Radiation induced cancer arises from a somatic mutation

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Abstract

Experimental data from the literature are presented to create a chain which links radiation induced cancer in animals to cell reproductive death and then to chromosomal aberrations and somatic mutations. The cancer data reveal the same peak value of cancer induction following different radiation exposures which leads to an association between cancer induction and cell killing. Other data show a direct correlation between cell survival and chromosomal aberration yield independent of whether a sensitiser is used or not. Data on the induction of somatic mutations in mammalian cultured cells show the same direct relationship between mutation frequency and cell killing following neutron and gamma ray exposures. Taken as a whole, the experimental data provide convincing evidence that radiation induced cancer arises from chromosomal damage.

1. Introduction

In a recent review of the cellular and epidemiological evidence for different RBE values for different low LET radiations, Hunter and Muirhead (2009) dismissed the evidence from cytological and cell transformation experiments which did indicate low dose RBE values of 2–3 for e.g. tritium and mammography x-rays, in favour of epidemiological analyses which did not indicate any increase in RBE. Their argument for discounting the evidence from the cellular data in their conclusions was that ‘there is still some controversy as to whether chromosome aberrations and transformations are indicative of an increased risk of cancer’. In other words, they are reluctant to accept that radiation induced cancer arises as a direct result of cytological damage. We were surprised by this reluctance as we have worked with the premise that cancer arises as a result of a somatic mutation for some 30 years, have found it a very useful concept, and have been encouraged by the developments in cancer genetics over the years. Stratton et al (2009) have recently reviewed the cancer genome.
presenting a substantial body of evidence supporting the link between somatic mutation and cancer. The classical example of an association between cytological damage and cancer is, of course, the association of the Philadelphia chromosome with chronic myeloid leukaemia. The Philadelphia chromosome was shown by Rowley (1973) to be a translocation between chromosome 9 and chromosome 22. This is now known to be a fusion of the \textit{BCR} gene on chromosome 22 with the \textit{ABL} gene on chromosome 9 leading to the continued activation of the \textit{ABL} kinase enzyme (Golub 2010). The Philadelphia chromosome abnormality also occurs in a substantial subset of acute lymphoblastic leukaemias, the rest of which are characterised by other cytological changes such as translocations, trisomies and deletions (Mullighan \textit{et al} 2008). Further evidence showing the association of cytological damage and cancer comes from the findings that increased frequencies of non-specific chromosomal damage in peripheral blood lymphocytes is a predictor for the risk of cancer in humans (Bonassi \textit{et al} 2007, Hagmar \textit{et al} 2004). Nevertheless, we do realise that our assumption of the association between mutation and cancer may not be as widely accepted as we thought and we wish, therefore, to present the data which, in our opinion, show conclusively that radiation induced cancer arises from chromosomal damage.

2. The data and its interpretation

The data come from the induction of cancer in animals where different radiation conditions have been used. Some data are presented in figures 1–4 for the induction of leukaemia or lung tumours in mice after both low LET and after fast neutron radiation over a wide dose range.
All these figures show that as dose increases the cancer induction, the fraction of animals developing cancer, rises to a peak value which is substantially less than unity (or 100% of animals with cancer) and decreases at higher doses as a result of cell killing. The crucial feature shown in each of these figures is that the peak value reached for the low LET radiation is the same for the neutron irradiations even though the dose kinetics are clearly different. The actual value of the peak height reached varies dependent on the strain and sex of mouse used and the type of cancer investigated. The fact that the peak height is independent of the radiation used indicates that the type of lesion which leads to the induction of cancer is the same as the type of lesion which leads to cell killing and is independent of the dose response relationship for that lesion.

This can be seen theoretically in the following example:

Let us assume that cell killing following low LET radiation has linear–quadratic dose kinetics and that survival \( S \) is given by

\[
S = \exp\left[-p(\alpha D + \beta D^2)\right],
\]

where \( p \) is the probability that a lesion induced with linear–quadratic dose kinetics leads to cell killing.

Irrespective of its theoretical origins, this equation has been shown to give as good a fit to cell survival data as can be expected from statistical considerations (Gillespie et al. 1975a, 1975b).

Now, assuming the same type of lesion is responsible for the induction of the cancer gives us an equation for cancer induction (CI) as

\[
CI = (1 - \exp[-q(\alpha D + \beta D^2)]) \exp[-p(\alpha D + \beta D^2)]
\]

where \( q \) is the probability that a lesion leads to the induction of cancer.

This equation has been used to draw the curves shown in the figures 1–4. The curves are not best fits but drawn to illustrate the same peak value.
This equation is similar to one derived earlier (Chadwick and Leenhouts 1981) for the cell transformation per irradiated cell. A comparable equation has been recently derived in a similar fashion by Jones (2009) independently of our previous publications, apparently.

Equation (2) can be rewritten as

\[ CI = (\exp[-p(\alpha D + \beta D^2)] - \exp[-(p + q)(\alpha D + \beta D^2)]) . \]  

(3)

In the peak, the first differential of CI with respect to dose is zero, so that

\[ \frac{d(CI)}{dD} = (-p(\alpha + 2\beta D))(\exp[-p(\alpha D + \beta D^2)]) + (p + q)(\alpha + 2\beta D) \times (\exp[-(p + q)(\alpha D + \beta D^2)]) = 0, \]

(4)

which reduces to

\[ p/(p + q) = \exp[-q(\alpha D + \beta D^2)]. \]  

(5)

Replacing in equation (2) reveals that the maximum value of cancer incidence (\( CI_{\text{max}} \)) is

\[ CI_{\text{max}} = [1 - p/(p + q)][p/(p + q)]^{p/q} \]

(6)

which is independent of \( \alpha, \beta \) and \( D \). This means that, as long as the lesion inducing the cancer is the same as the lesion causing cell death, then the maximum value of cancer induction is independent of the way in which the lesions are induced, i.e. independent of the type of radiation and exposure conditions used.

We can thus conclude that the data shown in figures 1–4 imply that the same type of lesion is responsible for cancer induction and cell killing but that the data say nothing about the nature of that lesion.
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Figure 4. Induction of leukaemia in mice after exposure to x-rays and fission neutrons (Mole and Davids 1982, Mole et al 1983)) revealing the same peak height.

However, there are other experimental data in the literature which correlate the yield of chromosome aberrations with cell killing for a variety of different radiation conditions (Greenblatt 1962, Dewey et al 1970, 1971b, 1971a, 1978, Bhambhani et al 1973, Franken et al 1999) and other data which correlate mutation frequency with cell killing for a variety of radiation conditions (Richold and Holt 1974, Thacker and Cox 1975, Cox et al 1977) examples of which are shown in figures 5 and 6.

Although Dewey and his colleagues scored unstable aberrations, recent studies with FISH techniques have shown that stable aberrations, more usually associated with cancer, also show the same dose response relationships. For example, for low LET radiation unstable dicentrics are induced with the same dose response as stable translocations (Moquet et al 2000) and can therefore be assumed to arise from the same type of initial lesion.

The single linear correlation in figure 5 satisfies the equation

\[
\ln S = -k_1Y_{CA}
\]

where \( S \) is cell survival, \( Y_{CA} \) is the yield of chromosomal aberrations and \( k_1 \) is a constant.

The most straightforward interpretation of the correlation is that the type of lesion which causes cell killing is the same as the type of lesion which leads to a chromosomal aberration.

The single linear correlation in figure 6 satisfies the equation

\[
\ln S = -k_2M
\]

where \( M \) is the mutation frequency per surviving cell and \( k_2 \) is a constant.

Again, the correlation can be interpreted to imply that the type of lesion which causes cell killing is the same as the type of lesion which leads to a mutation.
Figure 5. The single linear correlation between cell survival and the yield of chromosomal aberrations taken from the data of Dewey et al. (1970, 1971b, 1971a) for cells in different phases of the cell cycle with, and without, BUdR used as a sensitiser.

Figure 6. The single linear correlation between cell survival and mutation frequency taken from the data of Richold and Holt (1974) after fast neutron and gamma ray exposures.
The data in figures 5 and 6 relate cell killing directly to chromosomal aberrations and somatic mutations but once again, the data tell us nothing about the type of lesion except that, for chromosomal aberrations and mutations, DNA damage must be involved somewhere.

In order to demonstrate that the same peak height phenomenon found in the animal cancer data shown in figures 1–4 can also be found in mutation data we present, in figure 7, some data for the induction of pink mutations in Tradescantia stamen hairs after neutron and x-ray exposures in aerobic and anaerobic conditions taken from Underbrink et al (1975). The same peak height shown in figure 7 confirms that the type of lesion responsible for mutation induction is also responsible for cell killing.

Irrespective of the interpretation applied, the experimental data shown in figures 1–7 create a chain which links chromosomal aberrations and somatic mutations directly to cell killing and on to cancer induction and leave no doubt that radiation induced cancer arises as a consequence of a chromosomal aberration or a somatic mutation.

It is important to note that the experimental data themselves provide this crucial information and are independent of any theoretical model. The model has merely provided insight, forged the linkage and facilitated the interpretation of the data.

3. Conclusion

A chain of experimental data can be developed which show that radiation induced cancer arises from chromosomal damage and has the same dose kinetics as mutations and chromosomal aberrations.

The data have been available in the published literature for many years and some can be found in various parts of our book (Chadwick and Leenhouts 1981). We have subconsciously assimilated their significance although we have never, to our regret, put the data in the logical sequence presented here.
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