Molecular and Cellular Endocrinology 418 (2015) 245–263

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

The molecular, cellular and clinical consequences of targeting the estrogen receptor following estrogen deprivation therapy

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ARTICLE INFO

Article history:
Received 15 April 2015
Received in revised form
20 May 2015
Accepted 1 June 2015
Available online 5 June 2015

Keywords:
Breast cancer
Estrogen receptor
Antiestrogens
Estrogens
Estrogen-induced apoptosis
Resistance

ABSTRACT

During the past 20 years our understanding of the control of breast tumor development, growth and survival has changed dramatically. The once long forgotten application of high dose synthetic estrogen therapy as the first chemical therapy to treat any cancer has been resurrected, refined and reinvented as the new biology of estrogen-induced apoptosis. High dose estrogen therapy was cast aside once tamoxifen, from its origins as a failed "morning after pill", was reinvented as the first targeted therapy to treat any cancer. The current understanding of the mechanism of estrogen-induced apoptosis is described as a consequence of acquired resistance to long term antihormone therapy in estrogen receptor (ER) positive breast cancer. The ER signal transduction pathway remains a target for therapy in breast cancer despite "antiestrogen" resistance, but becomes a regulator of resistance. Multiple mechanisms of resistance come into play: Selective ER modulator (SERM) stimulated growth, growth factor/ER crosstalk, estrogen-induced apoptosis and mutations of ER. But it is with the science of estrogen-induced apoptosis that the next innovation in women's health will be developed. Recent evidence suggests that the glucocorticoid properties of medroxyprogesterone acetate blunt estrogen-induced apoptosis in estrogen deprived breast cancer cell populations. As a result breast cancer develops during long-term hormone replacement therapy (HRT). A new synthetic progestin with estrogen-like properties, such as the 19 nortestosterone derivatives used in oral contraceptives, will continue to protect the uterus from unopposed estrogen stimulation but at the same time, reinforce apoptosis in vulnerable populations of nascent breast cancer cells.

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http://dx.doi.org/10.1016/j.mce.2015.06.004
0303-7207/

"As most breast cancers are ER positive and given the worldwide prevalence of the disease, it is arguable that anti-estrogen treatments have had greater global impact than any other treatment intervention in cancer medicine." (Sledge et al., 2014)
"The development of therapeutics for ER-expressing breast cancer has been one of the great clinical advances of the past 50 years and has served as a paradigm for the development of targeted therapies in oncology." (Sledge et al., 2014)

1. Introduction

Breast cancer has the unfortunate distinction of being the cancer with the highest incidence of all disease sites in women. Annual incidence statistics in the United States of America are 92.93 cases per 100,000 women, United Kingdom 94.99, Brazil 59.46, Russia 45.64 and China 22.07 (Ferlay et al., 2013). It is estimated that each year there are a million new cases of breast cancer worldwide. Until 40 years ago, breast cancer also had the unfortunate distinction of having the highest death rate, but two things changed. Firstly, lung cancer death rates overtook breast cancer as the leading cause of cancer death in women; as the result of new generations of women embracing cigarette smoking. Secondly, at this time, a new targeted approach to breast cancer therapy was conceived. This approach was translated, through animal models to clinical trials and is now the standard of care (Jordan, 2015a).

The new successful approach was not, as anticipated, combination cytotoxic chemotherapy that was showing enormous promise in the 1970s as a curative strategy for breast cancer. This optimism for cytotoxic chemotherapy followed close on the heels of advances in the cure of childhood leukemia and Hodgkin's disease. If the correct scheduling of a lexicon of cytotoxic agents could be discovered, cures would then emerge and be amplified by agents with different mechanisms of action. This "logical" approach of combining non-specific agents with different mechanisms of action was planned to retard the development of drug resistance; a principle revisited in medical oncology today by simultaneously blocking cell survival pathways with precision targeting.

By contrast, the key to success of the new strategy to treat breast cancer was to emerge, strangely enough, from the fashion of medical research in the 1960s, reproductive endocrinology which was hot on the heels of the triumph of oral contraception that changed society forever. The goal in industry was to find new contraceptive approaches to expand the market. The new knowledge of "morning after pills" acquired during the reproductive revolution that started but then failed provided the new tools and targets to address the new medical challenge. The "War on Cancer" was declared on December 23, 1971 and signed into law by President of the United States Richard M. Nixon as the National Cancer Act. Henceforth, the translation of new treatment ideas from clinical cancer centers would be propelled into clinical testing through cooperative cancer clinical trial groups. The successful treatment strategy in this process would emerge as the unexpected silent kill of cancer cells with few of the onerous life threatening side effects of cytotoxic chemotherapy. The battle to defeat breast cancer with combination cytotoxic chemotherapy was, indeed, a fight to the death worthy of a war on cancer, whereas the new approach of targeting the estrogen receptor (ER) in breast cancer (Jensen and Jordan, 2003) turned out to be a stealth campaign. This heralded a new campaign in the war on cancer with clinical strategies in breast cancer of long-term adjuvant treatment and chemoprevention (Jordan, 2008a). The era of this therapeutic change (1970–2000), with countless lives saved or improved, would create the current era of molecular targeted medicine (Sledge et al., 2014) with the current promise that the power of molecular biology will solve the riddle of tumor complexity for the individual and neutralize the machinery of tumor growth. Precision interdiction promises to block off tumor survival routes. An attack at one moment in time in the evolution of tumor plasticity is planned and predicted to eradicate cancer and cure the patient. The key to success will be, as it has always been, which moment in time?

To appreciate the development of the new strategy of the targeted treatment of breast cancer, it is necessary to understand the process by which the pieces of the puzzle of hormone-dependent breast cancer were organized and arranged to derive the modern basis to treat breast cancer rationally. As in all human achievement, the process is based on individuals, serendipity, competition, trial and error, determination and fashions in research.

Reproductive endocrinology slowly underwent a metamorphosis in the early 1970s to become translational breast cancer research. That is where Federal funding now focused with the National Cancer Act. However, the process of change with cancer surgery and therapeutics started long before through clinical observation, trial and error. The first concrete clues that metastatic breast cancer was in some way regulated by the ovary occurred when Stanley Boyd at Charing Cross Hospital combined and analyzed all the available data on the outcomes of oophorectomy for metastatic breast cancer in Britain (Boyd, 1900). A case report published by Beatson (1896) triggered considerable interest in the possibility of tumor regressions following oophorectomy. Unfortunately, successful tumor regression, in the main, was short lived, but Boyd found a 30% response rate for endocrine ablation (Boyd, 1900). This 1/3 response rate has remained consistent for a century for any kind of endocrine therapy. However, the question to be addressed in the first half of the 20th century was: "which tumors would respond and which tumors would not?"

Laboratory studies in high incidence strains of mice with mammary cancer found that the ovary was necessary for tumorigenesis (Lathrop and Loeb, 1916). Subsequent work by Allen and Doisy (1923) identified estrogen as the principal hormone