The first experimental demonstration of the clonal origin of cancer

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TITLE	Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas.
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At the turn of the 20th century, Theodore Boveri pondered the genetic origins of cancer. He mused that it might originate in a single cell, but no experimental evidence supported his hypotheses.[1] Confirmation of a clonal origin of a neoplasm used the observation that one X chromosome in each diploid cell in the mammalian female is randomly inactivated in early embryogenesis.[2] This action provides equivalency of X chromosome gene dosage in both sexes. It also results in half of the somatic cells in the tissues of the female containing proteins encoded by the genes of the maternal X chromosome and half of the cells having proteins encoded by the genes of the paternal X chromosome, on average.

Inactivation of an X chromosome early in embryogenesis was shown experimentally by Mary Lyon[3] to explain the variegated coat color in female mice.[4,5] Similar results were found, virtually simultaneously, by Ernest Beutler[6] and colleagues in informative women, using the expression of the X chromosome-linked gene for glucose-6-phosphate dehydrogenase (G6PD) in red blood cells.[7] The expression of this enzyme was used, initially, to discern the clonal origin of tumors.

In the early 1960s, David Linder, a young pathologist at the Children's Hospital in San Francisco, received a 1-year National Institutes of Health fellowship to conduct research in the Department of Pathology at the University of Washington under the guidance of Stanley Gartler. Linder and Gartler had the idea of using G6PD isoenzymes to explore the question of the single cell origin (somatic mutation hypothesis) of neoplasms as contrasted with the field theory of carcinogenesis. They used leiomyomas for these experiments and compared them to intervening normal myometrium from informative women. Gartler remarked that there was no human investigation committee at that time, and no permission was required to use human tissue that was to be discarded (personal communication between Marshall Lichtman and Stanley Gartler, *circa* 2010).

Linder arranged with the surgical pathology laboratory to obtain excised uteri from patients of African descent who had undergone hysterectomy for leiomyomas. Initially, he homogenized a portion of the myometrium and did gel electrophoresis to determine whether the individual was informative, i.e. a compound heterozygote for G6PD isoenzymes A and B. Linder and Gartler devised an ingenious experiment to use the excised uteri containing leiomyomas from five women found to have compound heterozygosity to assess the tumors' cellular origin.[8] They found that 85 of 86 samples of myometrium had electrophoretic bands for both isoenzymes G6PD A and B in equal or nearly equal amounts, whereas 27 samples of leiomyomas from the same five heterozygous women contained either a G6PD A band or a G6PD B band. Moreover, G6PD A or B band-containing tumors were present in all uteri. They concluded that these findings were consistent with the hypothesis that the leiomyomas arose from a single cell. This conclusion was confirmed in other neoplasms by others, thereafter.[9,10] This ingenious first approach to defining the cellular origin of a neoplasm has stood the test of time, although some have discussed some possible complexities to the basic thesis.[11]

Disclosures

No conflicts of interest to disclose.

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