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저산소증과 NF-κB의 항암제내성과의 연관성 고찰

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Abstract

Hypoxia and NF-κB; The Relation to Chemoresistance

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항암치료는 현재 암환자의 주요한 치료임에도 불구하고 항암제내성과 같은 문제점을 가지고 있다. 약물내성은 다양한 기전에 의해 발생하는데 수송단백질의 과발현, 비독성화발현, 손상유전자의 복구, 세포사멸신호의 변화, STAT-3와 NF-κB의 발현 등이 포함된다. 암세포는 저산소환경에서 발생하며 일반세포에 비해 무산소해당에 상대적 의존도가 높고 이는 암세포의 성장과 전이를 촉진하는 인자가 된다. 항암제가 효과를 내기 위해서는 산소가 필요한데 저산소환경은 이를 방해하며 또한 유전자의 불안정화로 인해 약물내성이 유도된다. NF-κB는 주요 전사인자 중 하나로서 각종 염증과 암에서 지속적으로 활성화되며 암세포의 변화, 증식, 침윤, 전이에 관여한다. 환경적 스트레스 등과 대부분의 항암약제들이 NF-κB를 활성화시키며 임상적으로도 암환자의 생존과 연관된 중요한 예후인자이다. NF-κB의 발현은 항암제로 인한 암세포의 자멸을 회피하게 만들고 수송단백질을 활성화시켜 항암제내성을 유도한다. 강황, 적포도, 고추, 건칠 등 다양한 천연물에서 NF-κB를 억제시키는 효능이 발견되었으며 이는 항암제내성을 억제시키고 항암제의 효과를 증대시킨다. 저산소환경의 개선과 NF-κB의 억제는 상호연관성을 가지고 있으며 항암제내성의 개선뿐만 아니라 암치료제 개발의 새로운 연구목표가 될 수 있다.

Key words: Hypoxia, NF-κB, Chemoresistance

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Introduction

Since Richard Nixon has declared war to cancer about 30 years ago, a lot of efforts have been made in order to overcome this dreadful disease. Enormous financial resources have been invested in cancer research in the last three decades, yet most metastasized solid tumor are still considered incurable. The overall contribution of curative and adjuvant cytotoxic chemotherapy was assessed to 2.3% in Australia and 2.1% in the United States of America with a 5-year survival in adults based on data for 1998[1].

Under chemotherapy, cancer cells can develop gradually drug resistance acquired for instance by overexpression of transporter proteins (e.g., these belonging to the ATP-binding cassette type) and fractionation of the cancerous stem cells (which are less sensitive to exposure to cytostatics than more differentiated cancer cells), plus AKT and NF-κB overexpression as compensatory response to administered cytotoxic drugs[2-5].

Likewise, induced hypoxia may act as protective shield against tumor eradication by chemotherapeutics and radiation due to alteration of gene expression profiles related to hypoxia, which result in the inhibition of apoptosis[6].

In this brief review, the hypoxia and the overexpression of NF-κB, which are general conditions in microenvironment of cancer, will be described and discussed shortly focusing how these factors are related with chemoresistance.

chemoresistance

The development of tumor resistance to chemotherapy (chemoresistance) presents a major hurdle in cancer therapy. Further, complications emerge when cancer cells develop chemoresistance by multiple mechanisms.

The mechanisms of chemoresistance in tumor cells can be intrinsic (cells are resistant before the treatment), or acquired (resistance is developed during the treatment). The most important mechanisms of chemoresistance are increased drug efflux (associated with ATP-dependent multidrug transporters such as p-glycoprotein, LRP, MRP1), increased drug inactivation (mediated by the glutathione/glutathione S-transferase system), altered target molecules, enhanced DNA repair (mismatch repair, base excision repair, and nucleotide excision repair), altered growth factor signaling (EGFR), altered cell death signaling (down-regulating proapoptotic proteins such as p53, Bax and up-regulating antiapoptotic such as Bcl-2 and Bcl-xL), activation of STAT-3, and activation of NF-κB[7-11].

Warburg effect

Over 70 years ago, Otto Warburg observed that cancer cells frequently exhibit increased glycolysis and depend largely on this metabolic pathway for generation of ATP to meet their energy needs[12]. He attributed this metabolic alternation to mitochondria “respiration injury” and considered this as the most fundamental metabolic alteration in malignant transformation or “the origin of cancer cells.”

All nucleated animal/human cells have two

types of power plants, i.e., systems that make the “the high energy” compound ATP from ADP and Pi. One type is “glycolysis,” the other the “mitochondria.” In contrast to most normal cells where the mitochondira are the major ATP producers (>90%) in fueling growth, in human cancers mitochondria ATP production is estimated at about 40% and glycolytic ATP production at about 60%[13].

During the past several decades, the Warburg effect has been consistently observed in a wide spectrum of human cancers. Among the possible mechanisms, mitochondria malfunction and hypoxia in the tumor microenvironment are considered major factors contributing the Warburg effect. And these factors are closely associated with resistance to common anticancer agents.

Hypoxia and Cancer

A key environmental stressor associated with tumor progression and poor clinical prognosis is tumor cell oxygen deficiency, termed hypoxia. This condition is known to induce genes involved in the regulation of cell proliferation, extracellular matrix production, cell adhesion, and other hallmark of tumorigenesis.

Hypoxia seems to actually have a dual role: insufficient oxygen limits tumor cell division while at the same time selecting for more malignant cells and inducing cell adaptations allowing for more invasive behavior. Regarding tumor growth, cancer cells, similar to normal cells, need oxygen to generate energy as allow as well as acting as a substrate for many allow as well as cellular processes, including generating macromolecules. Yet, hypoxia is also strongly associated with tumor progression and l asstatic disease. This is likely because low oxygen tension is able to increase cell invasiveness, cause cells to switch to anaerobic metabolism, increase genetic instability, and promote angiogenesis[14].

Hypoxia is a feature of sites of chronic inflammation, for example in the RA synovium, in atherosclerotic plaques, in sites of bacterial infection and at growing tumours[15].This occurs when the cellular demand for oxygen, in order to meet the metabolic needs of the tissue to produce ATP, exceeds the vascular supply. While angiogenesis is a feature of hypoxic inflammation as well as being an adaptive response to decrease oxygen availability, the microvascular architecture is dysregulated in chronic inflammatory disease. Therefore, while there are more capillaries to deliver oxygen to a site of inflammation, the efficiency is poor. Furthermore, what limited oxygen is delivered to an inflammatory locus can be depleted further by oxygen consumption by high metabolically active resident and infiltrating cells[16].

Hypoxia and chemoresistance

In response to toxic insult, both normal and cancer cells try to limit the intracellular accumulation of the agent by upregulating the detoxifying mechanism. It has indeed been demonstrated that the main cause of acquired chemoresistance, known as “multiple drug resistance” (MDR), by cancer cells, is their ability to efflux toxins at an accelerated rate

through overexpression of certain transport proteins/efflux pumps. Hypoxia may participate in reduced intracellular concentration of cytotoxins, this decreases the sensitivity of cancer cells towards cytotoxins and inhibit tumor growth[6].

Many conventional anticancer drugs require oxygen for maximal activity. However, changes in phenotype following hypoxic shock may also participate in reduced cytotoxic properties. HIF-1alpha protein levels are elevated in normoxic cells undergoing physiological processes involving large scale microtuble reorganization, such as embryonic development, wound healing and tumor cell metastasis. Because many chemotherapeutic drugs such as Vincristine, Paclitaxel, and taxanes disrupt the microtubular system, HIF-1α overexpression in hypoxic cells may reduce the effectiveness of these compounds[6,17].

Some chemotherapeutic drugs are dependent on oxygen to be cytotoxic, others express little or not selectively based on cellular oxygenation status in culture but are more cytotoxic toward tumor cells in vivo when tumor oxygen content is increased and other drugs are selectively cytotoxic toward hypoxic cells. Additionally, there is evidence that hypoxia can enhance genetic instability in tumor cells thus allowing more rapid development of drug resistance cells[17].

Agents improving Hypoxia enviroment

Inhibition of glycolysis using 3-BrPA, a lactic acid analog, effectively killed cancer cells via necrotic cell death pathway in a hypoxic environment in which the cancer cell exhibit high glycolytic activity and decreased sensitivity to common anticancer cells. Depletion of ATP by glycolytic inhibition using 3-BrPA also potently induced apoptosis in multidrug-resistant cell, suggesting that deprivation of cellular energy supply may be an effective way to overcome multidrug resistance[18].

In a hypoxic microenvironment, the transformed cells initially have to rely on glycolysis for energy production. However, this early metabolic adaptation appears to also offer a proliferative advantage, suppressing apoptosis. Furthermore, the “byproduct” of glycolysis (i.e., lactate and acidosis) contributes to the breakdown of the extracellular matrix, facilitate cell mobility and increase the metastatic potential. Whether the metabolism of glucose will end glycolysis in the cytoplasm (converting pyruvate to lactate) or continue with glucose oxidation in the mitochondria is controlled by pyruvate dehydrogenase (PDH) and PDH is inhibited by phosphorylation by PDH kinase (PDK). Dichloroacetate (DCA) inhibits mitochondrial PDK, shifts metabolism from glycolysis to glucose oxidation, induces apoptosis, decreases proliferation, and inhibits tumor growth, without apparent toxicity[13].

NF-κB and Cancer

Nuclear factor of κB (NF-κB) first discovered in 1986, is a sequence-specific transcription factor that is known to be involved in the inflammatory and innate immune response. NF-κB is activated in response to tobacco, stress, dietary an the,

obesity, alcohol, infectious an the, irradiation, and environmental stimuli that account for as much as 95% of all cancers. One of the first genes that NF-κB activates is IkBα itself, wers. Oransports activated NF-κB from the nucleus to the cytoplasm. NF-κB activation is therefore an inducible, but transient event in normal cells. In tumor cells, different types of molecular alternations may result in an impaired regulation of NF-κB activation. In such cases, NF-κB becomes constitutively activated. Its activation controls the expression of genes that mediate transformation, proliferation, invasion, angiogenesis, and metastasis[19].

Several clinical studies also show that NF-κB is strongly associated with survival and they suggest NF-κB as important prognostic factor in various types of cancer[20,21].

Many chemotherapeutic agents have been shown to activate the transcriptional factor NF-κB in human lung and cervical cancers and in T cells. These agents are paclitaxel, vinblastine, vincristine, doxorubicin, daunomycin, 5-fluorouracil, cisplatin, and tamoxifen. Activation of NF-κB by these agents has been linked in turn with chemoresistance through serine phosphorylation of IkBα[17].

Hypoxia and NF-κB

NF-κB has been shown to be activated by hypoxia in a number of studies[22,23]. Cyclooxygenase2, TNFα, IL-6 and macrophage inflammatory protein are among the target genes identified for hypoxia-induced NF-κB, and these underline the factor's importance in inflammatory signaling[24-26].

Hypoxia activates NF-κB signaling via inhibitor of kB kinase. Under conditions of hypoxia, the hydroxylase-mediated repression of inhibitor of kB kinase (IKK) beta is suppressed-leading to enhanced IKKβ activity, enhanced IkBα phosphorylation and degradation as well as increased p65 NF-κB activity. Factor-inhibiting hypoxia inducible factor (HIF) inhibition by hypoxia or pharmacological inhibition reduces IkBα degradation.

NF-κB and Chemoresistance

Resistance to cancer chemotherapy can be caused in many ways. One mechanism of chemoresistance is caused by overexpression of MDR1, a transmembrane protein that functions to export chemotherapeutic compounds from cells. Another mechanism seems to be inducible or acquired resistance of the tumor to apoptosis, which blocks the ability of chemotherapies and radiation to induce tumor cell death[27]. Acquired resistance may result from mutations in p53 or overexpression of antiapoptotic proteins such as Bcl-2. A main pathway involved in inducible resistance is the activation of the transcription factor NF-κB within tumor cells in response to chemotherapy or TNFa. Inhibition of cancer therapy-induced NF-κB activation strongly enhances the apoptotic potential of these stimuli[28].

Substantial evidence indicates that NF-κB regulates oncogenesis and tumor progression. Many studies indicate that NF-κB activation, which is often seen in inflammatory-based disease, is associated with an increased incidence of cancer. NF-κB is known to inhibit

apoptosis through induction of anti-apoptotic proteins and/or suppression of pro-apoptotic genes as described above. Constitutive NF-κB activation, observed in many malignant tumours, protects the cells from apoptotic stimuli, including anticancer stimulate NF-κB activation, which can potentially lead to chemoresistance.

Most chemotherapy agents trigger the cell-death process through activation of the tumour-suppressor protein p53. However, NF-κB is also activated in response to treatment with cytotoxic drug, such as taxanes, Vinca alkaloids and topoisomerase inhibitors[29].

Many tumours have constitutive NF-κB activation that is thought to enable malignant cells to escape apoptosis. Constitutively activated NF-κB might be crucial in the development of drug resistance in cancer cells. For example, the basal levels of phosphorylation of IkB and activity of NF-κB in cisplatin-resistant ovarian cancer cells (Caov-3 cells) were significantly higher than those in cisplatin-sensitive cells (A2780 cells)[30-32].

Activated NF-κB antagonizes p53 function, possibly through the cross-competition for transcriptional coactiovators, and the inhibition of chemotherapy-induced stabilization and activation of p53 by NF-κB results in resistance chemotherapy[33].

In addition to its anti-apoptotic role, NF-κB also induces cell proliferation and cell-cycle progression by regulating the expression of target genes including growth factors, and also induce tumor angiogenesis through upregulation of COX2 and inducible NO synthesis. Furthermore, NF-κB regulates expression of intracellular adhesion molecule1 and vascular cell-adhesion molecule1 that are associated with tumour metastasis and a poor prognosis[34]. Consistent with these points, the finding that IkBa expression in tumor cells decrease the frequency of metastases indicates that the NF-κB pathway can promote metastases[35].

In addition, recent studies have indicated that NF-κB has a consensus-binding site for the human multidrug resistance gene (MDR1) and that, in vivo, NF-κB transactivates expression of MDR1, further stanorting a role for NF-κB chemoresistance. S, inal studies have demonstrated that inhibiting NF-κB activation results in the r, insal of chemoresistance. For example, stance ging the expression of p65 NF-κB stbunit by small intinfering RNA (siRNA) inhibitatesrinotecan-induced activation of NF-κB and increased the sensitivity of HCT16 cooon cancer cells to this drug[36].

Natural Products Inhibiting NF-κB as Chemosensitizer

In vivo models of ovarian cancer, colorectal cancer and pancreatic cancer have shown that NF-κB inhibition increases the efficacy of anticancer drugs[31,37-39]. It is thought that NF-κB inhibition prevents tumours from becoming resistant to chemotherapeutic agents. Therefore, development of NF-κB inhibitors could increase the efficacy of many anticancer drugs.

Several phytochemicals from different plants have been identified that can suppress NF-κB activation effectively. These include curcumin (tumeric), resveratrol (red grapes), guggulsterone

(guggul), ursonic acid (from holy basil), betulinic acid (birch trees), eugenol (cloves), gingerol (ginger), oleandrin (oleander), silymarin (artichoke), emodin (aloe), capsaicin (red chili), anethole (anise), genistein (from soyabean), Rhusvernicifluastokesandothers[19,40]. How these agents suppress NF-κB activation is becoming increasingly apparent. Genistein, a natural isoflavonoid found in soyabean products, in particular, sensitized pancreatic cancer cells to standard chemotherapeutic agents[41]. Curcumin acts chemosensitizer and radiosensitizer and also protect normal organs from chemotherapy and radiotherapy-induced toxicity[42]. Recently, in a phase 2 clinical trial, curcumin was found to beneficial for patient with advanced pancreatic cancer[43].

Conclusion

Given the shortcomings of current chemotherapy treatments for cancer management, it is obvious that such treatments in the future must be combined with more effective and safer drugs/compounds. Hypoxia is main characteristic of cancer cell and it is closely related with prognosis of cancer patients. NF-κB is also ubiquitous transcription factor and mediates tumor proliferation, invasion and metastasis. Improving hypoxia condition and suppressing constitutive NF-κB activation can make more sensitive to chemotherapy and bring good clinical outcome in treating cancer patients.

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