Chapter 1

Introductory Chapter: Genes Expression in the Control of Cell Cycle and Their Potential Value in Cancer Prognosis

Guy Joseph Lemamy

Additional information is available at the end of the chapter

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1. Introduction

The human body is made of up to trillions of cells. Those cells respond to three characteristics: the differentiation into up to 200 different cellular types which acquire specific functions, the cooperation between those cells using various signaling pathways to sustain the body's physiological unity, and the genetic programming of cell death (the apoptosis). The programmed cell death goes hand in hand with the sustainability of life highlighted at the cell level by the "immortality" of cancer cells, the permanent renewal process of certain tissues such as those of the intestine and blood, as well as the sustainability of the species.

The cancer is a genomic disease in which the early stage is represented by activation of oncogene and inactivation of suppressor genes, which result in transformed cells that grow out of cell cycle control. Two families of genes, the oncogenes and antioncogenes (also called tumor suppressor genes), cause and accelerate the carcinogenesis process when their structure or the regulation of their expression is altered. These genes are equivalent in cancer etiology but differ themselves by their functions and by the mechanisms of their activation. The expression of oncogenes and antioncogenes, respectively, controls in a positive and negative way the cell cycle progression [1] (**Figure 1**).

Among the oncogenes, HER2 is involved in the early stages of carcinogenesis. HER2 is located on chromosome 17 [2] and codes for a transmembrane tyrosine kinase receptor that belongs to a family of four members: human epidermal growth factor receptor (HER) [3]. HER is activated after the binding of its ligand which allows the phosphorylation of tyrosine residues in the intracellular domain of the receptor. This activation leads to signaling pathways promoting cell proliferation, survival, migration, adhesion, angiogenesis, or differentiation

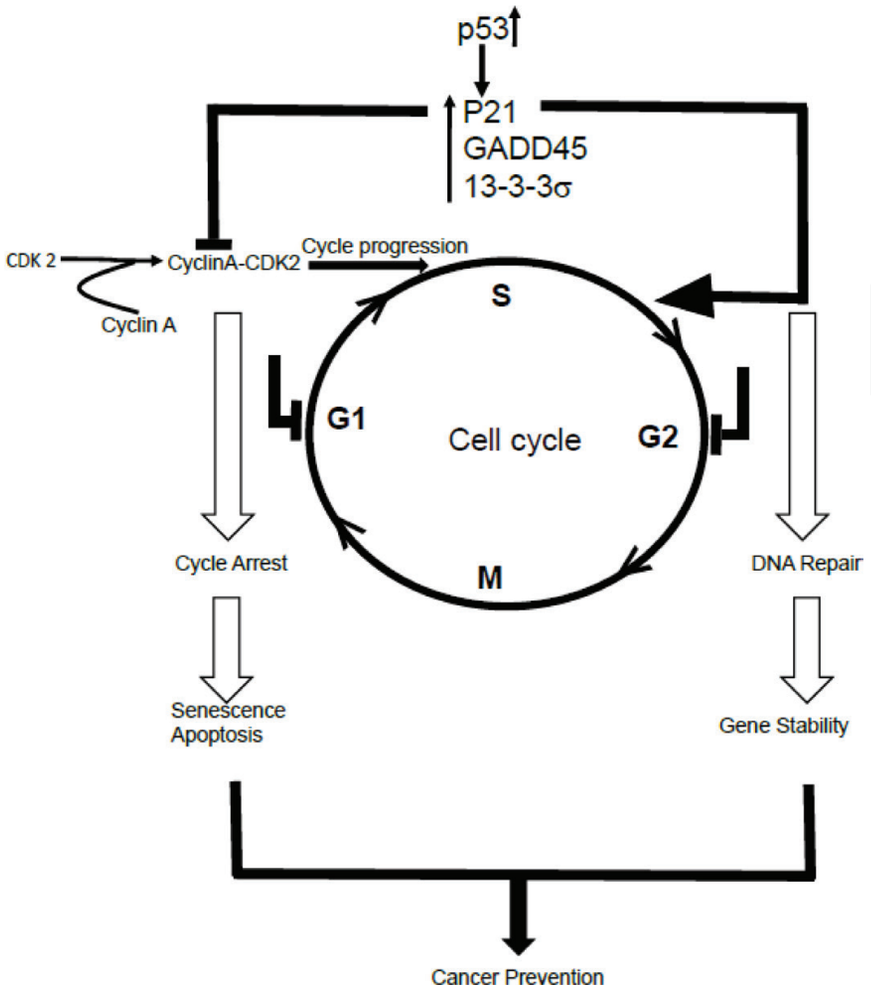

Figure 1. Signaling pathways of p53 in gene stability and cancer prevention. DNA damage increases p53 protein levels that stimulate expression of various genes such as p21, GADD45, or 13-3-3σ. The progression of cell cycle activated by cyclin-CDK complexes is temporarily inhibited by the resulting proteins at the G1 and G2 phases (⊥). Meanwhile, the exonuclease activity of p53 helps to repair damaged DNA. Cells with serious DNA mutations are directed to senescence or apoptosis.

[4]. In breast cancer cells, HER2 gene is amplified followed by the protein overexpression [5]. HER2 overexpression enhances cell proliferation through rapid degradation of the cyclin-dependent kinase (CdK) inhibitor p27 and the upregulation of factors that promote cell cycle progression such as CdK6 and cyclins D1 and E. HER2 is used as prognostic, prognosis, and predictive biomarker in breast cancer [6] (**Figure 2**).

In human cancer, the p53 tumor suppressor gene is the most commonly mutated gene. The p53 gene is mapped to the region 17p13.1, on the short arm of chromosome 17 [7], and codes for the p53 protein (tumor protein of 53 kDa) [8]. The p53 protein plays a main role in cell cycle control and cancer prevention. Damages in DNA occurring during the cell cycle or oncogene activation induce the p53 protein accumulation, resulting in temporary cell cycle arrest at the G1 and G2 checkpoints, DNA repair, differentiation, senescence, apoptosis, or antiangiogenesis. The p53 protein stimulates the expression of other genes such as p21, growth arrest and DNA damage-inducible 45 proteins (GADD45), 13-3-3σ, etc. These proteins are implicated in inactivation of cyclin-cyclin-dependent kinase (cyclin-CDK) complexes required for the progression of the cell cycle (**Figure 1**).

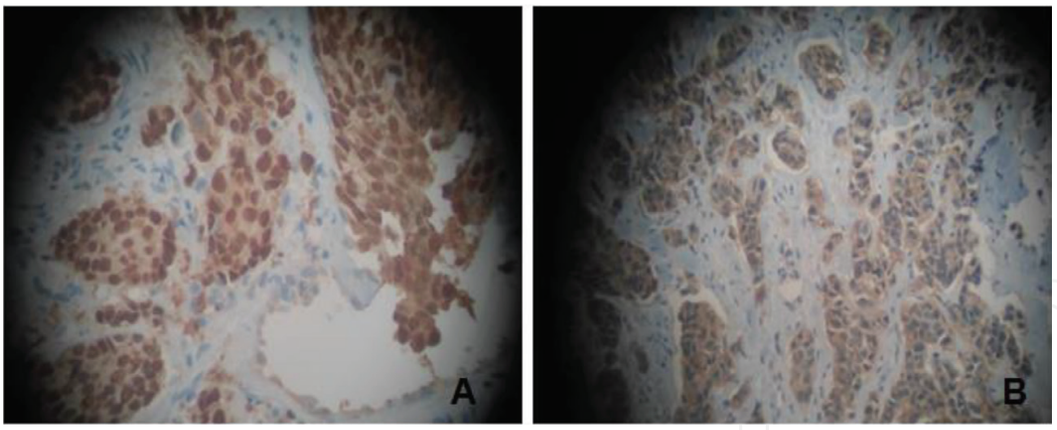

Figure 2. Immunostaining (brown) of estrogen receptor (ER) and HER2 in ductal invasive breast carcinoma. ER (A) and HER2 (B) were revealed, respectively, by their specific antibody. The tissue was counterstained by hematoxylin (blue). Magnification by light microscopy ×400 (from collaboration between Department of Surgical Pathology and Department of Cellular and Molecular Biology-Genetics; Faculty of Medicine, University of Health Sciences, Libreville, Gabon).

In breast cancer, other tumor suppressor genes such as BRCA1 or BRCA2 [9–11] code for proteins that repair DNA damages. Mutations of these genes result in mutated proteins that cannot repair DNA, and cells bearing such mutations will turn into cancers. Taken together, the mutations of BRCA1 and BRCA2 cause about 20–25% of inherited breast cancer and 5–10% of all cancers [12].

Breast cancer risk is of about 50–80% in women with a genetic predisposition [13, 14]. Furthermore, it has been shown that mutation of BRCA1 and BRCA2 is a predictive factor of a major risk of breast cancer [15].The tumor progression can be locally favored by mitogenic effects of hormones, or growth factors which stimulate the tumor's growth, or by activating vascular endothelial growth factor (VEGF) receptor to induce angiogenesis. Human breast cancer is characterized by its high sensitivity to estrogens and its high metastatic potential. About 50% of these cancers are sensitive to antiestrogen treatment [16]. Therefore, the presence of estrogen receptor (ER) is considered to be a predictive factor of response to hormone therapy. Moreover, ER has been shown to be an independent prognostic factor in mammary cancer [16] (**Figure 2**).

Furthermore, estrogens and growth factors induce proteases such as cathepsin D [17]. Cathepsin D is an acid aspartyl endoprotease that is routed through the trans-Golgi network (TGN), by binding to the mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2-R) via M6P signals, to lysosomes for degradation. In cancer cells, cathepsin D acts as mitogen promoting metastases [18, 19] and tumor angiogenesis [20, 21]. Clinical studies revealed that cathepsin D is an independent prognostic factor for metastasis risk in breast cancer [22]. In parallel, experimental studies in breast cancer cell lines showed deficiencies of cathepsin D routing to lysosomes, suggesting defects at the receptor level.

Therefore, the M6P/IGF2-R has been hypothesized as being coded by a breast cancer suppressor gene [23], and its potential prognostic significance in breast cancer has been suggested [24].

The cancer pathology includes more than 100 diseases that can cause serious illness or death if not detected in time. The purpose of this book is to present current developments in the methodology in cell and molecular biology which have deeply advanced in the understanding of cancer's prevention and prognosis. Among them, the research for biomarkers may be

essential since they can be the target of a preventive therapy, a marker of risk that can be used to identify populations with high risk or a marker of a drug's toxicity used in prevention which can help to monitor its tolerance.

Author details

Guy Joseph Lemamy

Address all correspondence to: guylemamy@yahoo.fr

Department of Cellular and Molecular Biology – Genetics, Faculty of Medicine, University of Health Sciences (Université des Sciences de la Santé - USS), Libreville, Gabon

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