RESEARCH COLLECTION ON

BREAST CANCER VOL. 1

INTECH

RESEARCH COLLECTION ON BREAST CANCER VOL. 1

Research Collection on Breast Cancer Vol. 1

http://dx.doi.org/10.5772/ 58061
Chapters from books edited by: **Rebecca Aft, Susan Done** and **Mehmet Gunduz**

Published by InTech

Janeza Trdine 9, 51000 Rijeka, Croatia

Edition 2014

Notice

Statements and opinions expressed in the chapters are these of the individual contributors and not necessarily those of the editors or publisher. No responsibility is accepted for the accuracy of information contained in the published chapters. The publisher assumes no responsibility for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained in the book.

Additional hard copies can be obtained from orders@intechopen.com

Research Collection on Breast Cancer Vol. 1

p. cm.

ISBN 978-953-51-1507-6

Contents

RESEARCH COLLECTION ON BREAST CANCER VOL. 1

Research Collection on Breast Cancer Vol. 1

http://dx.doi.org/10.5772/ 58061
Chapters from books edited by: **Rebecca Aft, Susan Done** and **Mehmet Gunduz**

Published by InTech

Janeza Trdine 9, 51000 Rijeka, Croatia

Edition 2014

Notice

Statements and opinions expressed in the chapters are these of the individual contributors and not necessarily those of the editors or publisher. No responsibility is accepted for the accuracy of information contained in the published chapters. The publisher assumes no responsibility for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained in the book.

Additional hard copies can be obtained from orders@intechopen.com

Research Collection on Breast Cancer Vol. 1

p. cm.

ISBN 978-953-51-1507-6


INTECH
open science | open minds

Contents

Preface

This is the first in a major, two-volume set, 'Breast Cancer', that provides a comprehensive resource of current knowledge, clinical information and new research in the field, drawing on expert contributions. Some of the major thematic areas covered include: new advances in biology, imaging and therapeutics, such as implications of circulating tumour cells; diagnostic optical imaging and radiotracer molecular imaging; new knowledge on the tumour microenvironment, stem cells and metastasis, for example, on mesenchymal stem cells and the role of interleukin-6; new and established alternative therapeutic modalities, such as boron compounds and lunasin; and current understanding of carcinogenesis, cell grown and signalling pathways, including discussions of signal transduction pathways, cross-talk between breast cancer cells and the immune system, and trastuzumab-resistance. Breast cancer is the most commonly diagnosed form of cancer, and the leading cause of cancer-related deaths among women. These volumes benefit from the high-quality and leading edge work of researchers around the world to provide a rich variety of perspectives on this prevalent disease. They will benefit physicians in oncology as well as providing many stimuli for new research.

TARGETING NEW PATHWAYS AND CELL DEATH IN BREAST CANCER

Edited by **Rebecca L. Aft**

DNA Damage Response and Breast Cancer: An Overview

Leila J. Green and Shiaw-Yih Lin
Department of Systems Biology,
The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

1. Introduction

The cells throughout the human body are constantly subjected to both internal forces and external insults that cause damage to their DNA. This damage to the DNA can be harmful to the overall integrity of the cell and the ability for replication. Accurate transmission of genetic information from one cell to its progeny is dependent upon mechanisms within the cell to monitor any defects within its genome and to repair these deficiencies so as not to pass them to subsequent generations. These mechanisms are mainly mediated through an array of DNA damage response proteins including DNA damage sensors, signal transducers and effectors. Sensors, such as ATM (ataxia telangiectasia mutated) and ATR (ATM-Rad3-related), have the ability to recognize areas of damage and activate signal transducers, which either activate or inactivate effectors. Effector proteins trigger cell cycle checkpoint and the cell may successfully repair the damage or proceed towards apoptosis if these damages are irreparable. These molecules are not only necessary for surveillance of occasional non-lethal DNA damage, but are also important for the survival of the cell and the organism. Moreover, mutations to these DNA damage response proteins may contribute to an unstable genome and the development of cancer.

In this chapter we will briefly review the cell cycle and relevant checkpoint proteins. We will also discuss in detail the DNA damage response signal transduction pathway and associated proteins: ATM, ATR, ChK1, Chk2, p53, BRCA-1, PARP-1, and BRIT-1,. Finally, we will discuss the future strategy in targeting the defects of these proteins in the treatment of breast cancer.

Key Words: DNA Damage Response, ATM, ATR, p53, BRCA-1, BRIT-1, PARP-1, PARP inhibitors, Triple Negative Breast Cancer

2. The cell cycle: A brief overview

The cell cycle, first described in 1979, has been accepted as the central dogma of cell replication and contains two main phases; Interphase and the Mitotic phase (Fig. 1.)

The G1 (Gap 1) phase of the cycle is the period in which the cell may grow and function normally. New proteins are synthesized and organelles that the daughter cells will need are created. The synthesis or S phase of the cell cycle follows the G1 phase and is the period of the cell cycle in which the genetic material of the cell is replicated. As stated before, accurate

DNA replication is needed to prevent genetic aberrations that may lead to cell death. The regulatory pathways and proteins that govern this event are highly conserved in eukaryotic cells.

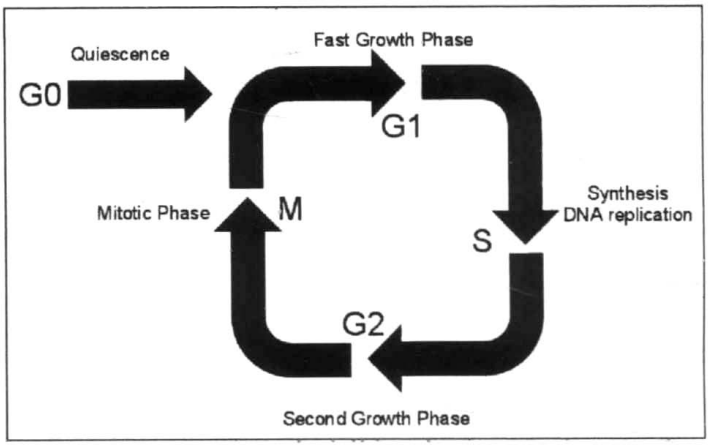

Fig. 1. The Cell Cycle

The G1/S phase transition is a major checkpoint in the cell cycle. The checkpoint response to DNA damage at the G1 phase is mediated by the ATM(ATR)/Chk2(Chk1)—p53/MDM1-p21 pathway, which will be discussed later in this chapter. Expression of ATM and Chk2 are relatively constant during the cell cycle while the concentrations of ATR and Chk1 increase closer to the G1/S transition (Kastan & Bartek, 2004). The end of the G1 Phase consists of the induction of Cyclin E and A, and CDC25A phosphatase, the activator of Cyclin E (A)/CDK2 kinase. In the event of DNA damage, Chk1 down-regulates CDC25A and in effect inhibits Cyclin E (A)/CDK2 kinase which stalls the transition from G1 to S. During the S phase of the cell cycle as the genome is replicated, intra S phase checkpoint networks can also be activated as a result of genotoxic insult. The two parallel branches of this checkpoint, controlled by the ATM/ATR signaling mechanism, will also be further discussed in the chapter.

Arguably, the most important phase of the cell cycle is the Synthesis and G2 phases. The G2 phase of interphase is the second growth period as the cell prepares for mitosis. Using a large number of highly conserved proteins, the G2/M checkpoint prevents cells from entering the mitosis should they experience DNA damage after the S phase, or if they should progress through G1-S-G2 with damage having occurred in previous phases that had been heretofore unrepaired (Kuntz & O'Connell, 2009). All forms of DNA damage, as well as incomplete replication, activate the checkpoint. The mitosis promoting Cyclin B/CDK1 kinase activity is a critical target of the G2 checkpoint. Cyclin B/CDK1 kinase is inhibited by the actions of ATM(ATR)/Chk2(Chk1) and/or p38 kinase mediated subcellular sequestration, degradation and inhibition of CDC25 family of phosphatases that normally activate CDK1 (Kastan & Bartek, 2004). The G2 checkpoint also relies on checkpoint mediators BRCA-1 and p53 which lead to the upregulation of cell cycle inhibitors p21 and GADD45a.

The G0 (Gap zero) phase of the cell cycle in which the cells enter a quiescent state. It can be viewed as an extended G1 phase or as a separate phase outside of the cell cycle. It is separate from apoptosis or senescence in that the cell is metabolically active may enter the G1 phase