HeLa Marker Chromosomes, Chang Liver Cells, and Liver-Specific Functions

Nelson-Rees and Flandermeyer have (1) indicted the Chang liver cell (2) as a HeLa cell contaminant. They have concluded that, regardless of designation, the Chang cell should be considered a de facto strain of HeLa. These authors based their conclusion on the following: (i) the electromobility of glucose-6-phosphate dehydrogenase (G6PD) and phosphoglucomutase of the Chang cell were similar to those of the HeLa cell; (ii) the Chang cell contained a complex of rearranged chromosomes or markers described for HeLa cell cultures; and (iii) there was no Y chromosome in the Chang cell. It is unfortunate that these authors failed to mention that Kaighn and Prince (3) had found the Chang but not the HeLa cell capable of producing serum albumin and fibrinogen, and that Bausher and Schaeffer (4) had demonstrated tyrosine aminotransferase activity in the Chang cell.

In 1953 to 1954 I made many attempts to cultivate cells from a variety of human tissues on the simplistic assumption that a specific differentiated cell might support in vitro the growth of a specific virus (for example, the human hepatocyte might support the growth of the human hepatitis virus). Since the goal was merely to obtain a sufficient number of cells that would support the growth of certain viruses under study, no effort was made to record the sex, race, age, and medical diagnosis of the tissue donor. The liver specimen, from which the Chang cell was derived (2), was obtained during biopsy from a patient undergoing exploratory laparotomy.

Since there is no record of the sex and race of this tissue donor, the absence of a Y chromosome and the presence of G6PD and phosphoglucomutase with specific electromigration patterns (similar to those found predominantly among the black race) cannot be used as evidence for indicting the Chang liver cell, because the tissue donor could be a black woman. Therefore, the indictment by Nelson-Rees and Flandermeyer is based solely on the morphologic appearance of chromosomes.

Ludueña et al. (5) have presented evidence that another protein characteristic of, but perhaps not unique to, differentiated liver cells (liver alkaline phosphatase) is synthesized by the Chang but not by the HeLa cell. They have found proteins characteristic of differentiated human liver cells in or secreted by the Chang liver cell. Other reported differences between these two cell lines include susceptibility to aflatoxin B1 (6) and the total and epinephrine-sensitive adenyl cyclase activities (7).

In view of these reports, I ask the following questions: If the Chang cell is derived from a culture of HeLa cell and not from a human liver biopsy as reported (2), what is the probability that the Chang but not the HeLa cell contains more than one liver-specific protein? Is chromosomal morphology sufficiently dependable to be used as the sole criterion in tracing the origin of an established line of human cells? Are we all aware of the seriousness of cross-line cell contamination in research involving cell cultures. But, to indict a cell line as a HeLa cell contaminant on insufficient evidence may be counterproductive.

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References

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“Chang liver cells” were first suspected of being HeLa cells in 1966 on enzymatic grounds (1). In 1974, Chang brought to my laboratory a culture of the “liver cells” for karyologic analysis. Our results were discussed with Chang and with Sussman, a co-author of the paper by Ludueña cited by Chang in his comment, and were summarized by us (2). Our results were confirmed by Lavappa et al. (3) on the “Chang liver cells” at the American Type Culture Collection (ATCC) (3). We indicted the cells as being HeLa cell contaminants because they possess a group of chromosomes originally described by Miller et al. (4) for HeLa cells. These “markers” consist of chromosomes whose banding patterns coincide with those of portions of specific human chromosomes, however rearranged (translocations, misdivision, nondisjunction). Besides these “Miller markers,” many HeLa strains share other identical markers which serve to characterize closely related strains of HeLa or the culprits in HeLa contamination of other cultures. In fact, we communicated to Chang that some markers that we observed in the “liver cells” were identical to some observed in the HeLa-contaminated cultures from Russian laboratories (5). In every culture analyzed to date, the cells that exhibit “Miller markers” and others also lack a Y chromosome and produce type A (fast moving) G6PD.

A sample of “Chang liver cells” supplied by the ATCC was studied recently by O’Brien (6) for additional enzyme polymorphism. The cells exhibited characteristics identical to HeLa and to other now well-known HeLa strains—H.Ep-2, KB, and J111—in the electrophoretic resolution of seven relatively polymorphic, human gene-enzyme systems previously studied by him [see (7)]. According to O’Brien the genotype frequency of HeLa, based on allelic frequencies of the seven tested enzyme loci in natural populations, is 0.013; or, as concerns all cells studied by him, the probability that another cell line would express the same genotype is .05.

Thus, while there is no record of sex, age, race, and medical diagnosis of the tissue donor for the original liver culture, the results of up-to-date karyology and enzymology speak more convincingly for its being now a strain of HeLa cells through the common occurrence of cross-cell-contamination than that of a liver derivative of which no other human line exists in spite of many initiation attempts. As to the liver functions detected in this strain of HeLa, we have re-
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