

The tremendous expansion in the field of cancer biology subsequently led to the advancement of early cancer detection techniques, treatment, and prevention arenas. During the late 1990s, scientists were more interested in developing drugs that targeted the key features of cancer cells – proliferation, apoptosis, and angiogenesis. From 1996 to 2000, the FDA approved drugs like anastrozole (an aromatase inhibitor that blocks the production of estrogen in the estrogen receptor-positive advanced breast cancer women in postmenopausal stage), rituximab (a monoclonal antibody used in patients with treatment-resistant, low-grade, or follicular B-cell non-Hodgkin lymphoma (NHL)), and trastuzumab (a monoclonal antibody that targets cancer cells showing overexpression of HER2 protein, for the treatment of HER2-positive early-stage and metastatic breast cancer).

In 2000, Douglas Hanahan and Robert Weinberg published an influential peer-reviewed article named "The Hallmarks of Cancer" (Hanahan and Weinberg 2000), which was further updated in 2011 (Hanahan and Weinberg 2011). These hallmarks signified the common traits that differently govern the transformation of normal cells toward the cancerous form. Herein, the authors have also described how these traits are linked to the most common signaling pathways that get altered in the state of cancer (as elaborated in Sect. 1.3).

In 2001, the drug imatinib mesylate (sold under the brand named Gleevec by Novartis Company) was launched in trial form for the treatment of chronic myelogenous leukemia (CML). It targeted a unique protein produced by the Philadelphia chromosome and is effective in stopping the growth of cancer cells in case of

gastrointestinal stromal tumors (GIST). The Gleevec trial was one of the most successful trials in the history of cancer research. With the completion of the Human Genome Project in 2003, the entire sequenced map of human DNA became available for the cancer researchers, and this facilitated the exploration of the genomic path of cancer. In the same year, it was shown that reducing the production of certain hormones can help culminate the risk of developing a particular form of cancer. For example, in 2003, it was found that the drug finasteride assisted in lowering the risk toward prostate cancer in men by about 25%, as it could significantly reduce the production of male hormones in the body. Concurrently, in 2006, the antiestrogen drug raloxifene was shown to reduce the risk of developing breast cancer in postmenopausal women as well as serious side effects of the previously introduced drug tamoxifen. In this way, hormonal therapy was molded, and chemistry was tweaked in every possible manner to introduce different combination of drugs so as to regulate the predisposition toward specific forms of cancer. In the same year, FDA approved Gardasil – the first cancer prophylactic vaccine that protected against infection by two types of human papillomaviruses (HPV-16 and HPV-18), the etiologic agent and major cause of cervical cancer. Subsequently, in 2009, a second vaccine – Cervarix – was introduced for cervical cancer. In 2010, the first immunotherapy-based cancer treatment vaccine, sipuleucel-T, was approved by the FDA. This vaccine is made by using a patient's own dendritic cells and is used for the treatment of metastatic prostate cancer, in cases where the patient no longer responds to hormonal therapy. The fundamental thought of using immunotherapy for treatment of cancer was conceived by the great surgeon Stephen A. Rosenberg. This treatment was meant to enhance the activity of one's own immune system to prevent the spread of cancer by encouraging the destruction of tumors. In the same lines, FDA permitted the use of the monoclonal antibody, ipilimumab (IPI), for the treatment of advanced or metastatic melanoma in 2011. To harness the capability of the human immune system, IPI was designed in a way that it stimulated the immune system by binding to the human T cell, targeted them toward the cancerous cells, and inhibited their unwanted proliferation by increasing the intensity of immune responses. In 2013, the FDA approved an antibody-drug conjugate named adotrastuzumab emtansine (T-DM1). This immunotoxin is made by chemically linking the monoclonal antibody trastuzumab to the cytotoxic agent mertansine. It works by inhibiting the cell proliferation in HER2-positive breast cancer patients by blocking the formation of microtubules. With the advent of the Cancer Genome Atlas (TCGA) project in 2006 (an effort funded by the US government), researchers were able to analyze the DNA and mark the diversity of the cancer cells by identifying the molecular changes in more than 30 types of human cancers. The project aimed at focusing on the genomic characterization and sequencing of different tumor types by using massive sampling and creating a data set that enables researchers to improve the early stages of detection, treatment, and prevention in case of different cancers. Based on differing tumor characteristics, they were able to identify that gastric (stomach) cancer actually includes four different diseases. The findings from

the TCGA project will help in simplifying our understanding of the incredibly complicated cancer genome. These discoveries will also help in delineating the rapid evolution of cancer cells through a new classification system based on their genomic variability and molecular abnormalities.

Besides the discoveries mentioned in this section, there were various other studies in the field of cancer biology that have been vividly and elaborately covered in different chapters of this book.

1.3 Hallmarks of Cancer

In the paper- "The Hallmarks of Cancer," Douglas Hanahan and Robert Weinberg have studied different signaling circuits that together control the overall sustenance of a particular cell. It also describes how slight abruption in any single part of this cellular machinery can derail the governance of molecular controls and lead to cancer. When a normal cell overcomes these molecular restrictions that oversee the stringent functioning of different cellular signaling pathways, it transforms to a cancerous state. The general traits that are dominated in this state have been divided into three categories: the acquired capabilities, the enabling characteristics, and the emerging hallmarks (Hanahan and Weinberg 2000).

In the paper published in 2000, these researchers described six different acquired capabilities that have been observed to be common in a number of cancer genotypes. These included self-sufficiency in growth signals, insensitivity to antigrowth signals, tissue invasion and metastasis, sustained angiogenesis, limitless replicative potential, and evasion of apoptosis (Fig. 1.2). Manifestation of these six essential alterations in cell physiology during the course of multistep tumorigenesis can overall dictate the fate of a cell toward tumorigenesis. However, over a decade later, as the complexity of tumor cell biology started to unravel with the prospect of the contributions of "tumor microenvironment" toward tumorigenesis, the review article was updated with four more hallmarks of cancer in 2011 (Hanahan and Weinberg 2011). The acquisition of the earlier six hallmarks is made possible by the two enabling characteristics: genomic instability and random mutations and tumor-promoting inflammation. Two other attributes of cancer cells that are considered to be essential for the development of cancer cells include reprogramming of cellular energy metabolism and evasion from the attack of immune cells and avoiding immune destruction (Fig. 1.2). There have been various signaling pathways that have been extensively studied with respect to these hallmarks, and various cancer case studies have led to the identification of important molecules that are involved in cancer progression (Hanahan and Weinberg 2011).

Thus, the basic researches based on these hallmarks of cancer have globally expanded the pool of knowledge available on tumorigenesis. This, in turn, has greatly enhanced the development of novel targeted drug therapy that could interfere with each of these well-known and unique traits of cancer cells.

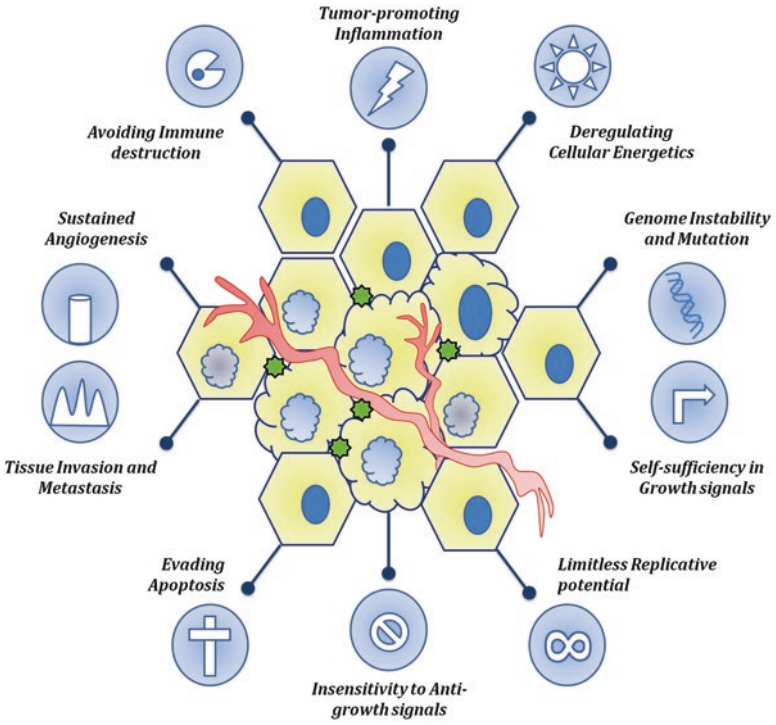

Fig. 1.2 Hallmarks of cancer

1.4 Conclusion

Over the years, as our knowledge in the field of cancer biology expanded, the revelation of various factors involved in cancer progression or suppression clarified our understanding of the intricate network and communication involved in case of different cancers. To a greater extent, it has led to the advancement in the field of technology that is now required to decipher the involvement of each of the cellular signaling network in the progression of different cancer phenotypes, their early detection, and subsequent manipulation of the treatment regimen for increasing the survival rates.

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