Chicken and egg: a cause-effect relationship between viral infections and cancers?

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Abstract

It is now well established that the multistep cellular transformation process involved in many types of cancer is initiated by viruses. Interestingly, there are anecdotal reports that cancers originating from non-viral causes (chemical, radiation, etc.) contain intracellular viruses. These viruses could have entered the transformed cells as secondary infections, but in this essay an alternative explanation is suggested: they are products of the cellular transformation process that generated the cancer.

There are two main models of viral origin: prebiotic ancestry, and "gene escape" from prokaryotic or eukaryotic cells. The former model has lately gained support. This is a developing field; the virosphere remains poorly characterized and many aspects of viral evolution remain obscure. Nevertheless, it is clear that at least some viruses are of recent origin, and in so far as the "gene escape" model is tenable, the conjecture that cancers act as wellsprings of viruses should merit consideration. If valid, it could imply that as the human population ages and the per capita incidence of cancer concomitantly rises, increasingly more novel and potentially carcinogenic viruses will emerge.

Viruses in the causation of cancers

Bergonzini et al. [1] among many others reviewed the literature exploring the role of viruses in human carcinogenesis. Experts have recently estimated that 15-20% of human cancers are definitely attributable to viral infections, and further information could prove this to be an underestimate. The idea that viruses can cause cancers was first mooted during the first decade of the 20th century [2, 3], but was not firmly established until around 1980. Virally-induced carcinogenesis suggests the possibility of vaccination to prevent the development of certain types of cancer, and indeed the results of large-scale clinical trials with a human papilloma virus vaccine undertaken during 2005 and 2006 [4] have led to the prediction that such vaccines could prevent more than 300,000 cervical cancer cases per year worldwide.

There is a direct relationship between the mechanisms by which viruses are now believed to trigger carcinogenesis and the genetic basis of some cancers. Some inherited cancers are primarily initiated by oncogenes, which are usually point mutations of proto-oncogenes (for example, BRCA1 and 2 in breast and ovarian cancers), whereas others involve defects in tumour suppressor genes (thus p53 is defective in some osteosarcomas). Viral infections can either introduce oncogenes into the host cell or inactivate tumour suppressor proteins. To date, something approaching 100 oncogenes have been identified in retroviruses, *src* being the paradigm example, and almost all of them encode cell signalling proteins that are crucial for the control of cell proliferation or apoptosis [5]. Some retroviruses that do not carry oncogenes in their genomes seem to induce the expression or the function of cellular oncogenes by insertional mutagenesis [5]. In other cases, oncogenic transformation of infected and transfected cells is attributable to interactions with different host cell transcription factors [6], and this has much the same effect as oncogene introduction. In contrast, a number of DNA viruses have evolved proteins that elude cellular antiviral responses by binding and inactivating tumour suppressor proteins, thus facilitating cell transformation. SV40 large T antigen is a well-known example [5]. Such viruses do not introduce oncogenes or activate cellular proto-oncogenes, but suppress endogenous mechanisms for inhibiting cancer growth.

Other well-known causes of cancer include environmental and other mutagens, the nitrosamines and polycyclic aromatic hydrocarbons in tobacco smoke being prominent examples; ionising radiations; hormonal changes such as oestrogen excess; and pathogen infections, including infections (HIV being the paradigm exemplar) that cause immunosuppression. In general, all these causal agents either activate oncogenes or inactivate tumour suppressors within the target cell; in other words, the mechanisms by which they transform cells converge with the mechanisms of viral carcinogenesis.

This parallelism could suggest that mutagens, ionising radiation, and other carcinogenic agents alter target cells in ways that lead to the endogenous production of oncogenic viruses. To what extent might this conjecture be compatible with current debates about viral origins and evolution?

Origins of viruses

For many years, debates about the origin of viruses have pivoted on 2 models: (1) viruses are ancient in origin, dating from the prebiotic Earth, i.e. arising before the last universal cellular ancestor; (2) they evolved only after the origin of true organisms, arising from genes that have “escaped” their host genomes and subsequently developing their own replication mechanisms [7]. The second model has dominated most discussion in this field [reviewed in 8]. Since all known viruses are parasitic on cells, it is tempting to assume that they have always been so and cannot exist without cellular organisms to give rise to them.

However, about three quarters of (for instance) mimivirus genes have no known homologues in either viral or cellular genomes, so their origins are unknown [11], the available data suggesting that they are unlikely to have arisen from the genomes of amoebae [12]. Also, conserved sequences, such as the so-called jelly-roll capsid, could indicate the existence of distinct "lineages" of virion architectures with ancestries that date back to the prebiotic world [13, 14]. These findings therefore support the first model.

Proponents of the "escaped gene" model might attribute such findings to convergent evolution among the viruses in question. However, the structures concerned are common to many viral lineages, so multiple convergence events would have to have been involved. Since there are several different capsid structures, not just one, convergent evolution seems yet more implausible. Alternatively, lateral gene transfer could be proposed, but this would entail a generally increasing genome size, which would presumably be disadvantageous to most viruses.

In view of these considerations, many in the field are now inclined to favour the pre-organism origin model. A particularly telling finding in support of this model is the strong inverse relationship between viral genome size and the mutation rate per genome replication [15]. Clearly, if viruses originated before organisms, *ipso facto* they do not arise from cancers and the conjecture offered in this essay is falsified.

However, there are strong reasons to suppose that at least some viruses are of recent origin. Thus, human hepatitis delta virus contains a ribozyme sequence that is closely related to the CPEB3 ribozyme identified in a human intron, implying that it originated from that part of the human genome [16]. The "gene robber" model of viral origins has clear support in other cases, leaving no doubt that some viruses evolved recently [9, 10]. It therefore seems most likely that the 2 contrasting models of viral origins on which debates have centred are *not* mutually exclusive. Many viruses probably have ancestries leading back to prebiotic times while others appeared in the biosphere more recently.

In most cancers the genome becomes disordered and parts of it can be fragmented. Intuitively, one would expect a statistical relationship between populations of fragments of a given size and the heterogeneity of each of those populations - the smaller the fragment size, the more heterogeneous the population. If recently evolved viruses have arisen from these fragments of disordered genomes in cancer cells, the relationship between mutation rate per replication and viral genome size could be consistent with the conjecture proposed herein. A group of viruses with the inverse correlation between genome size and relative mutation rate could therefore still be of recent origin; they could have been generated by cancers.

As studies of viral evolution and ancestry continue, further light will be shed on this possible relationship with cancers. In the meantime, it could be worth regarding this conjecture as a

tentative hypothesis - the causal connection between viruses and cancers might be 2-way, not one-way; it could be a chicken-egg relationship.

Implications

In view of the growing body of evidence favouring the pre-biotic origin of viruses, it would be absurd to propose that "all viruses originate from cancers". Nevertheless, it is clear that some viruses (though probably a minority) have arisen from organism genomes, and the disruption of genome organisation that commonly accompanies malignant transformation of cells would seem to afford the best opportunity for the generation of viruses from this type of source. The proposal that "some viruses originate from cancers" therefore seems plausible.

If it is correct, it could explain the frequent observation of viruses inside the cells of cancers that have been caused by carcinogenic mutagens, ionising radiation, or other non-viral agents. This cause-effect connection, if it is valid, is unlikely to have any implications for cancer treatment or even diagnosis, but it would be scientifically satisfying.

However, at least one other implication of the conjecture would have real clinical (or at least epidemiological) significance. The increasing per capita incidence of cancers of all types in an ageing population will mean an increasing supply of novel viruses, which could lead to new types of infection. Therefore, if increasing numbers of new viral infections are identified in the future, the explanation might lie not (or not wholly) in improved diagnostic techniques, but in the rising incidence of cancers as the population ages.

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