Breast Cancer Caused by BRCA1 in a Porcine Model System

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Description

BRCA1 is a tumour suppressor found in the breast and ovary. Breast cancer is predisposed to people who have BRCA1 mutations, and BRCA1 expression is down-regulated in 30% of sporadic cases. Although the function of BRCA1 is unknown, it appears to play an important role in DNA repair and the maintenance of genetic stability. In order to better understand the function of the gene in vivo, mouse models of BRCA1 deficiency have been created. However, because of the subtle nature of BRCA1 function and the well-known differences in human and murine breast cancer biology and genetics, mouse systems may be limited in their usefulness in identifying BRCA1 function in cancer and validating the discovery of novel therapeutics for breast cancer. Pig biological processes and cancer biology, in comparison to mice, tend to be more similar to their human counterparts. To see if inactivating BRCA1 in pig cells encourages transformation and can be used as a model for human disease, researchers created an immortalized porcine breast cell line and used miRNA to permanently inactivate BRCA1. The cell line took on breast cancer stem cell features and had a modified phenotype. These findings support the use of pigs as a model for studying BRCA1 mutations in breast cancer, as well as the establishment of the first porcine breast tumor cell line. Breast cancer is one of the most common cancers in women today and one of the leading causes of death. Breast cancer is estimated to kill up to 40,000 people every year in the United States alone. While the underlying causes of breast cancer are still being researched, we now know that the BRCA1 tumor suppressor gene plays a key role in many breast cancers. Women with a BRCA1 germ line mutation have a lifetime chance of developing breast cancer of 50–85 percent. While somatic BRCA1 mutations are uncommon in sporadic breast cancer, allele loss or epigenetic mechanisms down-regulate BRCA1 expression in about 30% of sporadic cases. The role of BRCA1 is still a mystery. It functions as a ubiquitin ligase and can regulate the stability and activity of proteins including Claspin. It also plays a role in DNA repair, replication fork stability, senescence, oxidative stress, genomic stability, and checkpoint-induced cell cycle arrest (Zhang and Powell). BRCA1's complex role in cellular homeostasis has complicated elucidating its main roles in cancer. In order to better understand the function of the gene in vivo, mouse models of BRCA1 deficiency have been created. While BRCA1 knockout causes embryonic lethality in mice, conditional BRCA1 knockout in breast tissue results in tumor development after a long latency period. By adding defects in the p53 tumor suppressor to the animal system, the latency time can be drastically reduced. These animal models have allowed for the testing of therapies for BRCA1-deficient tumors. Still successful therapeutic methods, however, resulted in the development of tumors that were resistant to treatment. Since mice have such a short lifespan, further research into ways to overcome resistance is minimal. Furthermore, because of the subtle existence of BRCA1 function and the well-known differences between human and murine breast biology and cancer genetics, mouse systems may be limited in their usefulness in defining BRCA1 function in human cancer. Since mice have such a short lifespan, further research into ways to overcome resistance is minimal. Furthermore, because of the subtle existence of BRCA1 function and the well-known differences between human and murine breast biology and cancer genetics, mouse systems may be limited in their usefulness in defining BRCA1 function in human cancer. The authors declare that there were no commercial or financial partnerships that could be construed as a possible conflict of interest during the study.

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