MCF Cell lines that transformed breast cancer research

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Breast cancer initiation, development and metastatic progression is a multistep process and MCF-7 cells and the MCF10 cell series (comprising MCF10AT, MCF10DCIS.com and MCF10CA1 derivatives emanating from MCF10A cells) represent many steps in that process. The MCF-7 cell line established by Dr. Herbert Soule in 1973 at the Michigan Cancer Foundation (MCF, now named Barbara Ann Karmanos Cancer Institute, KCI) represents the first hormone responsive breast cancer cell line and was derived from the pleural effusion of a woman with metastatic breast cancer. Establishment of the MCF-7 cell line led to the pivotal discovery of estrogen receptor (ER) and laid the path to future endocrine therapy research. The finding that estrogen stimulated MCF-7 cell growth whereas tamoxifen suppressed it, and that the tamoxifen suppressive effect could be reversed by estrogen, was "game changing" as it led to the concept of antiestrogens and the molecular cloning of ER. The MCF-7 cell line is used by researchers throughout the world as a model of ER positive breast cancer and for characterization of antiestrogen response and resistance. Before the advent of recombinant DNA technology, MCF-7 cells served as the source of human ER protein for development of ER-specific antibodies that would ultimately revolutionize detection and molecular classification of ER-positive clinical breast cancers. Clinical decisions for endocrine-targeted therapy continue to rely on ER expression status, and as two-thirds of all breast cancers express ER, this underscores the immense clinical value that MCF-7 cell research continues to provide.

Another important contribution to breast cancer research by MCF/KCI researchers stems from the landmark paper published in Cancer Research in 1990 by Dr. Soule et al. which reported the first spontaneously immortalized nontransformed breast epithelial line, MCF10A. The MCF10A cell line was established from a reduction mammoplasty performed on a woman with benign fibrocystic disease. Since establishment of the MCF10A cell line resulted from spontaneous immortalization (i.e., without chemical or genetic manipulations), this, combined with its characteristics that recapitulate those of normal human breast cells, has allowed researchers worldwide to universally use this model as a normal control for modeling processes involved in normal breast development, and for interrogating events related to initiation of breast cancer development. Several characteristics that make the MCF10A cell line especially valuable include its stem cell properties (i.e., its ability to differentiate into luminal and myoepithelial cells), its ease of forming acini that show remarkable resemblance to normal breast ducts, and the absence of transformation properties *in vitro* and *in vivo*. A quick search of Pubmed shows >3000 papers published with MCF10A named in the titles. The real number of publications, however, far exceeds this if papers containing MCF10A in the body of the text are included.

The MCF10AT system was derived by stable transfection of MCF10A cells with mutant *Ha-ras* and represents a model of progressive human proliferative breast disease in which cells can be followed from a histologically precancerous stage to development of ductal carcinoma *in situ* (DCIS) and frank invasive carcinoma. These histologic changes closely mimic those observed in the breasts of women who are at high risk for breast cancer with respect to morphology and intra-tumor heterogeneity. Much like human breast cancers that have lengthy natural histories, the

lesions produced by premalignant MCF10AT xenografts are slow growing and not yet committed to a single pathway of cancer unless they are manipulated by hormonal supplementation. MCF10AT is the only available human model that has been shown to exhibit the histologic stigmata identified in women who are at high risk for developing breast cancer. By clonal selection of MCF10AT cells, the MCF10DCIS.com cell line was isolated. A remarkable and invaluable property of the MCF10DCIS.com cell line developed by Dr. Fred Miller at MCF is its ability to reproducibly and rapidly produce pure comedo-DCIS tumors, a subtype of high-grade DCIS that progresses to invasive cancer with characteristic loss of myoepithelium and basement membrane encapsulation. Tumors produced by MCF10DCIS.com cells capture the stage of breast cancer that is diagnosed at high frequency. Since comedo-DCIS, unlike the other DCIS subtypes, is associated with a high risk for progression to invasive cancer and recurrence, it is the appropriate target for preclinical screening of new chemopreventive and therapeutic agents before embarking on expensive clinical trials.MCF10CA1 cells with malignant properties were derived from MCF10AT cells by multiple passages in immunodeficient mice. Unlike the slow-growing premalignant MCF10AT cell lines, MCF10CA1 cell lines grow rapidly and form invasive carcinomas (without evidence of precursor stages), and some MCF10CA1 derivatives show spontaneous lung metastases. MCF10CA1 cell lines can be Her2 positive or Her2 negative, and can be estrogen receptor (ER) negative or focally positive for ER. This shows that the MCF10CA1 model is not limited to a single cancer phenotype but accurately recapitulates the biological diversity underlying breast cancer heterogeneity.

The MCF10 series of cell lines capture the entire spectrum of premalignant to malignant breast cancer. Breast cancer is a heterogeneous disease, and the heterogeneous spectrum of disease progression exhibited by the MCF10 cell series reflects its multi-potentiality. They provide reliable starting points for screening new agents and therapies, and offer several unique advantages including reproducibility, cost savings and speed of testing. The fact that all MCF10 derivatives share a common genetic background should increase their potential for identifying critical genetic events underlying breast cancer progression that will ultimately lead to the design of more efficient therapeutics and better prognosis for cancer patients.