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Review

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Cancer genetics – A review

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ABSTRACT

Changes in DNA are the fundamental cause of cancers. These changes are brought about by chemicals, viruses, radiation, and mistakes made each day in the course of duplicating the billions of units in the DNA when a cell divides. Genes, the central molecules of life, are very vulnerable to damage. However, each cell has a remarkable ability to recognize damage and repair it. The imbalance between damage and the cell's ability to repair the damage results in the changes required in DNA to produce cancer. Because of hereditary predisposition or environmental factors or both, the DNA repair mechanisms – tumour suppressors – become defective and hence leading to accumulation of errors (mutations) throughout the genome. In times, genes important in controlling cell proliferation – cellular oncogenes – become altered; resulting in altered gene products necessary for cell cycle control. Loss of control over the cell cycle is the onset of cancer and its eventual progression. It was therefore concluded that, cancer is a disease of the genes. Further investigation into the matter was recommended.

Key words: Carcinogens, oncogenes, mutations, cell proliferation.

INTRODUCTION

The Illustrated Stedman's Medical Dictionary, 27th edition (2000) and the Dorland's Illustrated Medical Dictionary, 29th edition (2000) define cancer as being derived from the Latin word "cancer" and from the Greek word "karcinos", both meaning 'Crab'. Tomatis et al. (1990) stated that some types of malignant tumours were so described because swollen veins within them look like the claws of a crab, and like a crab, a tumour has a central core and limbs through which the disease spreads to the rest of the body. In ancient times, disease was ascribed to supernatural, pneumatic and humoral factors. However, the discovery by Pasteur and others of the role played by microorganisms in infection, and the study of cellular pathology by Rudolf Virchow in the 19th century were of utmost importance in establishing the true nature of disease (Tomatis et al., 1990). The first known reference to human cancer or at least to a disease which was probably cancer, goes back between 5300 and 4500 years (Grmek, 1975-1976; Shimkin, 1977; Cassileth, 1983). Of course, one can assume that human species was never completely sheltered from some form of deregulation of biological control of cellular growth that may have, as its end point, malignant tumours.

Cancer is today the second most frequent cause of death in many parts of the world, with most occurring in developing countries: 61% of global incidence in 1985 (Parkin et al., 1993). However, Sankaranarayanan et al. (1996) noted with

concern that only a few data are available on cancer incidences, mortality and especially survival in such countries. In the United States, cancer is also the second leading cause of death (after heart disease) accounting for 526,000 deaths annually (Boring et al., 1993).

This review analyses the relationship between genes and cancer, focusing on the role of oncogenes and tumour suppressor genes. Attempt is also made in highlighting genetic events in sporadic (environmentally-caused) cancers since they are far more common and complex than the hereditary ones.

BIOLOGY OF CANCER

The most remarkable progress in the last 30 years has been in our knowledge of cancer biology. We are finally beginning to understand what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously. The word "tumour" is frequently and incorrectly used interchangeably with cancer. However, tumour may refer to a benign (non-cancerous) or malignant (cancerous) growth. Both benign and malignant tumours result from the abnormal growth of cells. Whether a tumour will be benign or malignant is determined by the degree of differentiation, invasion, and matastasis. Malignant (cancerous) tumours unlike benign (non-cancerous) tumours, exhibit the properties of invasion and matastasis, and are highly anaplastic (undifferentiated). Cancer can arise as a consequence of accumulating multiple gene mutations in the genome (Knudson, 2001). Mutations in the genes controlling cell growth are responsible for the causes of many human cancers. The two gene classes: proto-oncogenes and tumour suppressor genes, account for much of the uncontrolled cell proliferation in major human cancers (Huang, 2006). Under normal conditions, the activities of these two gene classes are optimally balanced. Proto-oncogenes (i.e. cellular oncogenes) encourages cell growth, whereas tumour suppressor genes inhibit it. Over-activated proto-oncogenes can become carcinogenic oncogenes which drive excessive cell multiplication and cause proliferation. In contrast, inactivated form of tumour suppressor genes lose the inhibitory effect which is crucial to prevent inappropriate growth.

Gene products that directly affect cell growth and division can be classified into four groups – growth factors, growth factor receptors, signal transducers, and nuclear regulatory proteins (otherwise known as transcription factors). For stimulatory signal to reach the nucleus and initiate cell division, the four proteins must interplay in a sequential manner. First, the growth factor binds to its receptor on the cell membrane. The receptor now becomes temporarily activated by this binding event. This activation stimulates a signal to be transmitted, or transduced, from the receptor at the cell surface to the nucleus within the cell. Finally, transcription factors within the nucleus initiate the transcription of genes involved in cell proliferation. Anyone of these vital proteins could be defective if coded by a mutated gene. For example, the *ras* oncogene has a single defect in its nucleotide sequence, and, as a result, there is a change of a single amino acid in the protein which it encodes – an important protein in the signal transduction pathway. Thus, mutant protein encoded by mutant *ras* gene constantly sends activation signals along the cell cycle cascade, even when not stimulated to do so. Over-active *ras* proteins is found in 15 percent of all human cancers, including carcinomas of the pancreas, lung, and colon (Butel, 2000).

Genetic factors are quite important in familial cancers such as retinoblastoma and xeroderma pigmentosum. Thus, close relatives of such cancer patients have a twofold to threefold increased risk for those neoplasias, although not for other forms of cancer (Li, 1991). In hereditary cancers such as the Li-Freumeni Syndrome, breast cancer, sarcoma and central nervous system tumours, the tumour suppressor gene P_{53} has been found to be inactivated, and a point mutation in P_{53} gene has been identified in all the somatic cells of family members who have cancer (Malkin et al., 1994). Similarly, mutations in the adenomatous polyposis coli (APC) gene is linked to adenopolyposis colon cancer, with thousands of polyps in colon while young. And mutations in BRCA1 and BRCA2 lead to early onset of breast cancer in families carrying the mutated gene even in the heterozygous state (Lindor et al., 2006). They

further listed a number of features associated with hereditary cancer both in the individual patient and the patient family. In the individual patient: multiple primary tumours in the same organ, bilateral primary tumours in paired organs, tumours with rare histology, among several others. And in the patients' family: two or more first-degree relatives with rare tumours, two or more first-degree relatives with tumours on the same site, among others.

MOLECULAR BASIS OF CANCER

Many scientists now consider cancer to be a "disease of the genes" with several individual sites of genetic damage required to transform a cell to the malignant form (Knudson, 2001). Only mutations in those certain types of genes which play vital roles in cell division, apoptosis (programmed cell death) and DNA repair will cause a cell to lose control of its proliferation. Proto-oncogenes promote cell growth and mitosis, while tumour suppressor genes discourage cell growth, or temporarily halt cell division to carry out DNA repair (Lodish et al., 2004). Typically, a series of several mutations to these genes are required before a normal cell transforms into a cancer cell. Transformed cells do not enter a G_o phase in the cell cycle, but continue to replicate and divide. Evidences exist in support of the idea that damage to DNA is involved in neoplastic development and that many carcinogens are also mutagens. Some cellular oncogenes, notably of the *ras* family, can attain the ability to transform cell by virtue of specific point mutations in critical regions of their coding sequences (Seeburg et al., 1994).

Mutations in oncogenes with respect to carcinogens could be specific as discovered by Knudson (2001) that more than 50% of human cancers contain mutations in the P_{53} gene – a tumour suppressor gene. The P_{53} mutation database (includes more than 500 entries of sequenced P_{53} mutations for lung cancer. There is large percentage of G to T transversion mutations in those tumours. Such transversions are hallmarks of mutagenesis involving certain types of polycyclic aromatic hydrocarbons, including benzo-α-pyrene diol epoxide, BPDE. However, they can be induced by other agents, including oxidative DNA damage. Oxidative DNA damage refers to DNA damage caused by oxygen-derived species, including free radicals, which is frequently encountered by aerobic cells. When this type of damage occurs to DNA, it produces a multiplicity of modifications in DNA including base and sugar lesions, strand breaks due to oxidation of bases (e.g. 8-oxo-7,8-dihydroguanine) by reactive oxygen species, DNA-protein cross-links, and base-free sites (Cooke et al., 2003). If left unrepaired, oxidative DNA damage can lead to detrimental biological consequences in organisms, including cell death, mutations, and transformation of cells to malignant cells.

Furthermore, many cancers originate from a viral infection; this is especially true in animals such as birds, but less so in humans. The mode of virally-induced tumours can be divided into two: acutely-transforming or slowly-transforming. In acutely-transforming viruses, the viral particles carry a gene that encodes for an overactive oncogene called the viral-oncogene (v-onc). The infected cell is transformed as soon as v-onc is expressed. In contrast, the genome of slowly-transforming viruses is inserted near a proto-oncogene in the host genome, as viral genome insertion is an obligatory part of retro-viruses (Javier and Butel, 2008). The viral promoter or other transcription regulation elements in turn cause over-expression of that proto-oncogene, which in turn induces uncontrolled cell proliferation. Because viral genome insertion is not specific to proto-oncogenes and the chance of insertion near that proto-oncogene is low, slowly-transforming viruses have very long tumour latency compared to acutely-transforming virus, which already carries the viral oncogene (Javier and Butel, 2008). Viruses that are known to cause cancer such as HPV and cervical cancer, Hepatitis B and liver cancer, and EBV and a type of lymphoma, are all DNA viruses. Their mode of infection is slowly-transforming.

Although it is not possible to tell the initial cause for any specific cancer, modern molecular biological techniques have made possible to characterize the mutations or chromosomal aberrations within a tumour. For example, Knudson (2001) stated that up to half of all tumours have a defective P_{53} gene, since those tumour cells are less likely to go into apoptosis or programmed cell death when damaged by therapy. Burri (2004) observed

that other mutations enable the tumour grow new blood vessels (angiogenesis) to provide more nutrients, or to metastasize, spreading to other parts of the body. Mutant cells in neoplasms compete for space and resources. Thus, a clone with mutation in a tumour suppressor gene or oncogene will only expand in a neoplasm if that mutation gives the clone a competitive advantage over the other clones and normal cells in its microenvironment (Zhang et al., 2005). This is why Merlo et al. (2006) said the process of carcinogenesis is formally a process of Darwinian evolution, known as somatic or clonal evolution.

CONCLUSION

For decades, biologists have studied and catalogued differences between normal and cancer cells and compared them to changes induced in cell transformation by various carcinogens. One phenotype, in particular, of neoplastic cells emerged as paramount: that of uncontrolled proliferation. Uncovering the elements involved in cell proliferation have led to new approaches for the analysis and understanding of these events in molecular terms. Though each type of cancer expresses characteristics unique to itself, all share the same basic nature and process of development: damage to DNA. It is apparent that cancer is indeed a "disease of the genes". Although in some instances a single genetic event is sufficient for malignant transformation, in most instances, multiple genetic changes are necessary. More research is however needed to unlock the doors to understanding the genetic predisposition to cancer, and also to understand genes that cause sporadic cancer cases, which are far more common than those with familial inheritance pattern. Another need is the understanding of how these genes influence individual response to environmental exposure and life style factors and thus contributing to the total burden of cancer.

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