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REVIEW

Recent Advances in the Studies of Molecular Mechanisms Regulating Multidrug Resistance in Cancer Cells

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Abstract—Here we present new approaches to better understanding multidrug resistance (MDR) development in cancer cells, such as identification of components of a complex process of MDR evolution. Recent advances in the studies of MDR are discussed: 1) chemotherapy agents might be involved in the selection of cancer stem cells resulting in the elevated drug resistance and enhanced tumorigenicity; 2) cell–cell interactions have a great effect on the MDR emergence and evolution; 3) mechanotransduction is an important signaling mechanism in cell–cell interactions; 4) proteins of the ABC transporter family which are often involved in MDR might be transferred between cells via microvesicles (epigenetic MDR regulation); 5) proteins providing cell-to-cell transfer of functional P-glycoprotein (MDR1 protein) via microvesicles have been investigated; 6) P-glycoprotein may serve to regulate apoptosis, as well as transcription and translation of target genes/proteins. Although proving once again that MDR is a complex multi-faceted process, these data open new approaches to overcoming it.

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Multidrug resistance (MDR) refers to the mechanisms by which body cells develop resistance to a broad range of structurally diverse chemical agents with different modes of action in the cells [1, 2]. MDR is a serious obstacle on route towards successful cancer chemotherapy. However, MDR is not limited only to the resistance against chemotherapy agents but can be viewed as a defense reaction against the damage of cells, normal tissues, and entire organism. Exposure of host cells to one of the MDR agents might induce resistance to other drugs, even if the cells have not been previously exposed to them. The ability to develop MDR can be found at all organization levels and, apparently, is essential for survival of living organisms on Earth.

When speaking about drug resistance, it should be emphasized that MDR might precede therapeutic intervention (the so-called intrinsic or pre-existing MDR) or emerge in a course of drug therapy (induced MDR). MDR emergence and development are complex processes triggered by one or several specific molecular factors [1, 2] that, in their turn, might be influenced by altered activity of genes, especially those involved in the control of malignant transformation [2]. Anticancer drugs can elicit drug resistance (DR) and also serve as a factor for selecting the cells with developed DR including chemoresistant cells that have already existed (have preformed) in the heterogenous population of cancer cells [1]. At present, it has become apparent that intrinsic heterogeneity of tumor cells is a key to their high adaptability to environmental factors [3].

MDR has been most extensively examined in cancer cells and normal cells cultured *in vitro*; however, results from the *in vivo* studies of MDR at the organism level obtained in clinical trials have recently become available [4, 5]. In this review, we discuss new data on the molecular mechanisms responsible for the regulation of DR and MDR *in vitro* and *in vivo*.

Gottesman et al. identified two major components in the DR evolution: specific biological changes resulting in DR and factors that facilitate biological processes promoting DR emergence and evolution [2].

Abbreviations: ABC, ATP binding cassette; CAFs, cancer-associated fibroblasts; CSCs, cancer stem cells; DR, drug resistance; E-cad, E-cadherin; ECM, extracellular matrix; ES, Ewing sarcoma; MDR, multidrug resistance; *MDR1*, multidrug resistance gene 1, encodes Pgp; MVs, microvesicles; NFs, normal fibroblasts; Pgp, P-glycoprotein (according to the current ABCB1 classification); TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand.

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SPECIFIC MOLECULAR CHANGES UNDERLYING DR AND MDR

Mutations in the drug targets. Imatinib, which is currently used to treat chronic myeloid leukemia (CML), is a selective inhibitor of the BCR-ABL fusion tyrosine kinase that drives this disease. However, it is not uncommon that resistance to imatinib develops due to mutations (point mutations, deletions, and insertions) in the *BCR/ABL* gene [6].

Changes in the pathways of drug transport, metabolism, or sequestration in the cell. Activation of ABC (ATP-binding cassette) transporters that pump the drugs out of the cells is among the most common causes involved in this type of DR [7]. It was shown that DR development might be also related to the altered metabolism of cancer cells [8].

Cancer-specific changes in cellular mechanisms. Such changes include altered signaling pathways controlling cell differentiation, the presence of cancer stem cells (CSCs) in the population, changes in the homeostatic response to unfavorable factors, etc. DR of this type is often epigenetically regulated. Similar to tissue differentiation, epigenetic regulation of DR involves DNA and histone modification, stable modifications of regulatory proteins, and microRNAs. The importance of changes in cell signaling in the MDR development could be illustrated by the role of YB-1 protein in the regulation of the *MDR1* gene activity [9]. YB-1 was found in pro- and eukaryotic cells, where it performs multiple functions including regulation of gene transcription and translation.

Changes in the tumor substratum and local cell physiology, which can result from hypoxia, changes in the local blood supply, interactions between cancer cells and extracellular matrix or neighbor cells (e.g., stromal fibroblasts and immune cells) [2].

Recently obtained data show that in some body tissues, normal cells in the tumor microenvironment can contribute to tumor malignancy and chemoresistance of cancer cells [10, 11].

DRUG RESISTANCE-PROMOTING FACTORS

Cancer cell heterogeneity. It is well known that cancer cells represent a highly heterogeneous population. Such high heterogeneity increases the probability for emerging new subsets of cancer cells, including those resistant to drugs [12].

Elevated genetic and epigenetic variability of cancer cells is one of the essential features of tumorigenicity [13, 14] and also increases a risk for emerging new cell subtypes including drug-resistant cells.

Activation of cell survival signaling pathways results in the emergence of single cells able to adapt to the effects of cytostatic agents. With further treatment, such cell subtypes might acquire selective advantage that will allow them to proliferate.

Effect of tumor microenvironment. It was established that cancer cells are greatly influenced by their microenvironment. For instance, glioblastoma growth may be affected by the blood vessel cells, such as pericytes (vascular smooth muscle cells), and immune cells including T cells, macrophages, microglia, neutrophils, NK cells, and dendritic cells [15]. Stromal cells might release growth factors that would stimulate tumor cells replication via paracrine regulation [16]. Cancer-associated fibroblasts (CAFs) were demonstrated to affect tumor invasion [17].

CANCER STEM CELLS (CSCs) AND MDR

In the early studies, DR and MDR had been investigated in bacteria. The well-known Luria–Delbruck experiment (fluctuation test) showed that only a small portion of cells develop genetic changes and survive drug treatment (if the drug is administered at a proper dose) [18]. Cells that survive the drug exposure acquire a selective advantage that allows them to proliferate further. This observation has been later confirmed by numerous research groups. However, studies of the last decade have introduced the term *cancer stem cells* (CSCs) that dramatically transformed our understanding of the evolution of cancer cell types [19]. CSCs are highly tumorigenic, with a self-renewal potential. They are responsible for tumor cell heterogeneity and, therefore, MDR development (see above). CSCs are often drug-resistant, which explains their proliferation in the presence of chemotherapy agents. Therefore, the use of antitumor agents might facilitate CSC selection, hence, increase tumorigenicity [20].

EFFECT OF CELL–CELL INTERACTIONS ON MDR EMERGENCE AND EVOLUTION

Recently, principally new data on the effect of cell–cell interactions on MDR emergence and evolution have been obtained.

Cancer cell can interact with (i) neighboring cancer cell, (ii) normal cells of the tumor stroma, and (iii) extracellular matrix components.

Homotypic interactions between neighboring epithelial cells. Such type of interactions is mediated by E-cadherin (E-cad); anti-E-cad antibodies can disrupt intercellular contacts and elevate cell sensitivity to a number of antitumor drugs [21, 22]. Upregulated E-cad expression in breast and prostate cancer cells increases chemoresistance of these cells [23]. E-cad-linked DR is associated with the activation of canonical signaling pathways of cell proliferation control (e.g., ERK and AKT signaling cascades) [24]. On the other hand, downregulation

of E-cad expression increases the number of CSCs, thereby enhancing tumor DR [25]. Therefore, cell–cell interactions mediated by E-cad can have the opposite effects on MDR.

Contacts between neighboring cells mediated by proteins other than E-cad can also influence drug sensitivity of cancer cells, as it was demonstrated using antibodies against intercellular adhesion molecule 1 (ICAM-1, also known as CD54) [26]. ICAM-1 is a glycoprotein expressed mostly on endothelial and immune cells that binds to integrins CD11a/CD18 or CD11b/CD18. It was demonstrated that anti-ICAM-1 antibodies significantly enhance the cytostatic effects of tested drugs [26].

Interaction of cancer cells with normal cells of the tumor stroma. Tumor is a complex formation consisting of both malignant cells and genetically stable normal stromal cells, including endothelial cells, fibroblasts, and immune cells [27]. In last decade, it has become evident that stromal cells influence the key features of cancer cells and that it is a combined action of cancer and normal stromal cells that determines cancer development. One of the features of malignant cells that is affected by normal cells is tumor resistance to chemotherapy [27, 28]. Stromal cells influence the chemoresistance of cancer cells by (i) serving as a barrier that restricts drug influx, (ii) secreting factors promoting cell proliferation or release of anti-apoptotic factors, (iii) building up niches for CSCs, and (iv) modulating immunosuppression [27].

According to D. Hanahan, there are three major types of stromal cells: (1) cancer-associated fibroblasts (CAFs); (2) angiogenic vascular cells (AVCs); (3) tumor-infiltrating immune cells (TIICs) [29], that are distinguished based on the ability of these cells to influence the hallmarks of cancer described by Hanahan and Weinberg in [14]. Depending on the tumor type, CAFs, AVCs, and TIICs could be present in different proportions [29]. Stromal cells do not always enhance malignancy (although, they do in most cases). Sometimes stromal cells ameliorate the signs of malignancy [30, 31]. Thus, when co-cultured with cancer cells, normal connective tissue fibroblasts were found to inhibit cancer cell proliferation [29, 30]. Apparently, this effect was determined by the subtypes of cells in the studied cell populations.

Interactions between cancer cells and extracellular matrix components. A link between attachment of cancer cells to the extracellular matrix (ECM) and MDR has been recognized long ago [32]. A significant contribution to the understanding this association has been done by W. C. Dalton and colleagues who have demonstrated that cancer cell microenvironment, and particularly ECM components, contribute to the MDR emergence and evolution. This problem has received a significant development in the last decade. ECM is a network of fibrils that serves as a structural cell support, participates in the transduction of local signals, and regulates cell motility, proliferation, and differentiation [28]. ECM produced by cancer cells differs from that of normal cells; in particular, it is much stiffer [33]. ECM stiffness increases the cytoskeletal tension, which, in turn, affects focal contact formation and activates cell proliferation via activating signaling pathways including the ERK1/2–RUNX2 axis [34]. It was found that mechanical tension in a 3D cell culture mimics activation of the ERK1/2–RUNX2 pathway resulting in the DR development [34]. ECM mechanical properties influence cancer cell response to drugs [35, 36]. In recent years, 3D cell cultures or 3D models have been extensively used in experimental oncology and pharmacology [37, 38] to mimic tumor-stromal interactions. 3D cell cultures are often used to study the role of mechanotransduction in carcinogenesis and tumor progression.

Mechanotransduction – a mechanism of signal transduction between contacting cells. Mechanotransduction is any of various mechanisms by which cells convert mechanical stimuli into biochemical signals in order to adapt to a changing environment. Activation of signaling pathways involved in mechanotransduction modulates the set and the activity of transcription factors, thereby controlling expression of multiple genes [39]. For instance, in breast cancer cells, increased ECM stiffness induces translocation of the transcription factor TWIST1 to the nucleus followed by epithelial-mesenchymal transition and increases metastatic potential of these cells [38]. Mechanotransduction can be also linked to the changes in the chemosensitivity of cancer cells. Marturano-Kruik et al. demonstrated that mechanotransduction significantly influences the sensitivity of Ewing sarcoma (ES) cells [34]. Below, we'll discuss this work in more detail because (i) it has a crucial importance in this context of our review and (ii) it outlines a methodology level required for performing this type of studies.

In this elegant yet the only study available so far, the authors used a 3D matrix and custom-designed cell culture bioreactor for mechanical stimulation of cancer cells. ES cells were seeded into porous 3D scaffolds for 48 h and then placed into the bioreactor, where the cells were subjected to mechanical stimulation for 2 h. After that, the cells were plated into 96-well plates to evaluate their drug sensitivity to sorafenib and other antitumor agents using a general protocol. Sorafenib is a low-molecular-weight multi-kinase inhibitor that inhibits both intracellular kinases (c-CRAF, BRAF, and mutant BRAF serine/threonine kinase) and cell surface receptor tyrosine kinases, such as receptors for vascular endothelial growth factor (VEGFR-1, VEGFR-2, and VEGFR-3), stem cell factor (KIT), Fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor (PDGFR-β), and glial cell line-derived neurotrophic factor. It was found that mechanical stimuli enhanced ES cell resistance to sorafenib but did not affect cell sensitivity to doxorubicin.

NEW STUDIES OF THE ABC TRANSPORTER FAMILY

As mentioned above, one of the most common reasons for MDR is the elevated activity of ABC transporters that pump drugs out of the cells. Among ABC transporters, P-glycoprotein (Pgp; ABCB1 according to the current classification) has been most extensively studied because of its principal role in MDR [1, 2]. Nevertheless, new original scientific papers are published continuously that attract attention of the scientific community due to the high significance of presented results.

ABC transporters are transferred between the cells with microvesicles. In the last decade, it has demonstrated that Pgp is transferred between the cells via microvesicles (MVs) [40]. The role of different types of MVs in carcinogenesis, tumor progression, and DR has been broadly discussed before [41-44] and will be omitted from our review. However, it should be noted that MDR-positive cells might release elevated (compared to non-resistant cells) amounts of MVs [45], thereby stimulating further MDR development. It was also demonstrated that malignant cells release MVs at much higher levels than non-malignant cells [40, 46], which might also promote MDR development. Proteomics analysis of MVs from the breast cancer cells identified 120 proteins found only in the drug-resistant cells [47]. Pgp is transferred to the target cells via MVs together with CD44 antigen, ERM family proteins (ezrin, radixin, moesin), and some cytoskeletal proteins [47]. Apparently, this combination of proteins is not random and, according to the authors' opinion, represents a result of selective packaging. CD44, a hyaluronan receptor, is a membrane protein involved in cell proliferation, differentiation, adhesion, motility, and metastasis [48]. CD44 intracellular domain binds to actin filaments via ezrin, radixin, and moesin. It was demonstrated that in MDR-positive cells, Pgp and CD44 co-localize, co-precipitate, and are co-regulated [49].

Cell transfection with the *CD44* gene upregulates Pgp expression, whereas *CD44* knockdown substantially decreases Pgp functional activity and MDR [50]. CD44 and radixin are necessary for the Pgp-mediated drug efflux; all three ERM proteins play an important role in the transport of functional Pgp with MVs to the target cells [50].

YB-1 is a common regulatory protein for Pgp and CD44. As mentioned above, it was noted that YB-1 is a trans-activating factor implicated in *MDR1* transcriptional regulation [9]. The full-size YB-1 binds to the promoters of the *CD44* and *CD49f* genes and induces their expression, as well as regulates CD44 mRNA alternative splicing by increasing inclusion of exon v4 [51, 52]. Transfection of BT-474 cells (HER2-positive breast cancer subtype) with stably active YB-1 (S102D) mutant phosphorylated at Ser102 upregulated CD44 expression, whereas exposure to trastuzumab led to the selection of the drug-resistant cell population enriched with $CD44^+$ cells [53].

Proteins interacting with Pgp or regulating MV-mediated cell-to-cell transfer of functional Pgp. An appealing hypothesis has been proposed that drug efflux depends not on Pgp alone, but also on other proteins that regulate Pgp activity or interact with Pgp (table) [54].

As seen from the table, there are several proteins that can modulate Pgp expression and activity and, according to the proposed hypothesis, participate in the drug transport from the cells.

In recent years, new data have emerged showing that Pgp not only remove substances from the cells but exhibit other activities [55]. In particular, Pgp (i) protects cells from apoptosis and (ii) participates in the regulation of gene transcription and translation.

Pgp protects cells from apoptosis. It was demonstrated recently that Pgp makes cultured cells more resistant

Proteins interacting with Pgp in cells with MDR or regulating MV-mediated cell-to-cell Pgp transfer [54]

Proteins	Protein function	References
CD44	hyaluronan receptor	[48, 50]
ERM proteins (ezrin, radixin, moesin)	CD44 binding to actin cytoskeleton	[65, 66]
CD147	induces extracellular matrix metalloproteinases	[67, 68]
Caveolin (Cav10)	structural protein of caveolae	[69-71]
Rab family proteins	regulators of intracellular vesicle transport	[72]
Ubiquitin	regulation of intracellular protein degradation and protein functions	[73]
Heat shock proteins	molecular chaperones	[74, 75]
Glutathione-S-transferases	detoxifying enzymes	[76, 77]

to apoptosis induced by some non-drug factors (Fas, tumor necrosis factor (TNF), UV- and γ-irradiation, serum starvation) [56-59]. Studies of blood and bone marrow samples from patients with acute myeloid leukemia showed that Pgp is capable of protecting cells from spontaneous apoptosis [60, 61]. Interestingly, the anti-apoptotic effect of Pgp does not depend on the protein pump activity [60].

The anti-apoptotic activity Pgp is associated with (i) its effect on the assembly of pro-apoptotic membrane signaling complex, (ii) ability to suppress caspase activation, and (iii) capacity to modulate activity of calcium channels and, hence, control Ca^{2+} homeostasis [62]. Recently, a new anti-apoptotic mechanism of Pgp was identified [63]. It was found that Pgp regulates expression of endogenous TNF-related apoptosis-inducing ligand (TRAIL) protein and modulates TRAIL-associated signaling pathway, whose activation results in apoptosis. TRAIL belongs to the TNF superfamily; Apo2, a ligand of TRAIL, binds to the surface membrane receptors, thereby activating caspases [64].

Pgp regulates gene transcription and translation. It was found that transcription of genes for ABC transporters could be regulated by the *MDR1* mRNA through its action on miRNAs. The authors used drug-sensitive human acute lymphoblastic leukemia cells (CEM) and their derivatives with high MDR (E1000 and VLB100). The MDR of E1000 and VLB100 cells was related to the overexpression of *MRP1* (coding for ABCC1 protein) and *MDR1* genes, respectively. It was shown that downregulation of *MRP1* expression by miR-326 is modulated by the *MDR1* transcripts. Suppression if *MDR1* transcripts with specific siRNAs prevented *MRP1* knockdown with miR-326 [40]. Therefore, it was concluded that *MDR1* mRNA regulates transcription of the other genes encoding ABC transporters through acting on miR-326. We believe that new data on the effects of Pgp on the activity and expression of other ABC transporters will be unveiled in the future.

In conclusion, novel approaches to studying MDR have been developed during the last decade that resulted in the new data on the molecular and cellular mechanisms of MDR. One of this approaches that has considerably simplified analysis of such multi-layered phenomenon as MDR includes distinguishing two components of DR evolution: (i) specific molecular changes that promote DR and (ii) factors that facilitate DR emergence and evolution.

New results have been obtained while studying the trends in MDR emergence and evolution. In particular, it has been convincingly demonstrated that CSCs can undergo selection at the action of chemotherapy agents, which results in elevated tumor DR and enhanced tumorigenicity. Cell–cell interactions have been found to have a great impact on the MDR emergence and development. Mechanotransduction was proven to be an important mechanism for transducing signals between the cells. A considerable progress has been made in the understanding of the role of the ABC transporter family in the MDR development. It was shown that ABC transporters can be transferred between the cells via MVs, thus serving as important epigenetic regulatory agents. In particular, proteins regulating the MV-mediated transfer of functional P-glycoprotein (MDR protein) have been examined. It was found that P-glycoprotein might regulate apoptosis, as well as gene transcription and translation. Altogether, these data show again that MDR is a complex phenomenon that requires further investigation.

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