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Metabolic profile of endocrine resistance

Robert Clarke

Georgetown University Medical Center, USA

About 70% of newly diagnosed cases of invasive breast cancer in the U.S. will be estrogen receptor 1 positive (ER+). Endocrine therapy is the least toxic and most effective means to manage the hormone-dependent breast cancer in these patients, administered as an antiestrogen, *e.g.,* Tamoxifen (TAM) or Faslodex (Fulvestrant; ICI 182,780) or an aromatase inhibitor (AI), *e.g.,* Letrozole (LET). TAM produces a 26% proportional reduction in mortality; however, advanced ER+ breast cancer that has become resistant to endocrine therapy remains a significant clinical problem.We have shown that antiestrogen resistant breast cancer cells over-express X-Box Binding Protein 1 (XBP1) and glucose regulated protein-78 (GRP78;BiP), two integral signaling components of the unfolded protein response (UPR).XBP1 can regulate glucose homeostasis, and as glucose levels fall, GRP78 activates the UPR. Antiestrogen resistant breast cancer cells (MCF7/LCC9) utilize prosurvival UPR to maintain a higher level of basal autophagy compared to sensitive cells (MCF7/LCC1) that can provide raw materials to promote cell survival under stress from therapeutic insults. Abundance of metabolites from antiestrogen sensitive and resistant cells was compared and analyzed using UPLC-MS. Changes in selected metabolites were independently validated. Our findings indicate that resistant MCF7/LCC9 cells have an abundance of cAMP compared to MCF7/LCC1 cells. Glucose uptake in MCF/LCC9 control cells was 28-fold higherwhen compared to MCF7/LCC1 control cells, yet ATP levels in MCF7/LCC9 cells was 40% lower compared with MCF7/LCC1 control cells. cAMP has been recently identified as a potent inducer of autophagy. Our findings suggest that antiestrogen resistant breast cancer cells may have higher glucose (from the Warburg effect) and energy requirements, resulting in increased cAMPthat helps to maintain survival via autophagy under basal or treatment conditions. These metabolic adaptations are critical to the coordinated signaling from the UPR that both suppresses apoptosis and activates a prosurvival autophagy. Further studies will help to uncover the signaling mechanism involved in regulating the pathways that connect autophagy and metabolic pathways to maintain cell survival in resistance. The overall goal of this study is to provide more affordable diagnostic tools and to identify effective therapies and reliable biomarkers to predict accurately the response to antiestrogen therapy.

Biography

Robert Clarke, Ph.D., D.Sc., F.S.Biol., F.R.S.Chem., F.R.S.Med. (U.K.) is Dean for Research and Interim Director of the Biomedical Graduate Research Organization at Georgetown University Medical Center (Washington, DC, U.S.A). A Professor of Oncology, he is Co-Director of the Breast Cancer Program at the Lombardi Comprehensive Cancer Center. He completed his doctoral training in biochemistry at the Queen's University of Belfast in 1986 and his postdoctoral training at the Medical Breast Section of the National Cancer Institute (National Institutes of Health, Bethesda, MD, U.S.A.). Dr. Clarke joined the Faculty at Georgetown University in 1989. Currently, he serves on the editorial board of over a dozen peer review journals, e.g., Cancer Research (Senior Editor), Endocrine-Related Cancer, Clinical Cancer Research, Molecular Cancer Therapeutics, Cancer Prevention Research, British Journal of Cancer, and Breast Cancer Research and Treatment. He regularly serves on state, national, and international grant review panels. Dr. Clarke took over as chair of the N.I.H. Basic Mechanisms of Cancer Therapeutics (BMCT) peer review study section in July 2011.

An internationally recognized leader in breast cancer research, Dr. Clarke studies how hormones and growth factors affect breast cancer. Focusing initially on the interactions among hormones and anticancer drugs, his work expanded to include the cellular and molecular mechanisms that explain how breast cancers become resistant to hormone and cytotoxic drug therapies. He and his colleagues developed a series of hormone resistant breast cancer models that are widely used in the field. Dr. Clarke is currently developing and applying novel bioinformatic methods in translational breast cancer studies. He and his collaborators have recently described a molecular signaling network that incorporates the unfolded protein response to endoplasmic reticulum stress. This signaling network contributes directly to the hormonal regulation of breast cancer cell proliferation and cell death. One key gene in this network is IRF1, which was first implicated in affecting hormone responsiveness and breast cancer cell survival in Dr. Clarke's laboratory. His team has now shown that IRF1 is a new breast cancer suppressor gene. Other key network genes include XBP1, NFB, and BECN1 and select members of the BCL2 gene family. He has recently begun studying how cells use this and other signaling to modify their metabolomes to execute the cell fate decisions made in response to endocrine therapies. Dr. Clarke has authored/co-authored over 200 publications and he has several patents, mostly in the field of breast cancer research.