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TITLE: Crosstalk between Leptin Receptor and IGF-IR in Breast Cancer: A Potential Mediator of Chemoresistance

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Fort Detrick, Maryland 21702-5012

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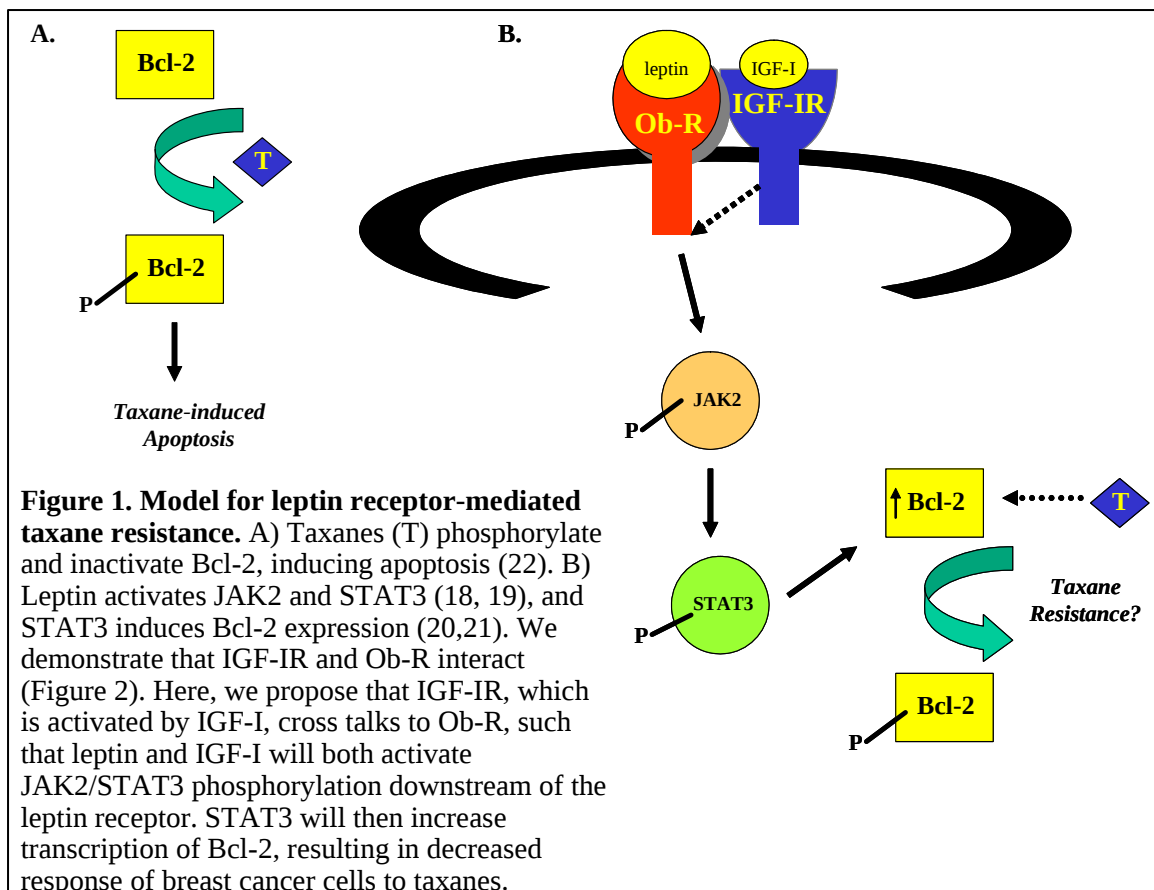
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14. ABSTRACT Obesity is a major risk factor for the development and progression of breast cancer, and is associated with reduced treatment response and reduced overall survival. The obesity-associated hormones IGF-I and leptin are found at high levels in the serum of breast cancer patients, and their receptors, IGF-IR and the leptin receptor (Ob-R) are overexpressed in a majority of breast tumor tissues. We have discovered by co-immunoprecipitation that IGF-IR and Ob-R physically interact in breast cancer cells. This interaction was associated with cross talk from IGF-IR to Ob-R, as IGF-I stimulation promoted signaling downstream of the leptin receptor, including increased phosphorylation of Ob-R, STAT3, and JAK2. Our preliminary data suggests that this cross talk is unidirectional, as leptin stimulation did not alter IGF-IR phosphorylation. Our ongoing studies will examine this cross talk in more detail, in part by determining the biological and molecular effects of inhibition of these growth factor receptors. We will then examine the influence of this cross talk on response to taxane-based chemotherapy.					
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INTRODUCTION

Obesity is an important risk factor associated with the development and progression of breast cancer (1-7), reduced therapeutic efficacy, and higher mortality rates among breast cancer patients (8-11). The obesity-associated hormones insulin-like growth factor-I (IGF-I) and leptin are found at high levels in breast cancer patients (12-15), and their receptors, IGF-IR and Ob-R (leptin receptor is also known as obesity receptor), are overexpressed in a majority of breast cancers (15-17). Increased expression of leptin and Ob-R correlate with increased risk for distant metastasis and reduced overall survival in breast cancer patients (15). Leptin induces proliferation of breast cancer cells via activation of STAT3 (18,19), a transcriptional activator of the anti-apoptotic protein Bcl-2 (20,21). STAT3-dependent overexpression of Bcl-2 was associated with resistance to the chemotherapeutic agent paclitaxel in breast cancer cells (21). We propose that IGF-IR and the leptin receptor interact, and that IGF-IR and leptin induce phosphorylation of Ob-R, activating STAT3 and upregulating Bcl-2, which in turn results in taxane resistance (illustrated as Figure 1). Our hypothesis is that high levels of leptin and IGF-I increase Ob-R signaling, contributing to taxane resistance in breast cancer. Our long-term goal is to establish markers of Ob-R signaling as predictors of taxane response. The rationale is that these markers of Ob-R signaling, including serum levels of leptin and IGF-I, and tissue levels of phosphorylated Ob-R, STAT3 and Bcl-2, can be used (1) to identify patients most likely to respond to taxanes, and (2) as therapeutic targets to improve response rates to taxanes in the treatment of breast cancer.



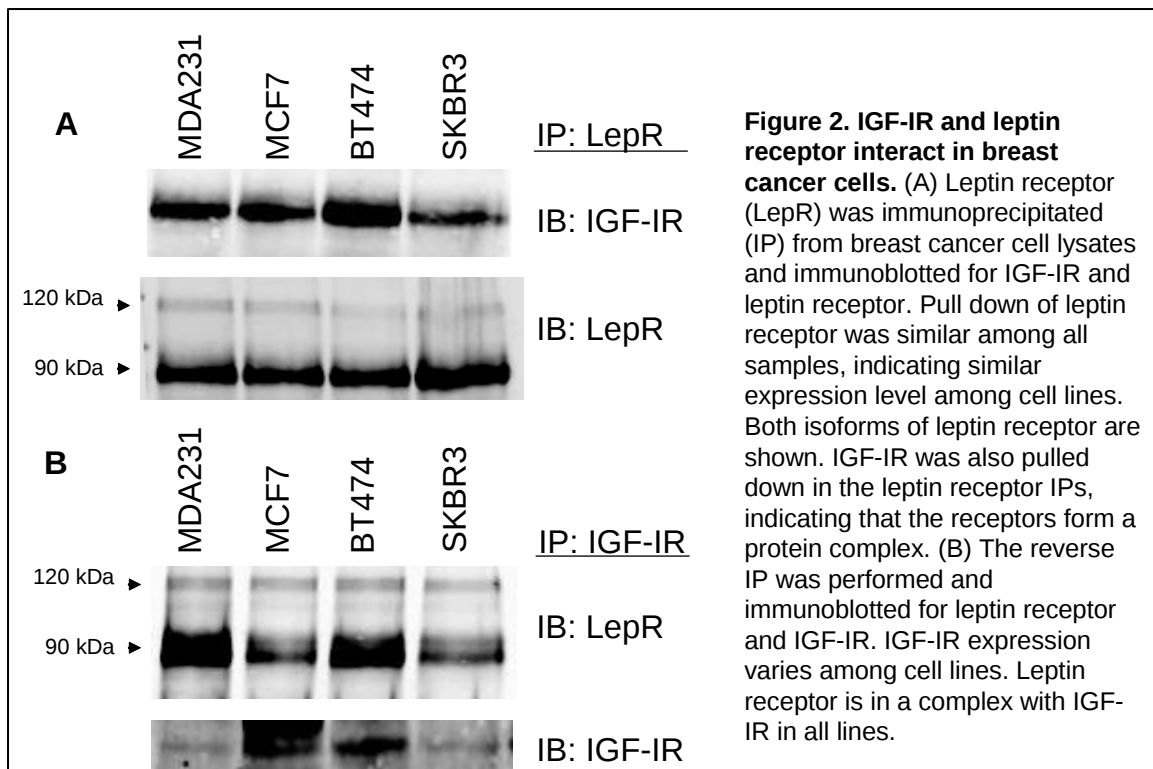
BODY

Task 1 Apply nanotechnology-based methods for visualization of IGF-IR and leptin receptor (Ob-R) in real time.

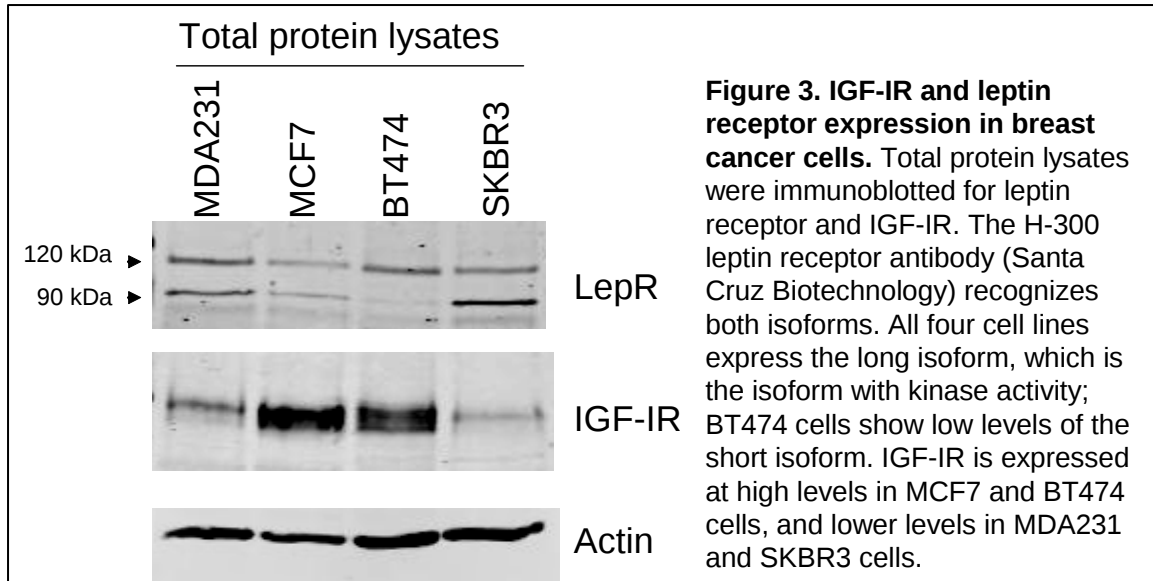
This aim is being done in collaboration with Dr. Konstantin Sokolov at MD Anderson. As labeling of antibodies with nanoparticles is often the limiting factor, his team has been working on this technique and has now successfully labeled antibodies with gold or silver nanoparticles. We are working to select the best cell lines to employ for these experiments and the results of the next task will dictate which cell lines we choose. Hence, task1 will continue into year 2. However, a large part of task 2 and part of task 3 has been completed, so there will not be any delay in producing results associated with the aims of the proposed research.

Task 2 Demonstrate that IGF-I activates the leptin receptor via IGF-IR crosstalk.

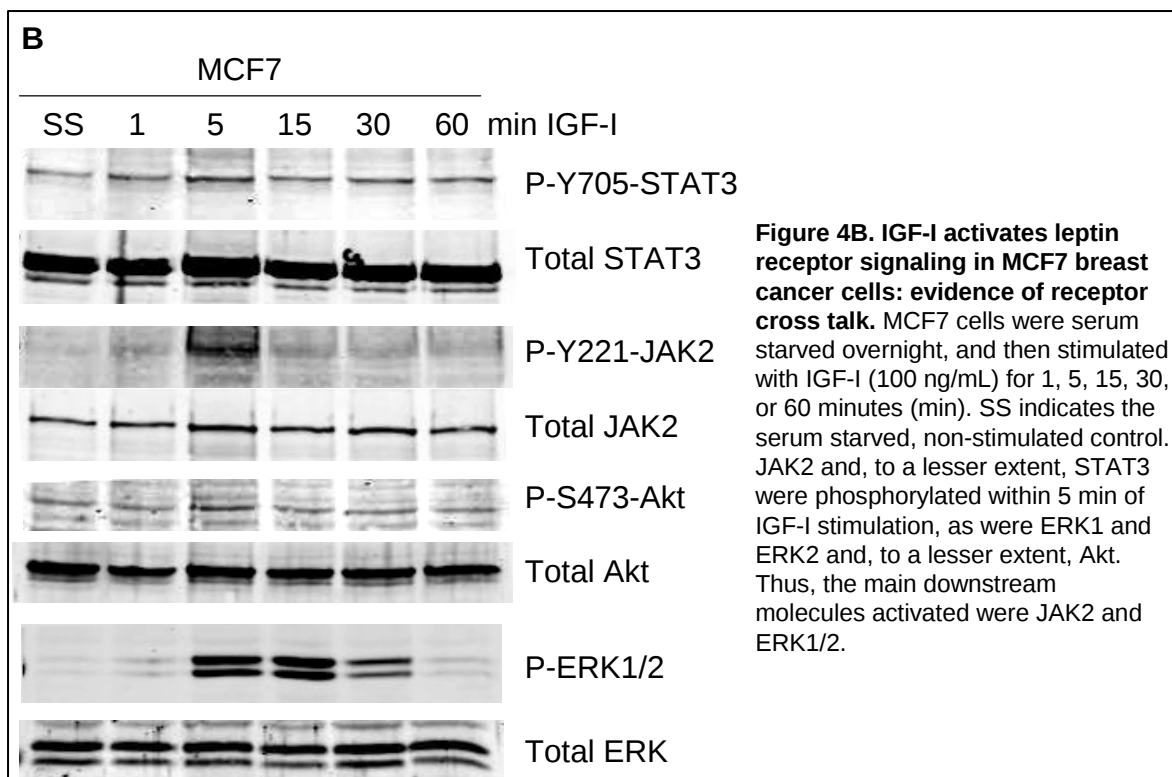
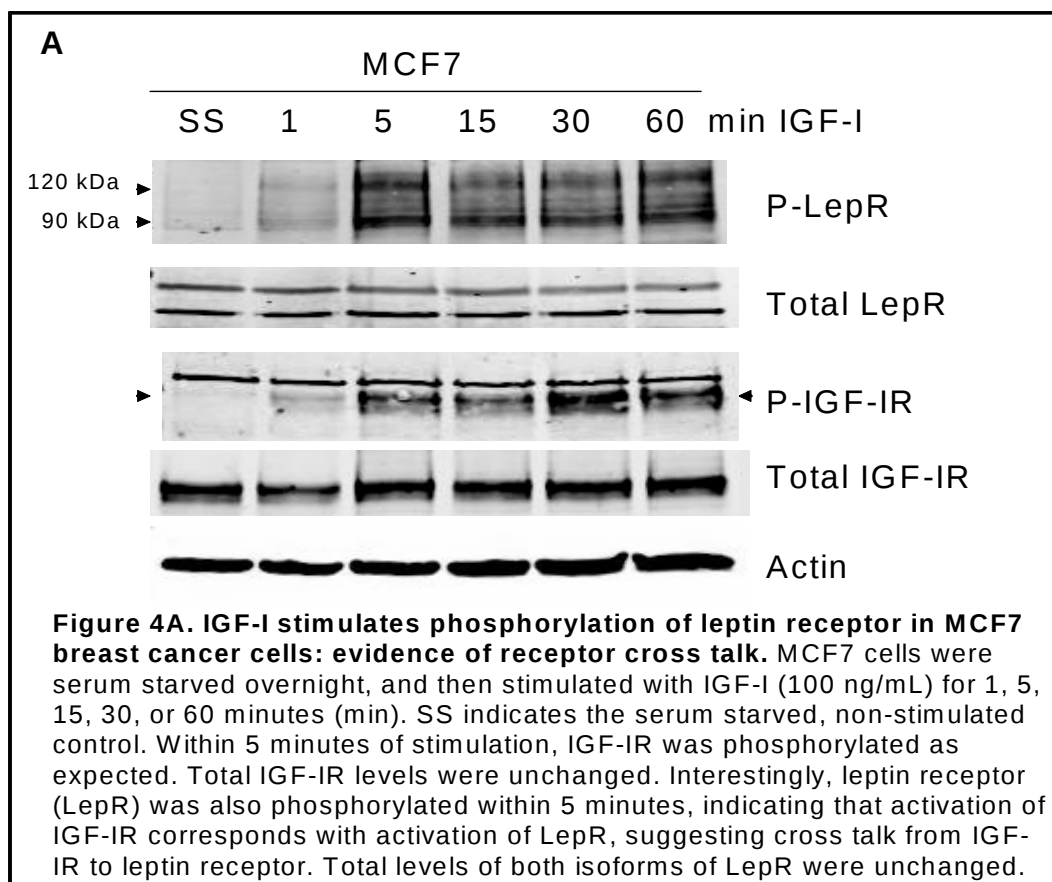
The breast cancer cell lines MDA-MB-231 (MDA231), MCF7, BT474, and SKBR3 were examined for IGF-IR and leptin receptor expression and interaction. Cells were lysed for protein and leptin receptor was immunoprecipitated from cells. Immunoblotting demonstrated that IGF-IR was pulled down with the leptin receptor, indicating that they form a complex (Figure 2A). Conversely, immunoprecipitation of IGF-IR showed pull down of leptin receptor in all cell lines (Figure 2B). Our preliminary results described in the initial proposal stated that only the MCF7 cell line failed to show interaction between these receptors. However, upon repeating the experiment multiple times, we have consistently observed that the interaction occurs in all four of the lines tested, including MCF7 cells.

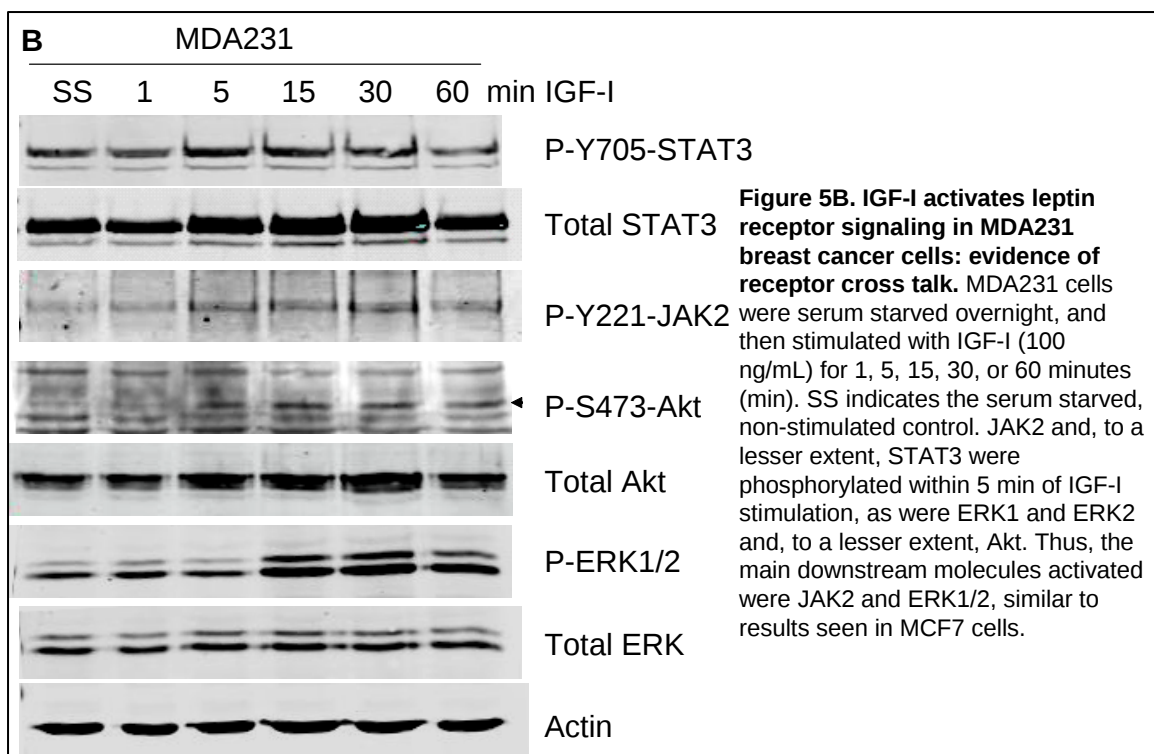
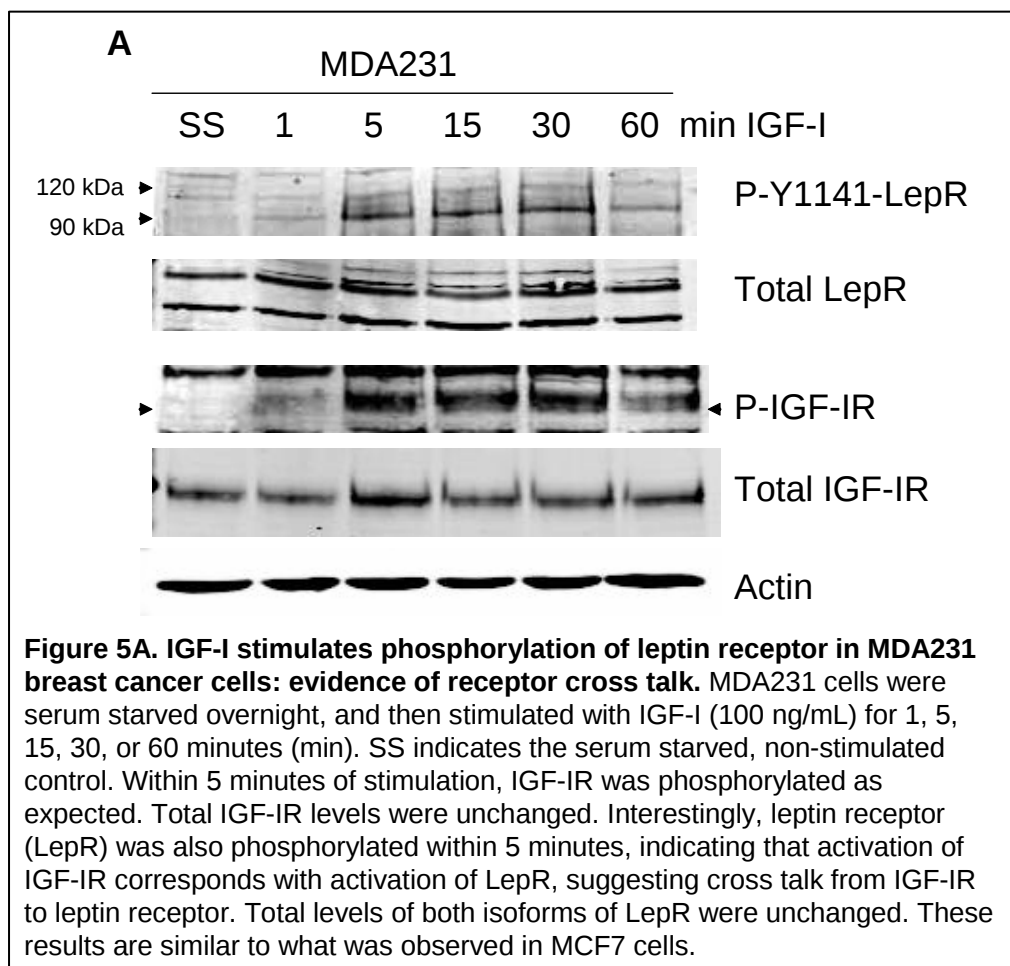


Total receptor levels were also examined in the cell lines (Figure 3). The leptin receptor has two isoforms. The long isoform is approximately 120 kDa, and possesses kinase activity. The short isoform is 90 kDa and lacks signaling capability, and its function is unclear. All cells showed expression of the long isoform of the leptin receptor, with BT474 cells showing very low levels of the short isoform. IGF-IR expression varied among lines, with MCF7 and BT474 cells showing highest levels.

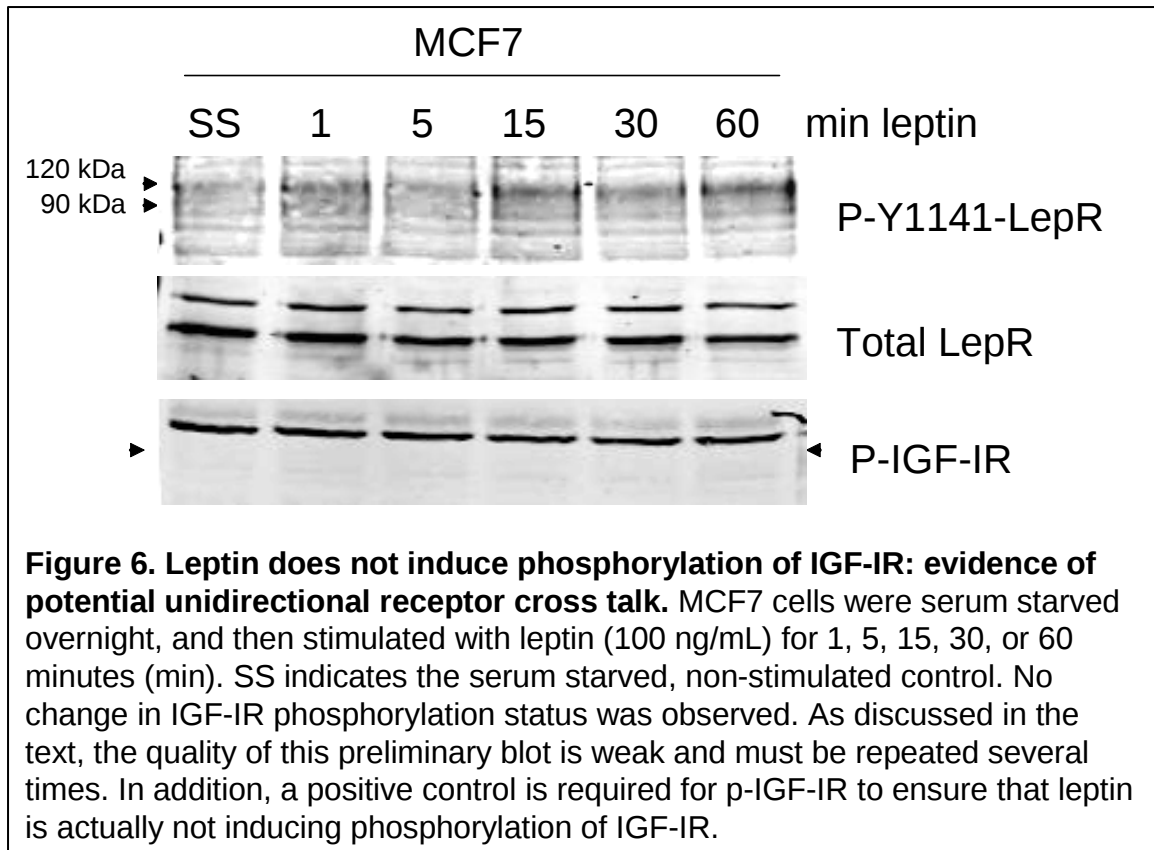


We next wanted to determine the functional consequence of this interaction. MCF7 cells were serum starved overnight to remove hormonal stimulation. Cells were then stimulated with 100ng/mL IGF-I for the indicated time course (Figure 4A). Cells were lysed for protein, and immunoblots were performed for total and phosphorylated leptin receptor (using phospho-tyrosine 1141- specific antibody for leptin receptor, Santa Cruz Biotechnology), and for total and phosphorylated IGF-IR (using anti-phospho-tyrosine 1162/1163 insulin receptor/IGF-IR antibody, Biosource). IGF-IR phosphorylation was stimulated within 5 minutes (min). Importantly, leptin receptor phosphorylation was also stimulated within 5 min, indicating that IGF-IR activation corresponds with activation of leptin receptor, suggesting potential cross talk from IGF-IR to leptin receptor. Total levels of IGF-IR and leptin receptor isoforms did not change. Downstream of the receptors, the signaling pathways including JAK2, STAT3, ERK1/2, and Akt were examined (Figure 4B). The major molecules activated were JAK2 and ERK1/2, and to a lesser extent STAT3 and Akt. We have also confirmed these results in another cell line, MDA231, in which we also observed phosphorylation of leptin receptor in response to IGF-I stimulation (Figure 5A) and activation of JAK2 and ERK1/2 as the major changes in downstream signaling (Figure 5B). Hence, the potential biological consequences of IGF-IR cross talk to leptin receptor may be mediated by the JAK2 and MAPK signaling pathways, and remain to be examined. Thus, we will follow up these results in year 2 by inhibiting IGF-IR, JAK2, and ERK1/2, as described in the original proposal, and examining the molecular effects on cross talk and the biological effects on these cancer lines.





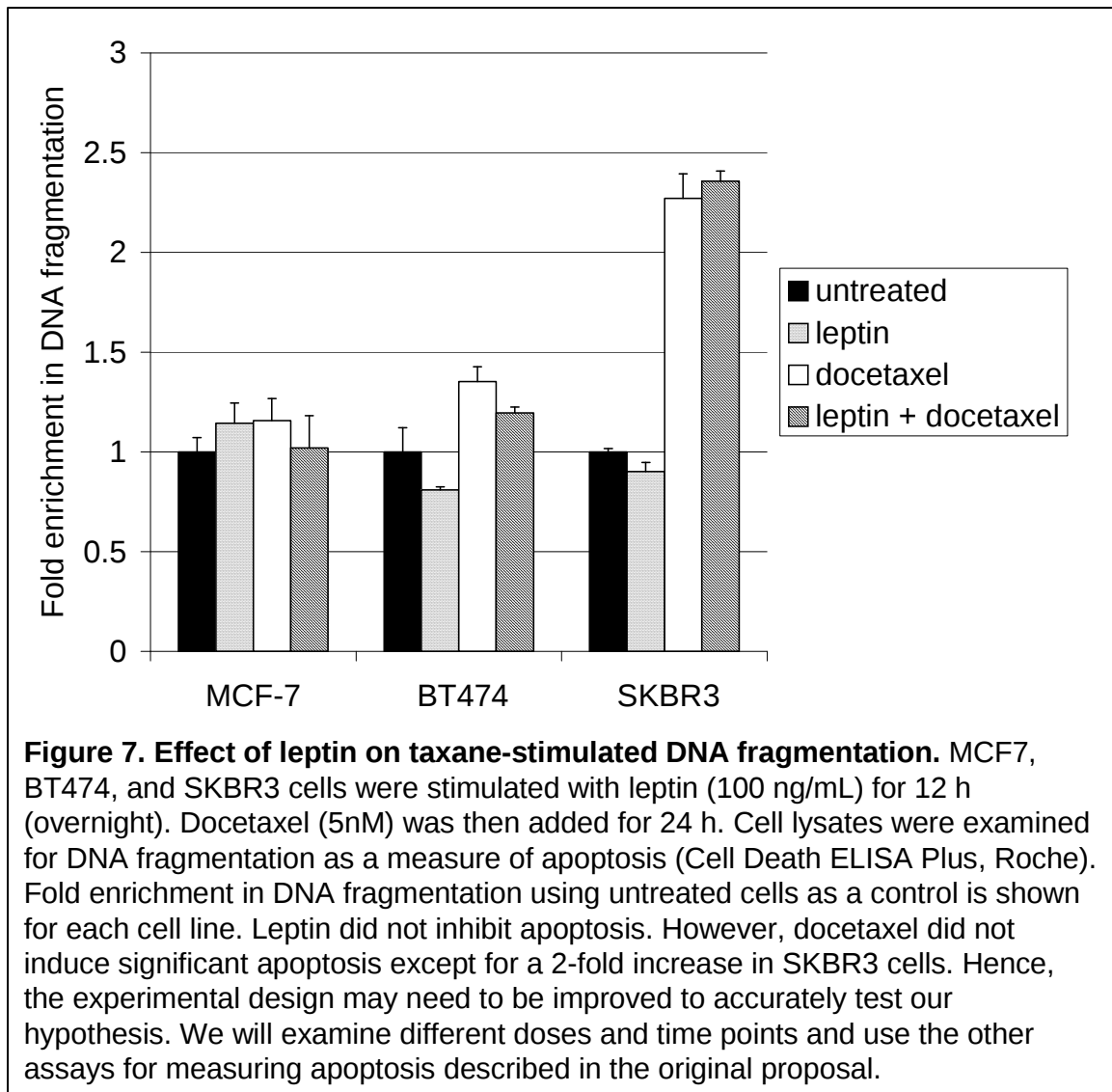
Cross talk in the opposite direction, from leptin receptor to IGF-IR, was also examined. For this experiment, MCF7 cells were serum starved overnight, and stimulated with 100ng/mL leptin for the indicated time points (Figure 6). Immunoblots of total lysates were probed for phospho-leptin receptor and phospho-IGF-IR. Our preliminary results indicated that leptin receptor is phosphorylated as expected, although the quality of the blot is weak and must be repeated. However, a signal was not detected for phospho-IGF-IR. Thus, a positive control for IGF-I-stimulated cells must be included on the next blot to confirm if this indicates that leptin does not promote phosphorylation of IGF-IR, suggesting that the cross talk is unidirectional. Hence, in year 2, this aim will be continued by examining leptin receptor cross talk to IGF-IR. We will also examine the effects of this cross talk on Bcl-2 as described in the original proposal.



Task 3 Demonstrate that Ob-R signaling activated by leptin or IGF-I contributes to taxane resistance.

MCF7, BT474, and SKBR3 cells were either untreated, treated with 100ng/mL leptin for 36 hours (h), 5nM docetaxel for 24 h, or treated with a combination of leptin and docetaxel, where cells were pre-treated with leptin for 12 hours and then docetaxel was added to the media for an additional 24 hours. DNA fragmentation as a measure of apoptosis was examined using the Cell Death ELISA Plus Kit (Roche Applied Science) per manufacturer instructions. With this particular experimental design, very little change in DNA fragmentation was observed in MCF7 and BT474 cells (Figure 7). In SKBR3

cells docetaxel alone caused a 2-fold increase in DNA fragmentation, and the added contribution of leptin was negligible. Hence, these negative results will be followed up by testing other doses and time points, as well as other assays (flow cytometry, trypan blue exclusion), as described in the original proposal. We are also working in collaboration with other investigators at MD Anderson to examine association of leptin receptor signaling molecules with resistance to taxanes in breast cancer patients, as described for years 2 and 3 of the proposal.



KEY RESEARCH ACCOMPLISHMENTS

- ❖ Discovery that IGF-IR and leptin receptor interact
- ❖ Discovery that IGF-I promotes leptin receptor phosphorylation

REPORTABLE OUTCOMES

- ❖ The grant recipient was selected to become a tenure track faculty member, in part based on the project funded through this award. (Please see the attached CV of the recipient in the attached appendix.)

CONCLUSION

We demonstrate that IGF-IR and Ob-R physically interact in breast cancer cells. We also show evidence that IGF-I stimulates phosphorylation of leptin receptor. We will confirm cross talk from IGF-IR by inhibiting IGF-IR in the presence of IGF-I and blotting for phosphorylated leptin receptor. Our preliminary data suggests that the cross talk may be unidirectional; however, we must perform the leptin stimulation experiments using the proper control (IGF-I-stimulated cells) and improve the quality of the immunoblots to determine if in fact leptin does not stimulate IGF-IR phosphorylation. Our future experiments will also examine the effect of this cross signaling on Bcl2, and on taxane responsiveness. The results so far are significant in that they suggest interaction between two growth factor receptor signaling pathways that play an important part in breast cancer biology. In fact, multiple agents targeted against IGF-IR are being developed for clinical use. The implication is that targeting one receptor may not be enough; dual targeting against IGF-IR and leptin receptor may be more appropriate if our hypotheses are proven. In addition, determining the role of these receptor pathways in taxane responsiveness will be important towards improving prediction of who will respond to this commonly used chemotherapeutic agent.

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APPENDICES

Please see the attached Curriculum Vitae.

SUPPORTING DATA

N/A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Rita Nahta	POSITION TITLE Assistant Professor		
eRA COMMONS USER NAME rnahta			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of North Carolina, Chapel Hill, NC	B.S.	1994	Chemistry
Duke University, Durham, NC	Ph.D.	2000	Pathology and Molecular Medicine
Harvard Medical School, Boston, MA	N/A	2000-2002	Postdoctoral
M. D. Anderson Cancer Center, Houston, TX	N/A	2002-2004	Postdoctoral

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

A. Positions and Honors.**Positions and Employment**

1990-1994 Lab Technician, Analytical and Environmental Chemistry Laboratory, The Virkler Company, Charlotte, N.C. (summers)

1995-2000 Ph.D. Candidate, Department of Pathology and Molecular Medicine, Duke University, Durham, N.C., Mentors: J. Dirk Iglehart, M.D., Professor, and Jeffrey R. Marks, Ph.D., Associate Professor

2000-2002 Postdoctoral Fellow, Department of Medicine and Tumor Biology, Harvard Medical School and Massachusetts General Hospital Cancer Center, Boston, MA, Mentor: Emmett V. Schmidt, M.D., Ph.D., Associate Professor

2002-2004 Postdoctoral Fellow, Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, Mentor: Francisco J. Esteva, M.D., Ph.D., Associate Professor

2004-2/2007 Instructor, Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, Mentor: Francisco J. Esteva, M.D., Ph.D., Associate Professor

2/2007-present Assistant Professor, Departments of Pharmacology and Hematology/Oncology, Emory University School of Medicine and Winship Cancer Institute

Other Experience and Professional Memberships

1993-1994 Volunteer Research Assistant, Department of Biology, University of North Carolina, Chapel Hill, N.C.

1994-1995 Volunteer Research Assistant, Department of Biology, University of North Carolina at Charlotte, Charlotte, N.C.

1997-1999 Tutor, General Biology, Chemistry, and English, Duke University Medical Center, Durham, N.C.

1997-2000 Supervisor in the laboratory, Undergraduate Research Program, Duke University Medical Center, Durham, N.C.

2003-7/2006 Associate Member, American Association for Cancer Research (AACR)

8/2006-present Active Member, American Association for Cancer Research (AACR)

2005-present Professional Member, American Association for the Advancement of Science (AAAS)

Honors

1990	North Carolina School of Science & Mathematics Graduate
2001	Invited Attendee, Gordon Research Conference on Chemotherapy and Experimental Therapeutics of Cancer, Colby-Sawyer College, New London, New Hampshire
2004	AACR-Amgen, Inc. Fellowship Award in Clinical/Translational Cancer Research
2004	M. D. Anderson Cancer Center Odyssey Special Fellowship Award
2004	Department of Defense Breast Cancer Research Program Concept Award
2006	Department of Defense Breast Cancer Research Program IDEA Award
2006	National Cancer Institute K01 Career Development Award

B. Peer-reviewed Publications (in chronological order).

Original research articles

1. Dong Q, Johnson SP, Colvin OM, Bullock N, Kilborn C, Runyon G, Sullivan DM, Easton J, Bigner DD, Nahta R, Marks JR, Modrich P, and Friedman HS. Multiple DNA repair mechanisms and alkylator resistance in the human medulloblastoma cell line D-283 Med (4-HCR). *Cancer Chemother Pharmacol* 43:73-79, 1999.
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(The first two authors contributed equally to this work.)
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Invited review articles

1. Nahta R, Hortobagyi GN, and Esteva FJ. Growth factor receptors in breast cancer: potential for therapeutic intervention. *The Oncologist* 8: 5-17, 2003.
2. Nahta R, Hortobagyi GN, and Esteva FJ. Signal transduction inhibitors in the treatment of breast cancer. *Curr. Med. Chem. Anti-Cancer Agents* 3: 201-216, 2003.
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C. Research Support

Ongoing Research Support

K01 CA118174 Nahta (PI) 8/01/2006-7/31/2011

NIH/NCI

HER-2/IGF-IR cross-talk and Herceptin resistance

This study investigates interaction and cross talk between HER-2 and IGF-IR as a potential molecular mechanism of Herceptin resistance.

Role: PI

W81XWH 0610452 (BC050796) Nahta (PI) 3/20/2006-3/19/2009

U. S. Department of Defense (DOD)

IDEA Award

Crosstalk between leptin receptor and IGF-IR in breast cancer: a potential mediator of chemoresistance

Principal Investigator/Program Director (Last, First, Middle): Nahta, Rita

This study investigates potential interaction and cross talk between the IGF-I receptor and the leptin receptor and how this contributes to resistance to taxane chemotherapy.

Role: PI

Pending

None