Biochemical Pharmacology 85 (2013) 1219–1226

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

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

Commentary

Molecular aspects of cancer cell resistance to chemotherapy

Magali Rebucci, Carine Michiels *

URBC – NARILIS, University of Namur – FUNDP, Belgium

ARTICLE INFO

Article history:
Received 8 January 2013
Accepted 12 February 2013
Available online 19 February 2013

Keywords:
Cancer
Resistance
Anti-cancer agents
Targeted therapies
Hypoxia
Cancer stem cells

ABSTRACT

Cancer cell resistance to chemotherapy is still a heavy burden that impairs treatment of cancer patients. Both intrinsic and acquired resistance results from the numerous genetic and epigenetic changes occurring in cancer cells. Most of the hallmarks of cancer cells provide general mechanisms to sustain stresses such as the ones induced by chemotherapeutic drugs. Moreover, specific changes in the target bring resistance to specific drugs like modification in nucleotide synthesis enzymes upon anti-metabolite exposure, in microtubule composition upon spindle poison treatment, in topoisomerase activity upon topoisomerase inhibitor incubation or in intracellular signaling pathways when targeting tyrosine kinase receptors.

Finally, the stemness properties of a few cancer cells as well as components of the tumor stroma, like fibroblasts and tumor-associated macrophages but also hypoxia, also help tumor to resist to anticancer agents. These processes provide an additional level of complexity to the understanding of the tumor resistance phenomenon.

This review aims to describe the different general mechanisms as well as some examples of specific on target modifications inducing cancer cell resistance to chemotherapy at the molecular level. Perspectives to develop more efficient treatment, using genomic signature or more specific biomarkers to characterize putative resistance mechanisms in patients before choosing the more appropriate treatment, will also be discussed.

1. Introduction

In its "Focus on Cancer" March 2011, Nature Medicine has defined four lines of research that still need enormous research efforts in order to ameliorate our understanding of the cancer pathology but also to develop new more efficient therapeutic strategies [1]. Amongst them, research on resistance mechanisms ("insights into treatment failure") remains a key challenge in the fight against cancer.

The first cause of therapeutic failure results from genetic alterations existing before treatment. This is the primary or intrinsic resistance. The second one is induced by drug treatment and is called secondary or acquired resistance. Both are due to mutations in the genome of cancer cells and/or to epigenetic changes. Unfortunately, resistance appears not only to conventional chemotherapy but also to targeted therapies, the so-called "smart drugs" such as kinase inhibitors and tamoxifen that binds to the estrogen receptor [2].

As reviewed by Hanahan and Weinberg [3], cancer cells result from a sequence of mutations in a particular subset of genes (tumor suppressor genes or oncogenes) that triggers unregulated proliferation but that also permits the acquisition of "hallmarks of cancer" that are observed in most cancers. Moreover, enabling characteristics, among which is genome instability, further accelerate tumor progression. Hence, cancer cells contain hundreds to thousands mutations as well as complex chromosome rearrangements [4,5]. Furthermore, each patient harbors a different cancer regarding which genes are mutated, regarding the nature of each mutation, i.e. different mutations for the same gene have been detected in several patients [6], and regarding the sequence of apparition of these mutations. Finally, tumors are very heterogeneous because of the clonal evolution of tumor cell populations driven by genomic instability [7]. These observations partly explain why different patients harboring the "same" cancer may respond differently to a same treatment regimen.

The purpose of this review is to give insight into the molecular mechanisms responsible for resistance of tumors to anticancer agents. They include the mechanisms inducing lower sensitivity to a large panel of drugs as well as the ones responsible for augmenting resistance to a more specific subfamily of therapeutic molecules. It will not overview pharmacological and physiological factors that impair drug delivery, enhance drug metabolism or favor drug elimination.

* Corresponding author at: URBC, 61 rue de Bruxelles, University of Namur, 5000 Namur, Belgium. Tel.: +32 81 724131; fax: +32 81 724135.
E-mail address: carine.michiels@fundp.ac.be (C. Michiels).

0006-2952/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bcp.2013.02.017

2. Mechanisms common to several drugs (Fig. 1)

2.1. Activating mutation of oncogenes or inactivating mutation of tumor suppressor genes renders cancer cells resistant to cell death per se

Dysregulated proliferation signaling pathways is the most described cause of cell transformation. Overexpression of growth factors enabling autocrine mitotic signal, mutation of growth factor receptors as well as mutation/overexpression of signal transduction proteins lead to sustained proliferative signaling and aberrant proliferation [8]. Less known is that proliferation circuits and viability circuits are intimately connected: indeed, proliferative signals do also simultaneously provide survival signals. These survival signals not only prevent cancer cell death per se but also promote cell viability when exposed to stresses, such as the ones generated by anticancer drugs.

One of the most well described examples is "gain-of-function" gene alterations in the PI3K/Akt/mTOR pathway. Phosphatidylinositol 3-kinases (PI3K) are lipid kinases activated downstream of growth factor receptors. These enzymes generated hyperphosphorylated phosphatidylinositol molecules that serve as anchoring platforms for two kinases, PDK and Akt, leading to Akt and mTOR activation. Both enzymes then phosphorylate different substrates involved in regulating cell cycle entry but also anti-apoptotic proteins [9]. Numerous activating mutations into PI3KCA as well as activation of Akt by genetic mutations, genome amplification or by mutations in upstream signaling components have been reported in human tumors [10]. Among Akt anti-apoptotic substrates are Bad, a BH3-only Bcl2 family member which is sequestered in the cytosol, hence maintained inactive, upon phosphorylation; caspase 9 whose phosphorylation is inactivating; FOXO1, FOXO3A and FOXO4 that are forkhead transcription factors which unphosphorylated, localize in the nucleus and induce the transcription of a wide array of target genes involved in the cell cycle and apoptosis such as CDN1B (p27Kip1) and CDN1A (p21Cip1), Fas-L (TNFL6) and BIM. Phosphorylation leads to FOXO sequestration in the cytosol; and ASK1 (apoptosis signal-regulating kinase 1) which, when phosphorylated, activates c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases, hence inducing apoptosis [11]. mTOR is also a major regulator of autophagy (see below).

A second signaling pathway that is often overactivated in cancer cells is the Ras/Raf/MAPK pathway. Ras is a small GTP protein also activated downstream of the growth factor tyrosine kinase receptor. It then activates the MAP (mitogen activated protein) kinase cascade of which Raf is the first enzyme. "Gain-of-function" mutations in the three genes encoding Ras, in BRAF, the gene encoding Raf, and in downstream transcription factors lead to unregulated proliferation but also in pro-survival signals.

Another example is addiction of cancer cells to NF-κB activation: constitutive activation of this transcription factor is observed in most cancer cells and inhibition of its activity suppresses the growth of these cells [12]. Several mechanisms have been described that explain this persistent activation both from genomic alterations but also as a consequence of the intratumoral inflammation [13]. NF-κB not only regulates the transcription of inflammatory proteins but also enhances the expression of anti-apoptotic proteins amongst which are BCL-xL and several IAPs.

In addition to the overall induction of positive growth signals, tumor cells also suppress proliferation inhibitors. This is achieved by inactivating mutations in tumor suppressor genes. The RB (retinoblastoma) gene was the first to be discovered as an anti-oncogene. RB "loss-of-function" mutations have been detected in various human tumors [14]. The protein Rb (pRb) regulates cell cycle progression by sequestering the EF2 transcription factor needed for cyclin E and A expression. Disruption of this pathway favors cell cycle entry as well as modulates cancer cell sensitivity to different chemotherapeutic molecules: both elevated and diminished sensitivity has been reported [15,16]. The mechanisms underlying these opposite effects are still unclear but may involve checkpoint bypass as well as regulation of chromosomal stability.

A second well described tumor suppressor is PTEN (phosphatase and tensin homologue deleted from chromosome 10). PTEN is a phosphatase that removes phosphate groups from the hyperphosphorylated phosphatidylinositol molecules generated by PI3K, hence reverting the mitotic signal originating from growth factor binding to their receptor. Inactivating methylation of PTEN promoter and disruptive mutations in PTEN gene result in unregulated activation of the PI3K/Akt pathway, hence as mentioned here above in potent survival signaling [16,17]. More and more reports showed that PTEN plays a role in the response of cancer cells to oncoprotein targeting molecules: loss of PTEN leads to both primary and acquired increased resistance [18].

One exception is p53 mutation, that according to the cancer type, may increase or decrease resistance to drug toxicity. p53, the guardian of the genome, is a transcription factor activated upon stresses amongst which is DNA damage, which increases the expression of genes involved in cell cycle arrest (e.g. p21), DNA repair (e.g. GADD45, PCNA) and, if the damage can not be resolved, in the induction of apoptosis (e.g. Bax, PUMA, NOXA, Fas,...). The gene TP53 is the most frequent target of genetic alterations, being mutated in more than half of human tumors [19]. There is evidence that, in addition to favor genomic instability, p53 mutation is also associated with changes in responses to anti-cancer agents since wild-type p53 induced apoptosis in response to these drugs. Hence, in general, studies in vitro in numerous cancer cell lines as well as in patients demonstrated that cells or tumors harboring mutated p53 are more resistant to drugs compared to wild-type p53 cells when treated with a wide variety of molecules (for a review, see [16]) and is associated with treatment failure [20]. This can be explained by the loss of the upregulation of the p53

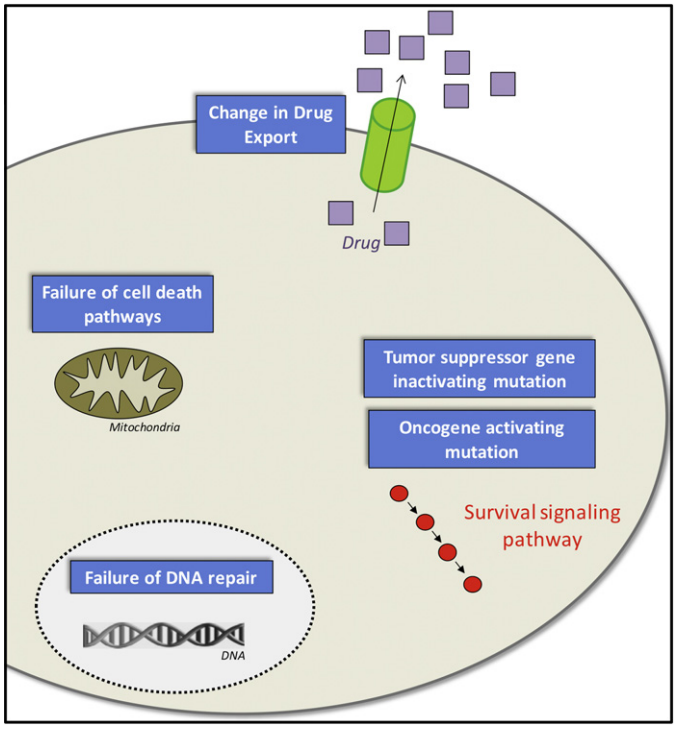

Fig. 1. Overview of drug resistance common mechanisms.