**ELECTRONIC LETTER**

Molecular changes in skin predict predisposition to breast cancer

V J James, B E Willis

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Fibre diffraction has been greatly enhanced by the advent of synchrotrons, the beams of which are sufficiently strong to enable weak changes, not visible in conventional x-ray diffraction studies, to be seen even with greatly reduced exposure times. Using this technique, James et al. have determined the structure of primordial embryonic fetal tendon and skin and observed subtle changes in the ultrastructure of the α-keratin of hair in breast carcinoma. Using synchrotron fibre diffraction, fetal-like tissue has been located in the skin of healthy females known to have a family history of breast cancer.

**BACKGROUND**

During a study of the changes in the molecular structure of dermal collagen with ageing and insulin dependent diabetes mellitus (IDDM), skin samples from 192 people aged between 18 and 90 were examined.

Analysis of fibre diffraction patterns of the 172 controls and of the 12 IDDM patients showed that the only change with age of the dermal collagen was a variation in the microfibrillar radius. However, the values obtained for the microfibrillar radius of the IDDM samples was much lower than those of the age related normal population, which suggests that the skin of these people appeared to undergo premature ageing. These results are illustrated in fig 1. All samples were obtained from routine surgery, necropsies, or from punch biopsies.

In this study, a specific molecular structural change was observed in eight women aged between 18 and 25, all of whom were subsequently shown to have a pathologically changed BRCA1 gene. A composite picture showing the typical diffraction patterns for both normal skin and those of skin from persons with such a predisposition to breast cancer is shown in fig 2. The samples illustrated were age matched.

The microfibrillar radii of these eight samples were calculated using a First Order Bessel Function Analysis and found to be in the upper fetal range. In addition, the normal collagen pattern is superimposed by a ring. The observed ring in the pattern has a radius of 43.8 nm, which is different from that of 32.1 nm observed for fetal skin and tendon. Hence, we have termed it a “fetal-like collagen”. To investigate this finding, a further blind study was undertaken.

**METHODS**

For this study, 19 fresh skin samples, approximately 1 mm x 10 mm were removed from the anterior axillary fold to ensure that they were free of actinic damage from sunlight. Immediately after excision, sutures were attached by the surgeons to both ends for tying the samples into the experimental cells and then all samples were placed in physiological saline and stored at -20°C until required. Before mounting in the cells, which have been specifically designed to maintain 100% humidity throughout the experiment, the skin samples were gently scraped to remove the epithelial and the epidermal layers to expose the dermal layer.

These samples were investigated at the BioCAT Facility, Advanced Photon Source, Argonne, USA, using a camera length of 1000 mm. The synchrotron fibre diffraction intensity distributions were recorded on FUJI BAS imaging plates and later extracted by electronic scan. A high precision analysis of the two dimensional data was carried out using the astronomy computing packages IRAF (1986) and SAO Image (1991). All experiments and procedures have been approved by the appropriate Ethics Review Committee of the Institutions.

**RESULTS**

After completion of the data analysis, only one sample was clearly identified in the set of 19 as having the altered “fetal-like” pattern observed in the eight earlier samples.

**DISCUSSION**

At the conclusion of the analysis, it was shown that all 19 volunteers involved in this experiment had recently undergone their annual check ups, which included pap smears and mammography, and all were declared to be in perfect health. The person identified as having the altered pattern was subsequently determined to be the only one in the set with a familial history of breast cancer. Her sister and all maternal female relatives from the previous two generations had died of breast cancer. Although the experiment was carried out with the approval of the Ethics Committee of the hospital, the participating surgeons were unaware of the family histories of the volunteers before the results of these experiments were

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**Abbreviations:** IDDM, insulin dependent diabetes mellitus
known, making this a totally double blind experiment. Statistically, the possibility of correctly identifying this person is of the order of 1 in 500 000.

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Authors’ affiliations

V J James, Research School of Chemistry, Australian National University, Canberra, Australia

B E Willis, Eastmoreland Hospital, Portland, Oregon, USA

Correspondence to: Professor V J James, Research School of Chemistry, Australian National University, Canberra ACT 0200, Australia; vjs@bigpond.com

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Figure 2 A composite picture of the typical synchrotron fibre diffraction patterns obtained for human skin. The normal pattern on the left was obtained for controls and the changed pattern with the additional ring on the right was obtained for persons known to have strong family histories of breast cancer including those shown to have a pathologically changed gene.