TECHNICAL PAPERS

The Species Character of Cancer Cells

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In our investigations of the cause of mammary cancer of inbred strains of mice (*11*), immunologic studies suggest that the species character of the cancer cells may be determined by the associated virus rather than by their origin from the tissues of the mouse.

The mouse mammary cancer virus is highly antigenic. Upon injection into rats or rabbits, it stimulates the production of immune bodies (*1, 8*). An antiserum made from immunized rabbits or rats will not only neutralize the virus but, *in vitro*, will also inactivate mouse mammary cancer cells (*5*). Normal rabbit serum and antiserum from rabbits immunized with normal mouse mammary gland tissue do not neutralize the mouse cancer virus, nor do they inactivate mouse mammary cancer cells. It therefore appears to be the specific immune bodies in the virus antiserum that accomplish both effects. Our further investigations utilizing absorption tests (*6*) show that the immune bodies in the antiserum will combine only with the mammary cancer cells, and that they will not combine with the normal lactating breast tissue cells from which the cancer cells are derived.

There are two indications in our data that point to some extremely close relationship, or combination, of the virus and the cancer cell. The first is that in absorption tests the virus antibodies combine with the cancer cell but do not combine with the normal cell of the same kind. While this finding demonstrates a specific absorption of immune bodies by the cancer cell, the absorption could be due to free virus contained within it. The second is that the virus immune bodies have an inactivating, or lethal, effect upon the cancer cell, which would seem to mean that some virus is not free but occupies a vital position in the cancer cell. The malignant animal cell seems to have become completely dependent upon the vital activity of the virus associated with it. The two findings together suggest not only that the virus is intimately associated with the cancer cell but also that the association is concerned with the species character of this cell, since these immunologic reactions are ordinarily species specific. Immunologically, the mouse mammary cancer cell appears to be a mouse cell with a substituted virus species.

These immunologic findings for the mouse cancer do not stand alone. Those of Kidd and Rous (*10*) for the Shope virus-cancer complex and of Kidd (*9*) for the Brown-Pearce cancer of rabbits fall into the same general pattern. The experimental results so far available for these two rabbit cancers can be interpreted to mean that in each case an antigen foreign to the normal rabbit cell is present in some close combination in the cancer cell. The antigens are foreign to the rabbit species, since in both cases the rabbit cancer cell stimulates antibody formation in the rabbit, which is the same animal species from which the cancer cell was derived. The rabbit cancer developing from the Shope papilloma does not appear to contain free virus, but upon its transplantation to normal rabbits the rabbits become immune to the Shope papilloma virus as the cancer transplant grows. Here the cancer cell is antigenic, and the species character of the cancer cell appears to be that of the associated Shope virus. In the case of the Brown-Pearce cancer, the foreign antigen associated with it is not known to be a virus. However, the foreign antigen is separable from the cancer cell and upon injection into rabbits produces a specific antiserum. Since, as Kidd (*9*) has recently shown, the antiserum injected into rabbits afflicted with the cancer has some effect on regression of the cancer, the immune bodies appear to combine specifically with the cancer cells, as we have demonstrated for the mouse mammary carcinoma. Thus, the results of immunologic studies on three animal tumors suggest that the species character of the cancer cell is not that of the animal of origin but that of an associated virus.

It appears to be biologically sound to consider viruses as simplified forms of microbes which have developed their small size and physiological dependencies as retrograde changes due to intracellular parasitism (*2, 4*). It seems logical, also, to conceive that an end result of the retrograde parasitic process could be an actual mergence, or hybridization (*3*), of the parasitic virus with the host cell. The data which we have obtained on the mouse mammary cancer definitely point to some sort of intimate combination, or hybridization, of the virus with the mouse mammary cell. It would seem that a hybridization resulting in a change in the species character of the cell might well result in a new type of parasitic cell (*7*), which would grow as a cancerous process quite independent of control by the animal organization of which it was formerly an integral part. A similar basic change in the species character of a cell might also be produced by coal-tar chemicals or by radiant energy, and these changes could also result in cancerous growth, since the species character modification would likewise remove the cell from the corporate growth control. From the standpoint of modification or substitution of the species character as a basic cause of cancerous growth of cells, the mechanism of cancer production by coal tar, by radiation, and by a virus seems to be basically and essentially the same process.

References

1. ANDERVONT, H. B., and BRYAN, W. R. *J. nat. Cancer Inst.*, 1944, 5, 143.
2. GREEN, R. G. *Science*, 1935, 82, 443.
3. GREEN, R. G. *Biodynamica*, 1938, No. 39.
4. GREEN, R. G. *Chemistry and medicine.* Minneapolis: Univ. Minnesota Press, 1940. P. 157.
5. GREEN, R. G. *Proc. Soc. exp. Biol. Med.*, 1946, 61, 113.
6. GREEN, R. G. *Minn. Med.*, 1946, 29, 277.
7. GREEN, R. G. *Biodynamica*, 1946, 6, 1.
8. GREEN, R. G., MOOSEY, M. M., and BITTNER, J. J. *Proc. Soc. exp. Biol. Med.*, 1946, 61, 115.
9. KIDD, J. G. *J. exp. Med.*, 1946, 83, 227.
10. KIDD, J. G., and ROUS, P. *J. exp. Med.*, 1940, 71, 813.
11. STRONG, L. C. *Cancer Res.*, 1942, 2, 531.