Medical Hypotheses (1996) **46**, 581–583

On the Origin of Cancer

E. Z. BLUMENTHAL

Hadassah University Hospital, Jerusalem (Correspondence to: Dr E Blumenthal, PO Box 137, Omer 84965, Israel)

Abstract — In this paper, I present a highly unorthodox and provocative hypothesis, namely that cancer is an evolutionarily derived phenomenon, dormant in every human cell and actively triggered in certain individuals. Cancer is shown to help maintain the integrity of the common gene pool through active elimination of individuals, thus serving a definite advantage for the survival of the species. Those individuals who are less capable of maintaining the integrity of their genome are stopped from inheriting defective genes, and even more important, from bequeathing defective deoxyribonucleic acid conservation traits to their offspring.

Genome stability is a primary prerequisite for survival. The spread of deteriorated, imperfect genes should have a disastrous effect on a species' chances for survival. Although we tend to focus our attention on mutations as evolution's driving force, the stability of the deoxyribonucleic acid molecule is what really maintains life on our planet. When observing evolution's end product, we tend to forget that the extreme stability of the genetic material is a genetic quality by itself, a product of a long evolutionary process. The hypothesis presented here is that the selection pressure imposed by cancer is one of the mechanisms leading to this stability.

Introduction

Cancer is probably one of the most intensively researched phenomena in biology. Students of life sciences are introduced to a wide spectrum of genes, genetic aberrations, biochemical responses and clinical patterns specific to each neoplasm subtype. As more knowledge is accumulating, repetitive patterns are noticed. Cancer is no longer a chaotic and unpredictable disease, but rather a predictable, co-ordinated response, showing specific markers, aberrations and clinical behavior.

An argument stating that the neoplastic transformation is genetically determined should not be lightly dismissed. Various cancer-related genes have been identified within the human genome (1), including several suppressor genes (2,3). In this manuscript, I go one step further, namely to discuss the evolutionary benefits of maintaining this extra load of 'cancer-related' genetic material in the genome of so many different life-forms. Carrying this large amount of seemingly useless and redundant genes must have some evolutionary advantage which explains why only species carrying such an 'extra load' survived the evolutionary battle of natural selection.

Difficulties with the current dogma

According to conventional wisdom, cancer is viewed as a collapse of the normal physiology. A single cell suddenly stops playing by the rules, and starts to act in

Date received 15 March 1995
Date accepted 5 October 1995

an unpredictable fashion. One of the current views on why each cancer subtype repeats itself in a fairly similar way in different individuals is that each organism is, in fact, an evolutionary microcosmos for the transformed neoplastic cell, the fittest of its decendents being determined by natural selection. It is, however, difficult to follow this logic to explain why each neoplastic subtype (medullary carcinoma of the thyroid, astrocytic glioma, pancreatic carcinoma, etc . . .) is similar in different individuals in terms of histological appearance, markers, clinical behavior, prognosis, susceptibility to treatment and so on. While many of the characteristics of the neoplastic descendant of a cell can be explained by the original cell type, it is not clear why we observe specific subtypes rather then a random continuous spectrum.

The hypothesis

Let us assume that cancer is an evolutionary related phenomenon that has reached a high level of differentiation. The genes, which I have termed 'cancer initiating genes' (4) have three distinct functions: first, they screen the genome for deterioration of contents, namely perform as a mutation-checking mechanism (similar to an anti-virus software, checking for 'mutations' in computer files). Second, they initiate a neoplastic transformation when a certain 'mutation threshold' is reached. Third, they determine various characteristics of the neoplastic clone. The final phenotype of the neoplastic cell is a result of the combined effect of the precancerous cell type, the characteristics of the specific cancer subtype triggered, and the selection pressure on the cancerous clone within the individual.

Characteristic features of various cancer subtypes may be attributed to specific cancer-initiating genes. Thus, it is possible that specific chromosomal aberrations and gene mutations are secondary to the neoplastic transformation rather than the trigger for it.

The neoplasia phenomenon itself is, according to this hypothesis, subject to the forces of natural selection. Therefore, present day types of cancers, especially in highly complex organisms, may be as complex and efficient as other physiological responses, such as the immune and the inflammatory responses.

The stages of the neoplastic transformation

According to this hypothesis the sequence of events underlying the neoplastic transformation is as follows:

1. The primary event is the accumulation of random deoxyribonucleic acid (DNA) mutations caused by carcinogenic factors such as cigarette smoke, coal dust, irradiation, chemotherapy or a virus. In this context 'carcinogenic' is in fact a synonym for any factor causing non-specific damage to DNA.
2. This genome deterioration is sensed by a special detection system, which alerts to the fact that DNA sequences have been altered, and hence that the genome is unstable to a significant extent. This detection system may function much like an anti-virus software, detecting alterations in binary files, though without the ability to pinpoint the precise location of change. It is possible that this system utilizes identical repetitive sequences within human DNA, as reliable zones which can be easily screened for sequence alterations.
3. When a threshold is reached, i.e. the total cumulative damage to DNA sequences is above a certain level, the neoplastic transformation is triggered (possibly certain key zones are scrutinized more intensely than others).
4. 'Cancer initiating genes' trigger the neoplastic transformation in a single cell. Each differentiated body cell has a very limited number of distinct neoplasia subtypes to which it can transform.

   According to this hypothesis, mutations at specific loci and chromosomal translocations are not perceived as the primary initiating step leading to the neoplastic transformation, but rather as secondary, intermediate steps in the transformation process. This implies that cancer may possibly initiate translocations and loci-specific mutations, contrary to the prevailing view that chance mutations in key zones give rise to cancer.
5. The transformed cell may, or may not, reach a clinical stage, depending on an interplay of factors that include, among others, the immune system.

Why cancer strikes mostly older individuals

One major problem of this model is to explain the well-known fact that most human cancers strike at an age well past the child-bearing years. Elimination of individuals after the reproductive age can hardly be regarded as a process of natural selection. While on the face of it this fact seems to contradict the model, I shall demonstrate that it is perfectly consistent with it. The prime assumption in the following discussion is that current biology represents an end-point rather then a starting point for the selection processes brought about by the cancer mechanism. Let me start by considering the situation at the beginning of human evolution. At that time, active DNA conservation was probably far less efficient, resulting in constant, significant random deterioration in the genome. It is

also probable to assume that there existed a spectrum where some individuals possessed better conservation mechanisms then others. Now let us assume that cancer hit mostly those individuals with the greatest deterioration in genetic contents so that only individuals with better conserved DNA sequences were left.

What was the cumulative effect on the entire population? As individuals with poor DNA conservation mechanisms were eliminated, those who remained inherited to their offsprings a more stable genome together with superior DNA conservation mechanisms. Since the active mechanisms involved in DNA stability and conservation are hereditary, the average age at which the total cumulative deterioration triggered the cancer sequence has steadily risen. Thus, the existence of cancer led to greater stability of the DNA molecule, to a smaller number of individuals who manifest significant deterioration at a young age, and to a more intact gene pool.

The older population, however, cannot avoid crossing the cancer initiation threshold at some point, since the cumulative random DNA deterioration can never be entirely eliminated. It can be said that every individual in our society must reach this threshold, and develop a histologically detectable cancer, at some point in time. However, due to the extremely efficient DNA conservation abilities which present day humans possess, this takes place at an increasingly older age. This assumption is validated with respect to prostate cancer. The incidence of this cancer subtype is steadily increasing with age, as shown by post-mortem histopathological examinations: 'Unsuspected (prostate) carcinoma has been identified in about 30% of autopsy specimens in males greater than 50 years of age. The rate increases progressively with age, tripling by the ninth decade' (5).

At present, cancer can be regarded as a watch-dog constantly scrutinizing for young, pre-reproductive, individuals with poor DNA conservation traits. There are several clinical examples of genetically determined inferiority of genome stability in which cancer appears at younger, pre-reproductive, age-groups. One such example is xeroderma pigmentosa (6,7). This hereditary condition of poor DNA conservation mechanisms exemplifies the importance of the cancer-screening process in avoiding a deterioration of the favorable end-point achieved.

In conclusion, the age distribution of present-day cancer can be regarded as a positive result of the natural selection imposed by the cancer mechanism during the process of evolution.

Conclusions

Cancer can be perceived as a unique biological phenomenon whereby a single cell is capable of destroying the entire organism. While the death of any single body cell is of little consequence, the ability of almost every cell type in the organism to trigger a neoplastic process, gives it the power not only to terminate the organism's existence, but far more important, to stop the spread of its genes to future generations. In this article it is suggested that cancer may, in fact, enhance the species' fitness for survival through a selection process.

References

1. Wooster R, Neuhausen S L, Mangion J et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12–13. Science 1994; 265: 2088–2090.
2. Weinberg R A. Tumor suppressor genes. Science 1991; 254: 1138–1146.
3. Hollstein M, Sidransky D, Vogelstein B, Harris C C. p53 mutations in human cancers. Science 1991; 253: 49–53.
4. Blumenthal E Z. Could cancer be a physiological phenomenon rather than a pathological misfortune? Med Hypotheses 1992; 39: 41–48.
5. Kozlowski J M, Grayhack J T. Carcinoma of the Prostate. In: Gillenwater J Y, Grayhack J T, Howards S S, Duckett J W, eds. Adult and Pediatric Urology, 2nd edn. St Louis, MO: Mosby Year Book, 1991: 1227.
6. Digweed M. Human genetic instability syndromes: single gene defects with increased risk of cancer. Toxicol Lett 1993; 67: 259–281.
7. Tanaka K, Wood R D. Xeroderma pigmentosum and nucleotide excision repair of DNA. Trends Biochem Sci 1994; 19: 83–86.