Cellular Signalling xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cellular Signalling

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

Review

Signaling pathways in breast cancer: Therapeutic targeting of the microenvironment

Armel Herve Nwabo Kamdje [a,*], Jean Marc Muller [b], Kiven Erique Lukong [c]

[a] Department of Biomedical Sciences, Faculty of Sciences, University of Ngaoundéré, P.O. Box 454, Ngaoundéré, Cameroon
[b] Université de Poitiers, Faculté des Sciences, Pôle Biologie-Santé Bât B36, 1, rue Georges Bonnet-BP633, 86022, Poitiers cedex, France
[c] Department of Biochemistry, College of Medicine, Room 4D30.5 Health Sciences Bldg, University of Saskatchewan, 107 Wiggins Road, Saskatoon, SK. S7N 5E5, Canada

ARTICLE INFO

Article history:
Received 27 June 2014
Accepted 28 July 2014
Available online xxxx

Keywords:
Breast cancer
Microenvironment
Signaling pathways
Targeted therapies
Chemo-resistance

ABSTRACT

Breast cancer is the most common cancer in women worldwide. Understanding the biology of this tumor is a prerequisite for selecting an appropriate treatment. Cell cycle alterations are seen in many cancers such as breast cancer. Newly popular targeted agents in breast cancer have been reported such as cyclin dependent kinase inhibitors (CDKIs) which are agents inhibiting the function of cyclin dependent kinases (CDKs) as well as Notch, Wnt, and SHH (Sonic hedgehog) which have recently been reported as a novel therapeutic target in breast cancer. They are categorized as selective and non-selective inhibitors of CDK. CDKIs have been tried as monotherapy and combination therapy. Palbocyclib is now a promising CDKI used in breast cancer. Nowadays palbocyclib is designed for a phase III trial for estrogen receptor (ER) positive breast cancer after showing favorable results in progression free survival in a phase II trial.
The tumor microenvironment is increasingly recognized as a significant factor in cancer treatment response. The tumor microenvironment is considered as a target for combination therapy of breast cancer. Recent findings of the signaling pathways in breast cancer are herein summarized and discussed. Furthermore, the therapeutic targeting of the microenvironment in breast cancer is also considered.

Contents

* Corresponding author. Tel.: +237 90190421; fax: +237 22251747.
E-mail addresses: armel.nwabo@gmail.com, ah.nwabo@univ-ndere.cm, kamdjewa@yahoo.fr (A.H. Nwabo Kamdje).

http://dx.doi.org/10.1016/j.cellsig.2014.07.034
0898-6568/

1. Introduction

Cancer consists of immortal cells that can be fatal for patients. Ironically, these cells must die so that the patients survive. Cell division and cell death are the two predominant physiological processes that regulate normal tissue homeostasis. Alteration of these two physiological processes has a pivotal role in the pathogenesis of cancer [1]. Great efforts to ascertain components of the cell cycle are guiding to novel approaches for the treatment of cancer.

Genes encoding components of the cell cycle such as cyclin, CDKs and their endogenous inhibitors which are found in normal conditions are often impaired in many human cancers [2]. For example, CDKs are overactive in some cancers depending on cyclin overexpression or downregulation of endogenous CDKIs [3]. According to this data, researchers focus on whether the strategy of CDK inhibition is able to render cancer treatment more successful. Some studies suggest that inhibiting CDKs may be an effective therapy in many cancers including breast cancer [4]. Hormone therapy is another form of systemic therapy. It is most often used as an adjuvant therapy to help reduce the risk of the cancer coming back after surgery, but it can be used as neoadjuvant treatment, as well. It is also used to treat cancer that has come back after treatment or has spread. The new research findings offer the possibility of expanding the ways patients with breast cancer are treated with hormone therapy by using drugs that block estrogen (a type of hormone) from attaching to estrogen receptors on tumor cells to prevent the cells from growing and spreading [5]. Some pathways such as Notch, Wnt, SHH (Sonic hedgehog) and other pathways have recently been reported as a novel therapeutic target in breast cancer [6–10].

The breast microenvironment consists of extracellular matrix (ECM) and numerous stromal cell types, including endothelial and immune cells, fibroblasts, and adipocytes [11]. Recent studies have reported that cancer-associated fibroblasts (CAFs) make up the bulk of cancer stroma and affect the tumor microenvironment such that they promote cancer initiation, angiogenesis, invasion, and metastasis [11]. In breast cancer, CAFs not only promote tumor progression but also induce therapeutic resistance. Accordingly, targeting CAFs provides a novel way to control tumors with therapeutic resistance [11]. The tumor microenvironmental cells, which express some of the Notch molecules and release factors that promote cancer cells survival and proliferation [12–14]. The tumor microenvironment is now recognized as an important participant of tumor progression and response to treatment [15]. As a result, there is increasing interest in developing novel therapies targeting the microenvironment, particularly as it relates to invasive and metastatic progression. Signals from the microenvironment, especially those from transforming growth factor-β (TGF-β), induce targeted de novo epigenetic alterations of cancer-related genes [15]. While TGF-β signaling has been implicated in two opposite roles in cancer, namely tumor suppression and tumor promotion, its deregulation is also partly induced by epigenetic alteration itself [15]. The present review summarizes and discusses the current understanding of the signaling pathways in breast cancer with a particular emphasis on the therapeutic targeting of the microenvironment.

2. Signaling pathways and hormones involved in breast cancer cell cycle and survival

Several proteins, pathways and hormones are involved in breast cancer cell cycle and survival such as CDKs (Cyclin dependent kinase), Notch, Wnt, SHH, estrogen receptor, HER2 (human epidermal growth factor receptor 2), and others. Fig. 1 show proteins, pathways in breast cancer cell cycle and survival.

2.1. CDKs

Cell cycle is regulated by cyclins, CDKs, and CDKIs. These three key classes of regulatory molecules determine a cell's progress through the cell cycle [16]. Cell cycle is divided into 4 distinct phases (G1, S, G2, and M). G0 represents exit from the cell cycle. Specific cyclin and CDK complexes conduct cell cycle progression by regulating transition through G0-G1-S-G2-M phases. Cell cycle is driven by CDKs, which are positively and negatively regulated by cyclins and CDKIs, respectively [17]. Cyclins form the regulatory subunits and CDKs the catalytic subunits of an activated heterodimer; cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin [18].

Animal cells contain lots of CDKs. Some of them are directly involved in cell cycle regulation, such as CDK1, CDK2 and CDK4. For example, CDK1, with its partners cyclin A2 and B1, alone can drive the cell cycle in mammalian cells [19]. When activated by a bound cyclin, CDKs perform a common biochemical reaction called phosphorylation that activates or inactivates target proteins to orchestrate coordinated entry into the next phase of the cell cycle. Cyclin–CDK complexes in earlier cell-cycle phase help activate cyclin–CDK complexes in later phases [20]. In addition, a second group of CDKs are responsible for the regulation of cellular transcription. They have role of maintenance

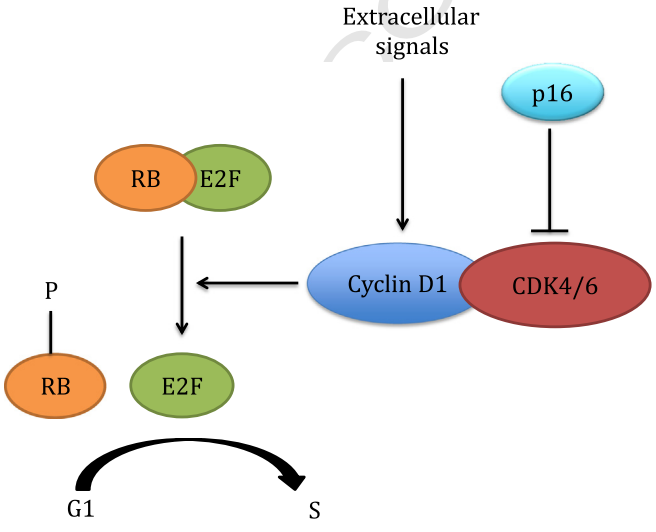

Fig. 1. Proteins, pathways in breast cancer cell cycle and survival: Cyclin D1/CDK4 and CDK6/Rb/E2F pathway for G1 to S transition [16–18].