Cancer and cell senescence

SIR — In their *News and Views* article "Step-by-step into carcinogenesis"[1], Cairns and Logan discuss the finding that oncogenic DNA can transform immortal established cell lines, such as mouse 3T3, but not diploid cells which have limited growth potential. They write that: "One of the built-in programmes protecting the whole organism against invasion by clones of uncontrolled variants is the programmed senescence that normally comes into play after a certain number of cell generations. This barrier has to be overcome whenever a cancer is formed or a cell line is established *in vitro*, and so it is not illogical to expect that transfection with any established cell line could show what changes are needed to circumvent programmed senescence". These are astonishing assertions based, as far as I am aware, on no direct evidence.

The hypothesis that the senescence of diploid cells is a protective device to prevent the indefinite spread of malignant cells, which was first proposed by Dykhuizen[2], runs into several serious difficulties. Human diploid fibroblasts have a growth potential of about 60 population doublings. Starting with a single cell, this represents 2^{60}cells, that is 10^{18} cells equivalent to approximately 10^6 kilograms of cells. It is clear that a clone of cancer cells with this, or any similar, proliferative capacity could easily kill the organism, whether or not it finally underwent senescence. This is clearly illustrated in the case of avian cells. It is well established that normal chicken cells can be transformed with oncogenic viruses to produce highly tumorigenic derivatives. Very few, if any, of these malignant strains have been passaged indefinitely, either *in vivo* or *in vitro*, yet they can kill the animal, before the "barrier of senescence" is reached. In addition, skin fibroblasts from certain inherited cancer-prone syndromes (such as Bloom's syndrome, ataxia telagiectasia, Fanconi's anaemia and Werner's syndrome) have a significantly shorter growth potential than cells from normal individuals[3].

If senescence is programmed, why should it be accelerated in these conditions, and if it is a barrier, why are the affected individuals not protected from metastatic growth of tumours?

Apart from the possibility suggested by Cairns and Logan that normal cells have programmed senescence and tumour cells do not, there are quite different explanations for their differences in growth potential. For example, finite growth versus infinite growth may be attributed simply to heterogeneity in the growth potential of individual clones.

As pointed out by Orgel[4], for a population with indefinite growth it is only necessary for each dividing cell to produce on average more than one viable daughter. It is therefore quite possible for a permanent line to contain many sub-clones which have limited proliferative potential, whilst retaining a "stem line" of potentially immortal cells. In populations of diploid cells, such a stem line may be lost during serial sub-culture[5]. Another possibility is that transformed cells have reverted to a de-differentiated, quasi-embryonic or germ-line state, and that they are able to avoid, or protect themselves from, the accumulation of defects in macromolecules, which may be responsible for the ultimate demise of differentiated somatic cells [6,7].

The demonstration of the relationship between transformation and infinite growth potential in rodent cells is of obvious importance, not least because it reinforces the view that a full understanding of the processes leading to the emergence of tumour cells may also depend on unravelling the mechanisms of cellular senescence.

ROBIN HOLLIDAY

Genetics Division,
National Institute for Medical Research,
Mill Hill,
London NW7 UK

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CAIRNS AND LOGAN REPLY — In the first half of his letter, Dr Holliday gives three reasons for thinking that programmed cell senescence is not a protection against the development of cancer. We believe that each of the arguments is fallacious.

The common human cancers, as described in textbooks of pathology, are full of terminally differentiated cells. Indeed, they often have a smaller proportion of cycling cells than the normal tissues from which they have arisen (perhaps for the trivial reason that a cancer lacks the structural organization that allows a tissue such as an epithelium to discard its differentiated progeny). So we have no notion how many divisions the stem-line has to undergo in order to produce a fairly small cancer containing, say, 2^{30} cells, save that it will be a lot more than 30 divisions. For all we know, clones that start uncontrolled growth may often find themselves permanently arrested because their stem-line hits 60 divisions. Certainly, many more invasive clones arise — and can be found in serial sections — than give rise to endlessly proliferating cancers.

The tumorigenic derivatives of normal chicken cells transformed by certain oncogenic viruses produce tumours that grow by recruiting host cells rather than by clonal expansion (the way most human cancers grow). Programmed senescence will never be a barrier to this kind of growth.

As for the inherited cancer-prone conditions such as Bloom's syndrome, we know that they raise the rate of production of certain kinds of genetic variants, and so we might expect them to be associated with an increased incidence of cancer. In the absence of accelerated senescence they might have shown an even higher rate.

Two of the three papers that we discussed in our *News and Views* article describe how cancerous clones, produced by transfection of normal rodent fibroblasts with certain oncogenes, become invasive and embark on unrestrained growth; but in the end the growth of the clones invariably ceases unless the cells have also undergone immortalization. These papers, published in the same issue of *Nature*, provide direct evidence that programmed senescence is a protection against cancer.

JOHN CAIRNS
JONOTHAN LOGAN

Department of Cancer Biology,
Harvard School of Public Health,
Boston, Massachusetts 02115, USA

"Microgravity"

SIR — The European Space Agency is currently inviting life scientists to participate in their Microgravity Research Programme to study effects attributable to "the abolition of gravitational influences" in an orbiting spacecraft. It should be pointed out, however, that it is not the gravitational field that is "abolished" in orbit. Indeed, if it were, there would be no orbit, no curvature of the flight-path. The relevant feature of the free-fall conditions of orbital flight is that objects can retain their relative position within the spacecraft without developing stresses (*g*-forces) in their mechanical supports.

When a weight is supported by a spring, the spring tension is a stress phenomenon, not a gravitational one. In orbit, it is the stress distribution, not the gravitational field, that is different from that familiar on the Earth's surface. The "*g*-forces" are stress phenomena in spite of the fact that the unit of acceleration, *g*, used to characterize them is defined in a gravitational context. For orbital conditions it would be preferable to use the expression "micro-*g*" in place of "microgravity". This might avoid the temptation to think in terms of field effects and might direct attention more appropriately towards the rearrangements of molecular architecture associated with stress gradients.

T.D.M. ROBERTS

11 Menzies Drive,
Fintry,
Glasgow G63 0YG, UK