Medical Xpress

Cancer researchers discover how BRCA1 mutation starts breast, ovarian cancers

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Scientists led by Drs. Mona Gauthier and Tak Mak at The Campbell Family Institute for Breast Cancer Research at the Princess Margaret Cancer Centre have solved a key piece in the puzzle of how BRCA1 gene mutations specifically predispose women to breast and ovarian cancers.

The answer, says Dr. Mak in research published today in the *Journal of Experimental Medicine*, is found in the way estrogen rushes in to "rescue" cells whose healthy functioning has been altered by oxidative stress, a well-established factor in cancer development. Without estrogen, these damaged cells would die a natural death and not threaten the host in the long run, but with estrogen, these cells not only survive, but thrive and develop breast and ovarian cancers. In Canada, about 1,000 women die from BRCA1-related cancers every year.

The research published today illuminates the interplay between the tumour suppressor gene BRCA1 and a master regulator – Nrf2 – that governs the antioxidant response in cells. In healthy cells of all tissues, BRCA1 normally repairs damaged DNA in partnership with Nrf2, and so the cells are protected against oxidative stress. However, when the BRCA1 gene is mutated, it loses its ability to repair DNA and can no longer partner with Nrf2, shutting off its antioxidative function. In most tissues, the resulting oxidative stress kills the cells that have lost BRCA1 function. However, in breast and ovary, the estrogen present in these tissues can swoop in to rescue BRCA1-deficient cells by triggering a partial turn-on of Nrf2. These unhealthy cells gain just enough resistance

to oxidative stress to keep them alive and growing. Over time, these surviving BRCA1-deficient cells accumulate more and more mutations due to their lack of ability to repair DNA damage, eventually leading to the development of cancer in these tissues.

Dr. Mak likens the actions of Nrf2 to a ceiling sprinkler that puts out visible flames (oxidative stress) but doesn't reach the smoldering fire – cell damage – below.

He says: "Our research confirms that anti-estrogens can delay the onset of breast and ovarian cancers in carriers of BRCA1 mutations. Thus, the challenge is finding a way to block the antioxidant activity of estrogen without affecting its other activities that are necessary for female health. Modification of this one aspect of estrogen function would disrupt this significant cancer-initiating process while maintaining the positive effects of this hormone."

Dr. Gauthier and Dr. Mak discovered this critical interaction between BRCA1, Nrf2 and estrogen in initiating women's cancers by making use of genetically engineered mice. By examining the links between BRCA1 and oxidative stress in these mutant animals as well as in normal breast cells and breast tumours, they were able to generate results that finally explain why loss of a tumour suppressor gene normally active in all tissues leads only to breast and ovarian cancers. The missing piece of the puzzle was estrogen and its unexpected effects on the antioxidant regulation mediated by Nrf2.

Dr. Mak, Director of The Campbell Family Institute for Breast Cancer Research, is an internationally acclaimed immunologist renowned for his 1984 cloning of the genes encoding the human T cell receptor. He is also Professor, University of Toronto, in the Departments of Medical Biophysics and Immunology.