This Week's Citation Classic®

Wolff S. Sister chromatid exchange. *Annu. Rev. Genet.* 11:183-201, 1977.
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Autoradiography for the detection of sister chromatid exchange (SCE) has been replaced by methods in which the sister chromatids stain differentially. The ease of visualization of SCEs, in addition to the added resolution obtained with the new techniques, has led to practical studies on the effects of chemicals on chromosomes and to basic studies on chromosome structure and the mechanisms involved in SCE formation. [The *SCI*® indicates that this paper has been cited in over 280 publications.]

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In 1958 J.H. Taylor was the first to directly observe sister chromatid exchanges (SCEs) in rod chromosomes. He grew cells in the presence of radioactive thymidine so that a chromosome's genetically identical sister chromatids were physically different from one another; that is, only one chromatid was radioactive.[1] In autoradiograms, it was then possible to identify these two chromatids and to detect exchanges between them.

Studies of SCEs advanced our knowledge of chromosome structure and of how DNA was arranged and distributed into chromatids. Nevertheless, because of inherent problems with the resolution obtained in autoradiograms, many problems remained unanswered and new problems arose. For example, a controversy arose about the number of DNA molecules in chromosomes because segments of the genome occasionally seemed to have both sister chromatids labeled (isolabeling).

In 1972, however, A.F. Zakharov and N.A. Egolina found that the growth of cells in the presence of analogues of thymidine, such as bromodeoxyuridine (BUdR), led to two sister chromatids that were chemically different from one another and that thus stained differentially.[2] Paul Perry and I were able to combine fluorescence staining with Giemsa staining of chromosomes containing DNA substituted with BUdR to produce permanent preparations that showed SCEs with great clarity.[3,4] When I showed J. Ploem the first dramatic photographs of chromosomes stained so that dark and light segments were seen to switch from side to side, he was reminded of the costumes of medieval clowns and remarked, "Oh, harlequin chromosomes," and a name was born.

The ease of making the preparations, coupled with the increased precision in resolving the points of exchange, quickly settled arguments raised from autoradiographic experiments and further allowed the induction of SCEs to be used as a simple mammalian short-term test system for mutagens and carcinogens.[5] In fact, a marked increase in the publication of biological papers with certain catchwords in their titles had already led to a humorous newspaper article on biologists' mysterious new interest in "nudes" (from the nude mouse) and "sisters."

The induction of SCEs by mutagens and carcinogens could also be used to gain biological insights into the system.[6] For instance, Anna Hill and I found that lymphocytes from pregnant women had more SCEs induced by diethylstilbestrol than did lymphocytes from men or postmenopausal women, and that the response to this compound, which induced increased levels of adenocarcinoma of the vagina in females exposed while *in utero*, was dependent upon the hormonal status of the cells. In other experiments, K. Morimoto and I carried out potency tests on SCE induction and were able to postulate which of the many metabolites of the weak leukemogen, benzene, might be the proximate cause of the cancers.[7]

This review was probably cited so often because the newer techniques attracted many people to the field who could for the first time use SCEs in their work. The review was perhaps popular among these people because I included more than just a litany of all the papers that had been published within the past year. I also presented a historical perspective of the biological problems involved and the questions that could now be addressed, along with those for which answers had already been obtained.

1. **Taylor J H.** Sister chromatid exchanges in tritium-labeled chromosomes. *Genetics* 43:515-29, 1958. (Cited 270 times.)
2. **Zakharov A F & Egolina N A.** Differential spiralization along mammalian mitotic chromosomes. I. BUdR-revealed differentiation in Chinese hamster chromosomes. *Chromosoma* 38:341-65, 1972. (Cited 180 times.)
3. **Perry P & Wolff S.** New Giemsa method for the differential staining of sister chromatids. *Nature* 251:156-8, 1974. (Cited 1,340 times.)
4. **Latt S A.** Microfluorometric detection of deoxyribonucleic acid replication in human metaphase chromosomes. *Proc. Nat. Acad. Sci. USA* 70:3395-9, 1973. (Cited 700 times.)
5. **Wolff S.** *Sister chromatid exchange*. New York: Wiley, 1982. 306 p. (Cited 55 times.)
6. ————. Sister chromatid exchange as a test for mutagenic carcinogens. *Ann. NY Acad. Sci.* 407:142-53, 1983.
7. **Morimoto K & Wolff S.** Increase of sister chromatid exchange and perturbations of cell division genetics in human lymphocytes by benzene metabolites. *Cancer Res.* 40:1189-93, 1980. (Cited 60 times.)

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