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Mechanisms of Chemotherapeutic Drug Resistance – An Overview

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ABSTRACT

Despite tremendous advancement in cancer treatment drug resistance is still a crucial problem. In this review, we discuss different mechanisms adapted by dynamic cancerous cells to resist treatment such as variation in drug transport and metabolism, mutation of drug targets and impaired apoptosis. A better understanding of the mechanisms of resistance will at least allow the physician to modulate the therapy on a need to do basis and influence the next generation of cancer therapies.

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INTRODUCTION

Chemotherapeutic resistance is the most common cause of cancer treatment failure and tumor recurrence. Some cancers are drug-resistant at the outset (intrinsic resistance), whereas others, develop resistance after chemotherapy treatment (acquired resistance).[1] Tumors are highly adaptable, and the activation of survival signaling pathways and the inactivation of downstream death signaling pathways can also lead to drug resistance.[2] Numerous mechanisms such as altered gene expression, epigenetic changes, local tumor microenvironment, cancer stem cells, aberrant apoptotic signaling, altered drug transport and metabolism and has been implicated to chemotherapeutic failure.

Gene Regulation

Genetic and epigenetic mechanism affects anticancer drug efficiency. *In vitro* studies on cell lines showed that expression of *ras* oncogenes show more resistance to some drugs.[3} Studies of methotrexate resistance revealed the phenomenon of gene amplification of dihydrofolate reductase genes. In most of prostate cancers, androgen receptor gene is amplified, causing resistance to leuprolide and bicalutamide. Imatinib resistance is caused by point mutations in the *ABL* gene and amplification of the *BCR-ABL* fusion gene.[4] Epigenetic changes such as DNA methylation and histone modification via acetylation or methylation can affect chemotherapeutic resistance. For example, tumor suppressor genes are often silenced via hypermethylation, and oncogenes are over-expressed via hypomethylation.[5]

Drug target

Mutations or modifications of expression levels of molecular target can ultimately lead to drug resistance. Mutations in the topoisomerase gene confer resistance to topoisomerase inhibitors. Factors such as hyperpigmentation, glucose, deprivation and hypoxia contribute to decreased topoisomerase activity.[3] Modified enzyme expression levels at drug target sites can also alter drug responses in cancer cells. For example, thymidylate synthase inhibitors such as fluorouracil, ultimately inhibit the transcription of *TS*.

Resistance to tubulin binding anticancer drugs such as taxanes, vinca alkaloids and epothilones involves alterations in tubulin isotype expression, post translational modifications of tubulin and changes in the expression levels of microtubule related proteins.[6]

Drug transport

Reduced accumulation of anticancer drug in cells may be attributed to mutation that may modify or eliminate drug receptor, transporter and endocytosis. Solute carrier transporter superfamily mediates cellular uptake of anti-cancer drugs and its mutation or low expression leads to resistance of drugs transported by them. Methotrexate influx may be due to mutation of folate transporter. Immunotoxins require cell internalisation by cell surface receptor mediated endocytosis and defective endocytosis of cancer cells may lead to its resistance.[7]

Multidrug resistance is characterized by overexpression of *mdr1* gene encoding P170 glycoprotein (Pgp). Cells adapt to a variety of environmental insults by up regulation of drug efflux pumps, which is fundamental importance in emergence of multidrug resistance in tumor cells exposed to anticancer drugs. Some tumors express Pgp before chemotherapy treatment (e.g. colorectal and renal cancers), while in others, expression increases after exposure to chemotherapeutic drugs (e.g., leukemia, lymphomas, myeloma). Drugs with a biplanar structure, excess positive charge and hydrophobicity are p-glycoprotein substrates.[3]

P-gp expression is regulated by various factors. Mutation of the p53 gene and overexpression of the p63 gene and/or the p73, gene random chromosomal rearrangements, stress signals, such as heat shocks, inflammation and hypoxia, exposure to xenobiotic, toxic metabolites, ultraviolet radiation, and glucocorticoids.[8] Pgp-mediated drug transport of daunorubicin and vinblastine was also affected by the fluidity of the membrane.[9]

Drug metabolism

Many anticancer drugs must undergo metabolic activation in order to acquire clinical efficacy. Hence, cancer cells develop resistance to treatments by diminished drug activation. Cytarabine is activated after multiple phosphorylations and down-regulation or mutation in this pathway can produce a decrease in the activation of cytarabine leading to its resistance.

The glutathione transferase system plays important role in detoxification of alkylating drugs, anthracycline and vincristine. Elevation of glutathione transferase expression in cancer cells enhances detoxification of the anticancer drugs, which results in less efficient cytotoxic damage and apoptosis of the cells.[5]

The presence of high level of glutathione limits the therapeutic efficiency of topoisomerase inhibitors.[3] One way resistance to platinum can occur is through drug inactivation by metallothionein and thiolglutathione, which activate the detoxification system. Epigenetic changes such as DNA methylation that modulates uridine diphospho-glucuronosyltransferase expression leading to resistance to irinotecan.[5]

Cancer cells exhibit abnormal metabolic properties such as increased aerobic glycolysis, increases fatty acid synthesis and glutaminolysis which contributes significantly to anticancer resistance. Targeting cellular metabolic enzymes opens avenues for cancer therapy and anticancer drug resistance. Export of the glycolytic end product, lactate and expression of carbonic anhydrases shift the pH ratio of the interior and exterior of the cell resulting in decreased passive transport of basic drugs. Signaling pathways activated by dysregulated metabolism also contribute to resistance, either via repressing pro-apoptotic signaling or activating compensatory pathways to circumvent drug-induced signal inhibition.[10]

Apoptotic signaling pathway

Changes to apoptosis-related proteins can also result in drug resistance. For instance, apoptosis is promoted by the tumor suppressor protein p53, in response to chemotherapy and mutation or deletion of this gene renders drug resistance. Alternatively, inactivation of p53 regulators, such as caspase-9 and its cofactor, apoptotic protease activating factor-1 can also lead to drug resistance.[5] Cancer cells demonstrate significantly elevated expression levels of IAPs, resulting in improved cell survival, enhanced tumor growth and subsequent metastasis.[11]

Tumor microenvironment

Most anti-cancer agents contribute to the generation of reactive oxygen species followed by target cells apoptosis. Hence continuous treatment with the same drug may result in less efficient ROS production that may lead to drug resistance. DNA damage, apoptotic cell death and angiogenesis are affected by hypoxia.[12] During epithelial to mesenchymal transition cells within a tumor reduce the expression of cell adhesion receptors, which help in cell-cell attachment and increase the expression of cell adhesion receptors that induce cell motility. Additionally, higher expression of metalloproteases on the surface of tumors helps to clear the road for the cells to move outward, promoting metastasis. For example, in ERBB2

(HER2) positive breast cancer, tumors that express high levels of β1 integrins develop more resistance to antibody inhibitors such as transtuzumab.[5]

Cancer stem cells

Recent the role of cancer stem cells (CSC) in the formation of metastatic cancer cells is widely recognized. The DNA damaging ability of alkylating agents and platinum group of chemotherapeutics is diminished by CSC due to excess aldehyde dehydrogenase detoxification, increased DNA repair and anti-apoptosis protein. Thomas ML CSC cause aberrant signaling of 3 key embryonic pathways, namely Wnt, notch and hedgehog pathways.[8]

CONCLUSION

With the advent of molecular studies tremendous advancement has been possible in the field of cancer drug treatment. However the ever-growing problem of chemo-resistance highlights the requirement for novel therapeutics in cancer treatment.

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