Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 7, Issue 3, 2015

Review Article

CANCER: A MOLECULAR CURSE?

NGUGI M. PIERO[1*], NJAGI M. JOAN[2]

[1]Department of Biochemistry and Biotechnology, [2]Department of Environmental Health, Kenyatta University, P. O. Box 43844-00100 Nairobi

Email: piero.mathew@ku.ac.ke

Received: 16 Mar 2015, Revised and Accepted: 28 Apr 2015

ABSTRACT

Cancer is one of the most common causes of death, taking over 7 million lives each year globally. The global incidence is remarkably rising. Massive investments in research are also on the rise to unravel the genetic and molecular basis of cancer as a prerequisite to design of more effective treatment strategies. This review explores causes of cancer, its molecular basis and the treatment strategies. Future perspectives regarding research on cancer and envisaged milestones of management and/or treatment interventions are also explored.

Keywords: Carcinogens, Mutations, Proto-oncogenes, Tumor-suppressor genes.

INTRODUCTION

Cancer is considered as the leading cause of death in economically developed countries and the second leading cause of death in developing countries. Its burden is increasing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and junk diets [1, 2]. According to GLOBOCAN estimates in 2008, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world [2]. In 2020, there are predicted to be 20 million new cases and 12 million deaths. This is partly attributable to the fact that life expectancy is steadily rising and most cancers are more common in an ageing population [3].

Causes of cancer

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and programmed death. When programmed cell death breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control [4].

Cancer is a complex genetic disease primarily caused by environmental factors. The carcinogens may occur in food and water, in the air, and in chemicals and sunlight that people are exposed to. Epithelial cells covering the skin, lining the respiratory and alimentary tracts, and metabolizing ingested carcinogens, it is no wonder that over 90% of cancers occur in epithelia [3]. Unhealthy lifestyles, particularly cigarette smoking and the adoption of high fat and low fibre diets are associated with the increasing cancer incidence. Tobacco use and diet each account for about 30% of new cancer cases, with infection associated with a further 15%. This means that much of cancer is preventable [3].

The said environmental factors mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behaviour leads to expansive masses of abnormal cells that destroy surrounding normal tissue and can spread to vital organs resulting in disseminated disease, and imminent patient death [5].

Gene mutations are regarded as a common feature of all cancers. In most cancers, the mutations occur in somatic cells and are not passed on to future generations. However, in about 1% of cancers, germ-line mutations are transmitted to offspring and cause susceptibility to cancer. Genomic alterations associated with cancer can involve changes as small as single-nucleotide substitutions or as large as chromosome rearrangements, chromosome gain or loss, or even the integration of viral genomes into chromosomal sites [6].

Large-scale genomic alterations are a common feature of cancer; the majority of human tumors are characterized by visible chromosomal changes. It is common knowledge that some types of cancer run in families. An analysis of familiar cancers has led to the identification of cancer susceptibility genes that increase the risk of cancer. Variant alleles of these susceptibility genes have an important role in sporadic cancers as well as familial forms of cancer. The likelihood that an individual will ultimately develop cancer depends upon the particular mutant allele, mutations in other genes, and environmental factors. These variables may influence the age of onset and the severity of the disease [6].

Cancer develops from a complex multi-factorial web of causes. A variety of processes occurring spontaneously inside cells can also contribute to mutagenesis and carcinogenesis, including spontaneous DNA damage as well as errors being made during the duplication of DNA [7]. Cancer is considerably caused by mutations and epigenetic changes in tumor suppressor genes and oncogenes [8]. Mutations may be missense, frameshift, or nonsense. Mutations, sometimes, do not affect the amino acid sequence, but instead influence the promoter sites. Mutations can occur via a raft of mechanisms viz; deletions of small or large DNA segments, inversions, translocations, looping leading to truncated sequence and the story is long! [9].

Although causation of mutation in many types of cancer is still obscure, the initial causes range from ultraviolet radiation to chemical and viral carcinogens. Perhaps diet and other environmental causes have role to play. It is, however, argued that cause–effect relationships are difficult to demonstrate conclusively because of the long time between initiation of a tumor and clinical presentation [10].

The steps leading from carcinogen to mutation are complex. Most chemical carcinogens are covalently modified inside cells by enzymes into chemically reactive intermediates. While

less toxic derivatives usually result, some metabolism leads to more toxic intermediates that react with the DNA nucleobases to form adducts. DNA adducts are more likely to be misread during DNA synthesis, often by specialized DNA polymerases. In most cases, though, cells avoid DNA repair, which removes DNA adducts and restores the sequence and integrity of DNA. DNA repair is multifaceted with many pathways, each targeted to a different kind of DNA damage [7].

Molecular basis of cancer

There are six identifiable 'hallmark features' of the cancer cell phenotype viz; disregard of signals to stop proliferating and of

signals to differentiate; capacity for sustained proliferation; evasion of apoptosis; invasion; and angiogenesis [11].

Mutations in proto-oncogenes and tumor-suppressor genes play key roles in cancer induction. These genes encode many kinds of proteins that help control cell growth and proliferation. Almost all human tumors have inactivating mutations in genes that normally act at various cell-cycle checkpoints to stop a cell's progress through the cell cycle if the preceding step has occurred incorrectly or if DNA has been damaged [12]. As an example, most cancers have inactivating mutations in the genes coding for one or more proteins that normally restrict progression through the G_1 stage of the cell cycle. Further, a constitutively active Ras or other activated signal-transduction protein is found in several kinds of human tumor that have different origins [12]. It thus can be said that malignancy and the intricate processes for controlling the cell cycle are two faces of the same coin. In the series of events leading to growth of a tumor, oncogenes combine with tumor suppressor mutations to give rise to the full spectrum of tumor cell properties [13].

Gain-of-function mutations convert proto-oncogenes to oncogenes. Of the many known oncogenes, all but a few are derived from proto-oncogenes whose products promote cell proliferation [12]. For instance, the *ras* gene is a proto-oncogene that encodes an intracellular signal-transduction protein; the mutant ras^D gene derived from *ras* is an oncogene, whose encoded protein provides an excessive or uncontrolled growth-promoting signal. Other proto-oncogenes encode growth-promoting signal molecules and their receptors, anti-apoptotic proteins, and some transcription factors [12].

Four mechanisms underlie production of oncogenes from the corresponding proto-oncogenes; point mutation in a proto-oncogene that results in a constitutively active protein product, chromosomal translocation that fuses two genes together to produce a hybrid gene encoding a chimeric protein whose activity, unlike that of the parent proteins, often is constitutive, chromosomal translocation that brings a growth regulatory gene under the control of a different promoter that causes inappropriate expression of the gene and amplification of a DNA segment including a proto-oncogene, so that numerous copies exist, leading to overproduction of the encoded protein. However they arise, the gain-of-function mutations that convert proto-oncogenes to oncogenes are genetically dominant [14].

Cancer-causing viruses contain oncogenes or activate cellular proto-oncogenes. Research indicates that Rous sarcoma virus (RSV), a retrovirus, reverse-transcribes its genome into DNA, which is incorporated into the host-cell genome. Further to the normal genes present in all retroviruses, oncogenic transforming viruses like RSV contain the v-*src* gene. Subsequent studies with mutant forms of RSV demonstrated that only the v-*src* gene, not the other viral genes, was required for cancer induction [15]. Loss-of-function mutations in tumor-suppressor genes are oncogenic. Tumor-suppressor genes generally encode proteins that in one way or another inhibit cell proliferation. Loss-of-function mutations in one or more of these "brakes" contribute to the development of many cancers [14]. Five broad classes of proteins are generally recognized as being encoded by tumor-suppressor genes: intracellular proteins that regulate or inhibit progression through a specific stage of the cell cycle (e. g., p16 and Rb), receptors or signal transducers for secreted hormones or developmental signals that inhibit cell proliferation (e. g., TGF-β, the hedgehog receptor patched), checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal (e. g., p53), proteins that promote apoptosis and enzymes that participate in DNA repair [16-18].

DNA-repair enzymes do not directly inhibit cell proliferation. However, cells that have lost the ability to repair errors, gaps, or broken ends in DNA accumulate mutations in many genes, including those that are critical in controlling cell growth and proliferation. It can thus be argued that loss-of-function mutations in the genes encoding DNA-repair enzymes prevent cells from correcting mutations that inactivate tumor-suppressor genes or activate oncogenes [19].

Inherited mutations in tumor-suppressor genes increase cancer risk. Individuals with inherited mutations in tumor-suppressor genes have a hereditary predisposition for certain cancers. Such individuals generally inherit a germ-line mutation in one allele of the gene; somatic mutation of the second allele facilitates tumor progression. A classic case is retinoblastoma, which is caused by loss of function of *RB*. The protein encoded by *RB* helps regulate progress through the cell cycle [20].

Aberrations in signaling pathways controlling development are linked to many cancers. During normal development secreted signals such as Wnt, TGF-β and Hedgehog (Hh) are frequently used to direct cells to particular developmental fates, which may include the property of rapid mitosis [21]. The effects of such signals must be regulated so that growth is limited to the right time and place [22]. Among the mechanisms available for mitigating the effects of powerful developmental signals are inducible intracellular antagonists, receptor blockers, and competing signals. Mutations that prevent such restraining mechanisms from operating are likely to be oncogenic, causing inappropriate or cancerous growth [14, 23].

Hh signaling, which is involved in development to control cell fates, is a classical example of a signaling pathway implicated in cancer induction. In the skin and cerebellum one of the human Hh proteins, Sonic hedgehog, stimulates cell division by binding to and inactivating a membrane protein, Patched1 (Ptc1). Loss-of-function mutations in *ptc1* permit cell proliferation in the absence of an Hh signal; thus *ptc1* is a tumor suppressor gene. Mutations in *ptc1* have been found in tumors of the skin and cerebellum in mice and humans [21].

Mutations in other genes in the Hh signaling pathway are also associated with cancer. Some such mutations create oncogenes that turn on Hh target genes inappropriately; others are recessive mutations that affect negative regulators like Ptc1. As is the case for a number of other tumor-suppressor genes, complete loss of Ptc1 function would lead to early fetal death, since it is needed for development, so it is only the tumor cells that are homozygous *ptc1/ptc1* [12, 21].

Treatment interventions for cancer

Cancer has historically been regarded as an incurable disease until the nineteenth century, when surgical removal was made more efficient by anaesthesia, improved techniques and histological control. Prior to 1950, surgery was most preferred treatment interventions. After 1960, radiotherapy found use to control local disease [24]. However, over time it was realized that neither surgery nor radiation or the two in combination could adequately control the metastastic cancer and that, for treatment to be effective, therapy needed to reach every organ of the body. Therefore, current efforts to cure cancer have been focusing on drugs, biological molecules and immune mediated therapies. The introduction of nitrogen mustard in the 1940s can be considered the origin of antineoplastic chemotherapy targeting all tumor cells [24, 25].

To date, cancer remains one of the most life-threatening diseases. Efforts to fight this disease were intensified when the US passed the National Cancer Act in 1971 and president Nixon declared a "war on cancer" [26]. Currently, over 30 years later, safe for the fact that there are no positive indicators of improved mortality rate or prolonged survival time for metastatic cancer as expected, the characteristics and pathways of different tumor entities have been identified. This milestone of knowledge has come in handy to generate specific tumor therapies either by directly targeting the proteins involved in the neoplastic process or by targeting drugs to the tumor [24].

Targeted therapy can be approached both directly and indirectly. Direct approaches target tumor antigens to alter their signalling either by monoclonal antibodies or by small molecule drugs that

interfere with these target proteins. Indirect approaches rely on tumor antigens expressed on the cell surface that serve as target devices for ligands containing different kinds of effector molecules [24, 26]. In these approaches, drugs can actively target tumors using tumor-specific monoclonal antibodies or peptide ligands binding to receptors that are present on tumor cells. Further to active targeting, tumors can also be passively targeted by macromolecules through

the "enhanced permeability and retention effects" attributed to the hyper permeable angiogenic tumor vasculature and the lack of effective tumor lymphatic drainage [24].

What lies ahead?

Cognizance that cancer is fundamentally a genetic disease is an impetus for new opportunities for its prevention and treatment. It is now feasible to assess the effects of carcinogens cell-cycle regulatory mechanisms. It is possible to recognize the genetic defects in the checkpoint controls for detecting damaged DNA and in the systems for repairing the damages. This can be exploited to explore the mechanisms of cancer. The multiple changes that must occur for a cell to progress into a tumor avail multiple opportunities for intervention.

Identity of mutated genes linked to cancer points to proteins at which drugs can be targeted. Diagnostic medicine is being transformed by the ability to monitor large numbers of cell characteristics. The traditional methods of assessing possible tumor cells, mainly microscopy of stained cells, will be augmented or replaced by techniques for measuring the expression of tens of thousands of genes, focusing particularly on genes whose activities are identified as powerful indicators of the cell's growth properties and the patient's prognosis. Currently, DNA microarray analysis permits measurement of gene transcription.

In the future, it is envisaged that techniques for systematically measuring protein production, modification, and localization, all important measures of cell states, will afford scientists more refined portraits of cells. Earlier detection of tumors, based on better monitoring of cell properties, should allow more successful treatment. The molecular cell biology of cancer avails avenues for new therapies. However, prevention remains crucial and preferable to therapeutic approeaches.

Avoidance of common carcinogens can significantly reduce the incidence of cancer. Antibodies against cell surface markers that distinguish cancer cells provide light at the end of tunnel, especially after breakthroughs with the clinical use of monoclonal antibodies against human EGF receptor 2 (Her2). Additional steps must involve medicine and science.

Understanding the cell biology of cancer is a critical first step toward prevention and cure. Many cancers remain difficult to treat and cause enormous suffering. Since cancer is a a group of highly diverse diseases, interventions that are successful for one type may not be useful for others. Nevertheless, the world is reaping big the benefits of decades of research exploring the molecular biology of the cell. It is hoped that molecular biologists will move on with research to surmount the obstacles that lie ahead to ameliorate the remaining gaps of knowledge so that cancer is better understood and treated. Thus, is cancer a molecular curse? May be, may be not!

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. WHO. The Global Burden of Disease. 2004 Update. Geneva: World Health Organization; 2008.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward EM, Forman D. Global cancer statistics. CA: Cancer J Clin 2011;61(2):69-90.
3. Malcolm RA. Cancer. Imperial College School of Medicine: London, UK; 2001.
4. www.dhsd.limpopo.gov.za
5. Sikora K. Developing a global strategy for cancer. Eur J Cancer 1999;35:24–31.
6. Klug WS, Cummings MR. Essentials of genetics. 5th Edition. Pearson Prentice Hall; 2010.
7. Clapp RW, Howe GK, Jacobs MM. Environmental and occupational causes of cancer a review of recent scientific literature". Lowell center for sustainable production; 2005.
8. Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, *et al*. A census of human cancer genes. Nat Rev Cancer 2004;4:177-83.
9. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the swedish family-cancer database. Int J Cancer 2002;99:260–6.
10. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al*. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78-85.
11. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
12. Hunter T. Oncoprotein networks. Cell 1997;88:333–46.
13. Hesketh R. ed. The oncogene and tumor suppressor gene facts book. 2d ed. Academic Press; 1997.
14. Sherr CJ, McCormick F. The Rb and p53 pathways in cancer. Cancer Cell 2002;2:103-12.
15. White R. Tumor suppressor pathways. Cell 1998;92:591-2.
16. Planas-Silva MD, Weinberg RA. The restriction point and control of cell proliferation. Curr Opin Cell Biol 1997;9:768–72.
17. Paulovich AG, Toczyski DP, Hartwell LH. When checkpoints fail. Cell 1997;88:315–21.
18. Mathon NF, Lloyd AC. Cell senescence and cancer. Nat Rev Cancer 2001;1:203–13.
19. Sherr CJ. Cell cycle control and cancer. Harvey Lect 2000;96:73–92.
20. Classon M, Harlow E. The retinoblastoma tumour suppressor in development and cancer. Nat Rev Cancer 2000;2:910–7.
21. Taipale J, Beachy PA. The Hedgehog and Wnt signaling pathways in cancer. Nature 2001;411:349-54.
22. Polakis P. Wnt signaling and cancer. Genes Dev 2000;14:1837–51.
23. Moon RT, Bowerman B, Boutros M, Perrimon N. The promise and perils of Wnt signalling through beta-catenin. Sci 2002;296:1644–6.
24. Wu H, Chang D, Huang C. Targeted-therapy for cancer. J Cancer Mol 2006;2:57–66.
25. Papac RJ. Origins of cancer therapy. Yale J Biol Med 2001;74:391–8.
26. Dunn FB. National cancer act: leaders reflect on 30 years of progress. JNCI J Natl Cancer Inst 2002;94(1):8-9.