Short Communication
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Strategies of Cancer Treatment and Relapse

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Short Communication

Cancer is one of the major diseases causing human death. With today advancement of medical technology, the current treatment is still not good enough to cure the disease. Although current cancer treatment could suppress the disease, relapse is the common phenomenon leading to treatment failure. Profiles of gene expression have indicated cell cycle dysregulation is a token of disease development and poor prognosis [1]. Current treatment strategy would use the induction of cell cycle arrest to promote apoptosis of cancer cells [2-4]. The ability to manipulate the cell cycle is critical for the success of cancer treatment.

Various anti-cancer agents would exert their action via the cMyc/p53 and AKT/14-3-3 signaling pathways [5,6], inhibition of p38 mitogen-activated protein kinase (MARK) [7], with [2,8] or without [9] inducing endoplasmic reticulum (ER) stress for the promotion of apoptosis. Chemotherapeutic agents would introduce stress condition causing DNA damage leading to cell cycle arrest [10], in which DNA damage is one of the critical determinants to induce p53 signaling pathway [11], and other pathway independent to p53 via protein kinases ATM/CHK2 pathway [12]. DNA damage caused by Top II poisons targeting topoisomerase II have been frequently applied to cancer treatment [13]. Chemotherapy or radiotherapy induced DNA damage activates the Chk1-dependent DNA damage response (DDR), which accompanied with the phosphorylation of ATM, Chk2, p53 and histone H2AX was observed [14]. As the decrease of mitochondrial membrane potential with the upregulation of Bax and downregulation of Bcl-2, it suggests the activation of the mitochondrial pathway is involved [11].

When the ROS is increased by reducing GSH caused by cysteinase would lead to cell cycle arrest and death in cancer cells [15]. Chrysophanol caused necrotic cell death in Hep3B cells also accompanied with the promotion of ROS level and Ca^{2+} production, decrease in mitochondrial membrane potential and ATP levels [16]. Using Zearalenone to induce cell cycle arrest and cell apoptosis was associated with ROS generation causing ER stress and activates the ATP/AMPK pathway to induce apoptosis [17]. The toxicity caused by heavy metal Cr(VI) accompanied with the reduced activities of mitochondrial respiratory chain complex I and II leading to ROS accumulation. It caused ATP depletion and cell cycle arrest that can be reversed by antioxidant N-acetyl-L-cysteine [18]. The use of ROS generation in clinical therapy known as photodynamic therapy is already adopted for cancer treatment [19].

Proton leak is a physiological phenomenon in which electron and proton are detoured from their original pathways of electron transport chain leading to the reduction of ATP production and ROS level. Although there is not a lot of studies directly on the relationship of proton leak in cancer treatment, proton leak determines the level of ROS, which plays a modulating role in cancer treatment strategy. Cancer cells are found to have upregulated expression of UCP2, which increase the antioxidant UCP2 mediated proton leak decreasing ROS and leading to drug resistance. When the level of UCP2 mediated proton leak was suppressed, it would increase ROS level improving the chemo-sensitivity of cancer cells to cisplatin treatment [20]. UCP2 is often overexpressed in drug resistant cancer cells, which moderates the ROS levels and limits drug toxicity. Glutathionylation of UCP2 deactivates proton leak through UCP2, which can serve as a therapeutic strategy for cancer treatment [21].

Increase in proton leak would reduce the production of ATP, which would affect the energy status of the cells. It negatively affects to the necessary energy processes in body. ATP is known to play a critical role in cell arrest and cell proliferation. ATP depletion is associated with the inhibition of cell proliferation [22], and the activation of AMP-activated protein kinase (AMPK) leads to cell cycle arrest [23,24]. Inhibition of basal glucose transport decreases the metabolic generation of ATP

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would induce cell cycle arrest, senescence and necrosis in cancer cells, while adding ATP extra cellularly would save the cancer cells being treated with chemical [25]. The study has suggested the importance of intracellular ATP in the mechanism of cancer treatment. The promotion of ATP level by drug would increase the cell size and mitochondrial content [26]. Applying ATP synthase inhibitor citreoviridin to ectopic ATP synthase induced cell cycle arrest and inhibited proliferation in lung adenocarcinoma cells. [27]. Although UCP2-transfected Hepa 1-6 cells did not show reduced cellular ATP, it increased levels of glutathione with less proliferative and most cells blocked at the G1 phase. The effect of UCP2 on cell cycle arrest could not reversed by adding ATP or oxidant supply [28]. For antioxidant Carnosine, it decreases both ATP and ROS, but still induces cell cycle arrest [29]. The reduction of mitochondrial oxidative metabolism is an important bioenergetic phenomenon that characterized in malignancy, which may have an adaptive role in carcinogenesis. Targeting mitochondrial respiration is a promising strategy for cancer treatment [30].

Relapses are the major barrier of cancer treatment. Recent findings have suggested the involvement of cancer stem cells (CSCs) in the process. Population of CSCs is found to be resistant to chemotherapy. Many cases of treatment failure in breast cancer patients induced by the chemo-resistance of CSCs were reported. It is suspected the stem cell like cancer cells playing an important role of disease relapses. Theoretically, stem cell like cancer cells is in dormant stage, they very likely escape from the severe damage caused by the radiotherapy and chemotherapy treatment. The survived CSCs hiding in the tissue would wait for the suitable condition to arrive before they would proliferate again and cause metastasis.

One of the possible problem of the current treatment method may be due to the overstress of killing tumor cells and less focus on the eradication of CSCs. If CSCs would behave as the normal stem cells with their role to maintain homeostasis, CSCs would help to repopulate the tumor, whenever the tumor cells population is reduced by cancer treatment. It would be the possible mechanism of recurrence [31]. CSCs would be the key factor to drive the growth and metastasis of tumor, and has the ability of initiating tumor formation, self-renewal and differentiation into tumor-propagating cells [32].

The involvement of CSCs in the communication between neoplastic cells and normal cells leading to the suppression of immune systems was reported. Exosomes, vesicles of endosomal origin, are reported to be secreted in prostate and breast cancer stem cells, which serve to communicate with neoplastic cells and normal cells leading to the suppression of immune systems, regulation of neoplastic growth and metastasis [33]. There is a strong connection between autophagy and exosomes released from CSCs [33]. Mechanisms that regulate wound healing and inflammation have been associated with the growth and transformation of malignant cells, and the increase of CSCs populations. The mechanical properties of epithelial to mesenchymal transition (EMT) in cancer cells have been identified to be one of the modulators to determine the effectiveness of treatment [34]. As CSCs are highly resistant to current treatments, it would help to repopulate the tumor after treatment, which is the major cause of local and systemic recurrences [35].

Although CSCs have been recognized to play an important role in relapses, their regulation at molecular level is not clear. It is anticipated the regulation would respond to the extracellular signals, mutations and epigenetic control [36], upon which a myriad of signaling pathways was sent leading to different kinds of gene expression in CSCs [36]. Some of the inherent signaling pathways in embryogenesis, development and hemostasis e.g. Wnt, Hedgehog, and Notch pathways are found to be dysfunction in various types of tumor and malignancies. The activation of signaling pathways Notch, Wnt/β-catenin, TGF-β, Hedgehog, PI3K/Akt/mTOR and JAK/STAT pathways are associated with treatment resistance and recurrence [37]. Atypical activation of these pathways may involve in the modulation of CSCs [38]. Irregular expression of miRNA is also reported to occur in CSCs, and the abnormal miRNA may be promising therapeutic targets [39]. Reversing the downregulation of miR-489 [40] in CSCs improves the chemotherapy.

CSCs are emerging as a promising target for the development of translational cancer therapies. Understanding the biology of CSCs and characteristics of their microenvironment would help to develop specific therapeutic strategies to combat cancer [41]. Dopamine may destroy CSCs, as it significantly improves the effectiveness of sunitinib in treating the drug-resistant breast cancer [42]. Several promising approaches targeting on CSCs have been explored including targeting the surface markers to block the necessary signaling pathways of CSCs, promoting the differentiation of CSCs, modifying the microenvironment that may nurture CSCs, and inhibiting ATP-driven efflux transporters [43], immunotherapeutic approach targeting on the CSCs associated antigens, developing metabolites to destroy CSCs, and using RNA/DNA interference small molecules to target CSCs [37]. Park and Choi [44] have suggested a novel platform for metastatic cancer treatment. Prodrug is used to activate enzyme or anticancer cytokine to promote the expression of stem cells, which successfully alleviate the proliferation of cancer cells [45]. Using engineered viruses to express anticancer genes and specific cancer targeting molecules provides an alternative ways to treat metastatic cancer.

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