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Multidrug Resistance (MDR) in Lung Cancer: Finding the Holy Grail of MDR Reversal

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Multidrug resistance (MDR) in cancer cells continues to pose a major challenge for the clinicians and pharmacologists to effectively treat this disease by chemotherpeutic agents. MDR is defined as insensitivity of cancer cells to cytotoxic and cytostatic actions of a number of structurally and functionally unrelated drugs. Cancer cells are intrinsically resistant to anti-cancer agents because of genetic and epigenetic heterogeneity. These cells also acquire resistance to a wide variety of chemotherapeutic drugs through alteration in absorption, metabolism and excretion of a drug. Besides this, there are some host factors which include poor absorption, rapid metabolism and excretion that can result in Low serum drug levels [1,2].

For the last several decades, investigators have been trying to understand various mechanisms by which cancer cells grown in culture become resistant to anticancer drug(s). Some of these mechanisms, such as loss of a cell surface receptor or transporter for a drug, specific metabolism of a drug, or alteration by mutation of the specific target of a drug have since been identified [2]. Initially, it was thought that the use of multiple drugs with different cellular targets can lead to effective chemotherapy and high cure rates. However, such strategies also quite often initiate cancer cells to evade cell death by expressing mechanisms of resistance known as MDR that can result from changes that limit accumulation of drugs within cells by limiting uptake, enhancing efflux, or affecting membrane lipids. These changes block (a) the programmed cell death (apoptosis) that is activated by most anticancer drugs, (b) activation of general response mechanisms that detoxify drugs and repair damage to DNA, and (c) alterations in the cell cycle and checkpoints that render cells to acquire resistance to chemotherapeutic agents [2-4].

In lung cancer, non-small cell lung cancer (NSCLC) cells are often intrinsically resistant to certain anticancer drugs, whereas small-cell lung cancer (SCLC) cells can acquire resistance with continued administration of the drug [5,6]. Additionally, at the time of diagnosis, the majority of patients with lung cancer most often already have metastatic disease, making it difficult to use other therapeutic options, such as surgery and radiation. Thus, a better understanding of the different mechanisms underlying drug resistance at the molecular level is of utmost importance. It has been observed that patients under chemotherapeutic treatment gradually develop genetic mutations [3-6]. These mutations may result from either activation of proto-oncogenes or inactivation of tumor-suppressor genes. This causes genomic instability which eventually leads to tumor progression and metastatic changes, making treatment difficult in such patients; coexisting drug resistance of the tumors makes it even more difficult to treat the primary and metastatic lesions. Moreover, tumors that are resistant to one particular drug are either already cross-resistant or develop resistance to other chemotherapy drugs [2-7]. For example, even though patients with SCLC carcinoma initially respond to chemotherapy, these patients invariably experience a relapse, and the tumor becomes resistant to chemotherapeutic treatment. Therefore, overcoming drug resistance in lung cancer has remained a challenge resulting in a poor 5-year survival rate that remains less than 15% for NSCLC and 5% for SCLC. MDR in lung cancer was previously thought to be only because of the high expression of drug efflux pumps such as p-glycoprotein (Pgp) and multidrug resistance associated family of proteins (MRPs) [2-6]. However, this paradigm has since been shifted with the discovery of the lung-resistance associated protein (LRP) which constitutes a major part of vault proteins believed to mediate bi-directional nucleocytoplasmic transport of cytotoxic drugs [8]. Unlike Pgp and MRP, LRP is not associated with cell membrane and is present in the cytoplasm. In cells, LRP is often associated with vesicles and lysosomes which may be relevant to its function of sequestration of drugs in to vesicles. It may be possible that after such sequestration drugs are excluded from cells by exocytosis.

Blocking of drug efflux pumps such as PgP and MRPs has been pursued with the aim to reverse MDR in cancer cells [9]. For example, the calcium channel blocker verapamil, phenothiazine derivatives, and the calmodulin antagonists have been demonstrated as Pgp mediated MDR reversing agents. However, these inhibitors of Pgp-mediated drug efflux were found to be of limited effect. Similarly, certain chemosensitizers like cyclosporin, MK-571 and PAK-104P which have been shown to affect MRP-mediated drug transport have been shown to be only partially successful in reversing MDR [10-14]. Inhibition of drug transport function with polyclonal and monoclonal antibodies has been shown in a number of laboratory studies [15]. However, because of their inherent pharmacological effects, MDR modulators quite often exhibit severe toxicity. Moreover, since some of the efflux pumps are also involved in the maintenance of critical cellular physiology, these MDR-modulators may actually impair cellular functions of healthy cells. While some drug resistance reversing agents have shown great promise in laboratory studies, they failed to improve the chemotherapeutic response of various anticancer agents.

Besides the acquired resistance of lung cancer cells to various chemotherapeutic agents via accelerated efflux of anticancer agents, as indicated above there are other mechanisms by which these cells become resistant to these drugs. These mechanisms include alteration in the expression of proteins involved in the apoptotic signaling such as p53, Bcl2 family of proteins [7,16], those involved in the transcription of detoxification/antioxidant enzymes and heat shock proteins e.g. upregulation of Nrf2 and HSF1 respectively [17,18]. There is still no

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uniform mechanism known for the problem of drug resistance in lung cancer. Perhaps, there is yet to be identified mechanism which directs the cellular genetic apparatus to respond to a particular toxic insult by activation of multiple proteins and signaling pathways. Therefore, establishing a link between Pgp, MRP and LRP-mediated MDR and other cancer mechanisms (e.g. their correlation with the mutations in p53) may be an important area for developing strategies to modulate drug resistance [19] which draws strong support for a recent study indicating a correlation between MRP and mutant p53 expression in NSCLC, which can be used for prognosis [7]. Many other such correlations with high potential may be identified through pharmacogenomic analysis of cancer multidrug resistance, where patient variability to anticancer agents could be localized conceivably to some of these gene families. It is necessary to identify as many mechanisms as possible in the same patient simultaneously. With this information, resistance profiles can be defined and individualized treatment strategies can be based on them. Recent studies have suggested that a number of phytochemicals found in medicinal plants of east-Asian countries exhibit powerful MDR-reversal properties [20]. Therefore, research in the areas of complimentary and alternative medicine accompanied by pharmacogenomic studies should be actively pursued to find the holy grail of MDR reversal.

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