Gene silencing critical for normal breast development

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From left: Dr Michael Milevskiy, Professor Jane Visvader and Dr Ewa Michalak. Credit: Walter and Eliza Hall Institute of Medical Research

Researchers have discovered that normal breast development relies on a genetic 'brake', a protein complex that keeps swathes of genes silenced.

The team demonstrated that a complex of proteins called PRC2 (Polycomb Repressive Complex 2) was essential for the development of mammary (breast) tissue from stem cells. They also identified that certain breast cancers may develop as a result of the loss of PRC2.

The research, which integrated cutting-edge tissue culture systems and bioinformatics techniques, was led by Dr. Ewa Michalak, Professor Jane

Visvader, Professor Gordon Smyth and Professor Geoff Lindeman. It was published in the journal *PLOS Biology*.

At a glance

The development of breast tissue from stem cells is a highly regulated process impacted by many genes, which may be switched on or off at different stages and in different cells.

The researchers demonstrated breast development relies on a genetic 'brake' called PRC2, a protein complex which silences many genes. Errors in this process may be linked to the development of poor prognosis breast cancer.

The research relied on a tissue culture system called mammary organoids, which enabled the researchers to pinpoint how PRC2 enables normal breast tissue development.

Silencing genes

The genome contains many genes that are required for specific processes in different parts of the body, or are only required at distinct times during development. Systems that correctly switch certain genes on or off in particular cells are critical for the normal biological functioning, and disruptions in this process have been implicated in driving many types of cancer.

Professor Visvader said PRC2 is a complex of proteins that prevents large areas of the genome from being expressed. "This silences swathes of genes simultaneously, with substantial impacts on the cell," she said. "We had previously identified the role of some of the proteins in PRC2 during breast development, but we wanted to understand the importance

of the entire protein complex to this process."

The team discovered that without an intact PRC2 complex, mammary tissue could not develop, Dr. Michalak said. "We were able to attribute this to the loss of mammary progenitor cells, which are precursor cells involved in tissue development. Through our collaboration with bioinformatics experts we could pinpoint the genes that became activated by the loss of PRC2, and how this stifled mammary development," she said.

The research may have implications for understanding how breast cancer develops, said Professor Lindeman, who is also a medical oncologist at the Peter MacCallum Cancer Centre.

"Some poor prognosis breast cancers have disrupted PRC2 activity, suggesting this complex silences the genes that drive cancer development," he said. "The bioinformatic studies, led by Professor Smyth, of gene expression in mammary tissue lacking PRC2 suggested that this tissue had many similarities to 'claudin low' breast cancers, which have a particularly poor prognosis. This reinforces our conclusion that cells with faulty gene regulation are predisposed to develop into cancerous cells."

Success through innovation

The team's discoveries relied on genetic models that contained no PRC2 complex, but this presented substantial technical hurdles. "Without PRC2, mammary glands cannot develop – meaning there are no cells to study using conventional models," Dr. Michalak said.

"We took advantage of a recently developed tissue culture system, mammary organoids, which are grown from single mammary stem cells into 3-D structures that can be grown in the laboratory but recapitulate

the normal development of breast tissue.

"Using this approach we could allow mammary development to commence, and then remove PRC2 from the system – so we could study the impact of its loss on breast tissue development."

Professor Visvader said this was the first time mammary organoids had been used to overcome the challenge of studying genes that are essential for complex processes. "There are many genes that exert complex and critical influences on developmental processes, and these have traditionally been very difficult to study.

"We are excited about the potential of using mammary organoids to investigate other regulators of gene control."

More information: Ewa M. Michalak et al. Canonical PRC2 function is essential for mammary gland development and affects chromatin compaction in mammary organoids, *PLOS Biology* (2018). DOI: 10.1371/journal.pbio.2004986

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