

Introduction

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Over the past five years there has been an explosion of “targeted therapies” for cancer treatment. In most cases, these therapies have been based on pre-clinical data showing that specific molecules play an important role in regulating the malignant phenotype. In breast cancer, there is compelling rationale that such targeted strategies should be successful. Targeting of estrogen receptor α ($ER\alpha$) has proven to be a successful way to reduce breast cancer risk, decrease the risk of death and recurrence in an adjuvant setting, and remains the first choice of treatment for advanced disease. With this success, it is hoped that other molecular pathways could also be successfully exploited. This edition of Breast Diseases reviews the role of the insulin-like growth factors (IGFs) in breast cancer.

Over 100 years ago George Beatson made an intuitive leap connecting breast cancer therapy with ovarian function [1]. Beatson removed the ovaries from a premenopausal woman with breast cancer; he reasoned that ovarian function regulated normal mammary gland function, therefore the ovaries may influence the malignant phenotype. In this volume, Hadsell discusses the function of IGF action in the normal mammary gland using mouse model systems where expression and function can be manipulated. Stull and Wood discuss the patterns of expression of the IGFs, their binding proteins, and their receptors in the normal gland. Just as sex steroids regulate normal mammary gland function, their reviews provide abundant evidence that the IGFs play a critical role in normal gland function.

Studies of human populations suggest ways in which cancer etiology can be determined. Indeed, the widely used Gail model shows that several factors related to estrogen exposure (age of menarche, age at live first birth) are important risk factors for breast cancer development [2,3]. Hankinson and her colleagues were among the first to demonstrate an association between serum

IGF-I levels and breast cancer risk. Here, Hankinson and Schernhammer review the existing data demonstrating a link between serum levels and breast cancer development.

While it is difficult for epidemiological studies to prove causation, there are several lines of evidence suggesting that the IGF system contributes to the malignant phenotype. Kucab and Dunn outline the role for the type I IGF receptor (IGF-1R) in regulating cancer cell invasion and metastasis. Van Den Berg discusses the survival pathways regulated by this receptor system. Given the evidence that the IGFs function as mitogens for breast cancer cells, it is clear that activation of this signaling system can support many aspects of the malignant phenotype.

One hundred years of estrogen receptor therapies have suggested that a single target can be a successful strategy in breast cancer. Unfortunately, the IGF system may not be as simple. The two ligands, IGF-I and IGF-II may interact with several receptors. MacDonald and Byrd examine the role for the type II IGF receptor (IGF-2R) in breast cancer. Frasca and colleagues review the evidence that the insulin receptor plays an important role in regulating IGF action. Unlike many growth factors, the IGFs can also bind a non-receptor protein with very high affinity. Perks and Holly review the roles for the IGF binding proteins in breast cancer. Despite this complexity, it is becoming clear that an important role for the IGFs may be in the modulation of the ER signaling. Thorne and Lee review the potential ways that these two important signaling pathways can interact.

Lastly, strategies to inhibit IGF action in an intact organism are required to prove that this system has relevance in human breast cancer. Zhang and Yee discuss the potential ways that IGF action could be inhibited.

Thus, the body of evidence suggests that the IGFs have a role in normal and malignant mammary epithelial cell biology. Unlike Beatson, we have appropriate technology to identify the mechanism of action of the IGFs in breast cancer. By providing a clear identification of the molecules critical in regulating IGF response, we hopefully won't have to wait 100 years to exploit this pathway as a cancer therapy.

REFERENCES

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