Stem cell 'daughters' lead to breast cancer

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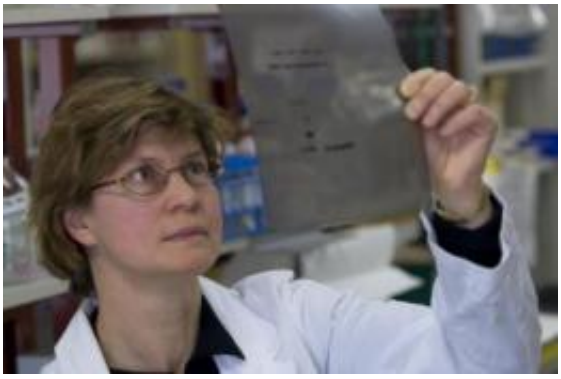

Associate Professor Geoff Lindeman and Dr. Jane Visvader (pictured) from the Walter and Eliza Hall Institute have found that a population of breast cells called luminal progenitor cells are responsible for breast cancers that develop in women carrying mutations in the gene BRCA1. Credit: Walter and Eliza Hall Institute

Walter and Eliza Hall Institute scientists have found that a population of breast cells called luminal progenitor cells are likely to be responsible for breast cancers that develop in women carrying mutations in the gene BRCA1.

BRCA1 gene mutations are found in 10-20 per cent of women with hereditary breast cancer. Women with BRCA1 mutations often develop 'basal-like' breast cancer, which is a particularly aggressive form of the disease.

A team led by Associate Professors Jane Visvader and Geoff Lindeman from the institute's Victorian Breast Cancer Research Consortium

Laboratory have discovered that luminal progenitor cells - the 'daughters' of breast stem cells - are the likely source of basal-like breast tumours. Their finding, published in today's issue of the international journal *Nature Medicine*, represents a major shift in the way scientists think breast cancer develops.

Dr Visvader said it had been thought in recent years that breast stem cells gave rise to BRCA1 tumours. "However, research carried out at the institute by Drs Elgene Lim and François Vaillant has shown that breast tissue from women with BRCA1 mutations has unexpectedly high numbers of luminal progenitor cells," she said.

"Further, our gene expression studies have revealed that BRCA1 breast tissue and basal breast tumors are more similar to normal luminal progenitor cells than any other cell type in the breast. This places the spotlight on errant luminal progenitors, rather than breast stem cells."

Dr Lindeman, who also heads the Familial Cancer Centre at the Royal Melbourne Hospital, said that now the importance of luminal progenitor cells in breast cancer was known it opened the way for the development of new drugs or therapies to treat breast cancer, one of the biggest causes of premature death in women.

"BRCA1 women have approximately a 65 per cent lifetime chance of developing breast cancer. Following surgery, treatment options available to these women are often limited to chemotherapy and radiotherapy, so identifying new treatment and prevention strategies is a priority for us," he said.

Luminal progenitor cells in women with BRCA1 mutations have 'forgotten' how to behave, Dr Lindeman said. "Usually, luminal progenitor cells multiply rapidly in the presence of certain growth factors. In BRCA1 women these cells don't even require growth factors

to proliferate - they misbehave from the outset.

"We also know that the BRCA1 gene is required for normal DNA repair. There may therefore be a triple whammy effect - faulty growth control, faulty DNA repair and expanded luminal progenitor cell numbers -ultimately resulting in breast cancer in some BRCA1 mutation carriers."

Dr Visvader said in the long-term, breast biopsies might be able to reveal misbehaving luminal progenitor cells. What's more, certain 'markers' might one day help guide diagnosis and treatment. "For example, c-KIT is a key marker of the luminal progenitor cell and I expect we will see an increase in pathologists routinely using this as a diagnostic marker for basal-like tumours," she said. "It may even be possible to develop new drugs that target c-KIT, since drugs are already available that target different forms of this marker."

Dr Lindeman said the identification of stem cells, luminal progenitor cells and other cell types in the breast was now beginning to reveal a breast cancer roadmap - highlighting cancer-prone cell types and key genetic pathways. "Hopefully this will lead to new, tailored therapies for the next generation of women."

Dr Visvader said the research had only been possible through the generous donation of breast tissue by women undergoing breast surgery, together with the support of their surgeons and pathologists. The study was facilitated by the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer.

Source: Walter and Eliza Hall Institute