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Molecular mechanisms of chemotherapeutic resistance in lung cancer

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Abstract

Lung cancer mortality is mainly due to the high rate of chemotherapeutic resistance frequently found in lung cancer patients. In order to develop the novel strategies for effective treatment, the molecular basis regarding adaptive machineries of lung cancer cells in acquiring chemotherapeutic resistance is critical. In this review, we focus on the mechanisms involving in an activation of survival pathways as well as a disruption of apoptosis process. We emphasize on the novel knowledge regarding the regulatory role of Caveolin-1 protein in cancer aggressive behaviors and chemotherapeutic resistance. Altogether, this review summarizes the possible mechanisms of chemotherapeutic resistance that may benefit the overall understanding of cancer biology and the design of novel therapeutic approaches.

Key Words: Chemotherapeutic resistance, Lung cancer, Bcl-2, Akt, Caveolin-1

Chemotherapeutic resistance in lung cancer

In lung cancer, high mortality and low 5-year survival rates are caused by two determinants; metastasis and chemotherapeutic resistance [1, 2]. Intrinsic and acquired resistances to chemotherapy are fundamental problems that limit the outcome of cancer treatments. Non-small cell lung cancer (NSCLC) cells are often intrinsically resistant (evident from the first course of therapy) to certain anticancer drugs, whereas small-cell lung cancer (SCLC) cells can acquire resistance (arising during the course of treatment) with continued administration of the drug [3].

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Apoptosis or the process of programmed cell death is essential in homeostasis of normal tissues as well as pathological processes [4]. Apoptosis is characterized by distinct morphological characteristics, such as shrinkage of cell, membrane blebbing, chromatin condensation and DNA fragmentation, and cell molecular characteristics including activation of caspases and cleavage of cytoskeletal proteins [5]. Apoptosis has been known to play an important role in the development of chemotherapeutic resistance [4, 6] and almost all of chemotherapeutic agents ultimately induce cancer cell death by the induction of apoptosis [7-9]. Chemotherapeutic agents may use different cytotoxic mode of actions to induce apoptosis of cancer cells. However, the end result of those is the activation of intrinsic apoptotic pathways [6, 10].

Because the important part of the success of chemotherapy is due to the efficiency in induction of cancer cells apoptosis [7, 8], decreasing the cellular apoptotic response by many means eventually leads to cancer cell survival and progression of the cancer [6].

Molecular mechanisms of chemotherapeutic resistance

Failure to activate the process of programmed cell death or apoptosis represents an important mode of drug resistance in cancer cells. Disruption of cellular apoptotic signals is probably influenced by intrinsic properties of the cells such as an increase of anti-apoptotic proteins as well as up-regulation of survival-related cellular pathways such as Akt and caveolin-1 (Cav-1).

Intrinsic apoptotic pathway and Bcl-2 family proteins

Intrinsic pathway has been reported in determination of cell survival. Most evidence highlights the importance of Bcl-2 family proteins as key regulators of mitochondrial membrane permeability [11]. There are two groups of these proteins which are pro-apoptotic proteins (the proteins that act to promote cell death e.g. Bax, Bak, Bad, etc.) and anti-apoptotic proteins (the proteins that act to prevent cell death e.g. Bcl-2, Mcl-1, Bcl-xL, etc.).

Indeed, pro- and anti-apoptotic members of the Bcl-2 family interact in order to regulate cellular apoptosis. The balance of these Bcl-2 family members determines whether the fate of cell is survival or death (Figure 1). Shifting this balance by cellular stress (e.g. DNA damage, oxidative stress), resulting in the release of cytochrome c and other apoptotic inducing factors from mitochondria leads to the activation of the caspase cascade and the induction of apoptosis [13]. On the contrary, pro-survival stimulation promotes cellular survival by increasing the amount of anti-apoptotic proteins [12].

• *B-cell lymphoma-2 (Bcl-2)*

Bcl-2, a member of anti-apoptotic Bcl-2 family proteins, acts to prevent apoptosis by heteromerization with Bcl-2-associated X protein (Bax). Anti-apoptotic proteins and Bax interaction prevents oligomerization of Bax and inhibits cytochrome c release [12-14].

Overexpression of the Bcl-2 occurs in many different solid tumors including lung cancer [15, 16]. Upregulation of Bcl-2 has been found to prevent cell death induced by anticancer drugs [17-20]. Ectopic expression of Bcl-2 increases resistance to drug-induced apoptosis in lung cancer cell lines [21], whereas downregulation of Bcl-2 expression by a small interfering RNA sensitizes cancer cells to cisplatin [22]. Furthermore, inhibition of ubiquitination and degradation of Bcl-2 promotes resistance to cisplatin-induced cell death in NSCLC cells [23].

These evidences have provided conclusive evidence that upregulation in Bcl-2 expression may, at least in part, cause resistance to chemotherapeutic drugs, while downregulation in this protein can sensitize cancer cells to apoptosis induced by chemotherapeutic agents.

• *Myeloid cell leukemia sequence 1 (Mcl-1)*

Mcl-1, another anti-apoptotic member of Bcl-2 family proteins, can also inhibit Bax conformational change at mitochondrial membrane. Lung cancer cells constitutively expressing human Mcl-1 are resistant to apoptosis induced by several chemotherapeutic drugs including cisplatin, etoposide, paclitaxel and gefitinib, whereas depletion of Mcl-1 levels by antisense Mcl-1 oligonucleotides induces apoptosis as well as sensitizes such cells to apoptosis induced by chemotherapy agents [24].

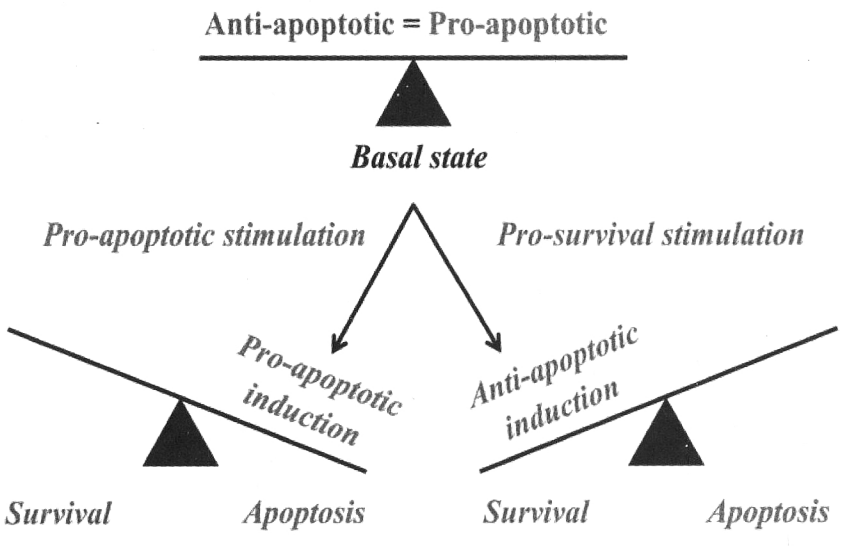

Figure 1 The balance of pro- and anti-apoptotic members of the Bcl-2 family dictates cellular survival

Survival-related cellular pathways

• *Protein kinase B (Akt)*

Akt, a 57 kD serine/threonine kinase, is a downstream effector of PI3K via a multistep process known as PI3K/Akt signaling pathway. Additionally, Akt regulates diverse cellular processes including cell survival, proliferation, growth and migration [25].

Focusing on chemotherapeutic response, the PI3K/Akt acts as a central mediator of cellular survival pathways and attenuates overall response of the cells to death stimuli. Akt has been implicated as an anti-apoptotic factor in many different kinds of apoptotic stimuli, including chemotherapeutic drugs, resulting in delay of cell death or a resistance to chemotherapeutic drugs [26]. In many cancers, the components of PI3K/Akt signaling pathway are shown to be frequently upregulated [27] and such increase is found to associate with poor prognosis and chemotherapeutic resistance [28]. For lung cancer, overexpression of phosphorylated Akt (p-Akt) is observed in comparison to the low level in normal lung tissue [29]. Upregulation of activated Akt (p-Akt) was found to promote chemotherapeutic resistance in this type of cancer [30, 31].

• *Caveolin-1 (Cav-1)*

Cav-1 is a main protein component of caveolae. Although the role of Cav-1 in cancer is quite diverse, recent evidences have agreed that Cav-1 may play a role as cancer promoting protein. Several studies have reported that the upregulation of Cav-1 in many malignant tumors is linked to the poor prognosis of the diseases [32].

Recently, the significant impact of the Cav-1 on various lung cancer cell behaviors including migration and invasion [33], anoikis resistance [34-36] and adhesion to endothelial surface [37] has been reported. Moreover, Cav-1 involves in chemotherapeutic resistance. For example, Cav-1 expression is significantly correlated with chemotherapy response and a poor prognosis in advanced stage lung cancer patients treated with gemcitabine-based chemotherapy [38]. Furthermore, ectopic Cav-1 expression in Ewing's sarcoma cells increases resistance to doxorubicin- and cisplatin-induced apoptosis, whereas Cav-1 knockdown sensitized Ewing's sarcoma cells to doxorubicin and cisplatin [39].

Conclusion

Taken together, lung cancer cells acquired resistance to chemotherapy by many means, and in most cases they adopt several pathways in combination. Active compounds that possess ability to suppress both survival proteins and anti-apoptotic proteins named herein are promising to be used for supportive therapy. In addition, the mediators that can upregulate pro-survival proteins or other anti-apoptotic members of Bcl-2 family proteins found in cancer cells or their environments should be identified as possible molecular targets for drug development.

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