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Cancer Stem Cells and Chemoresistance

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1. Introduction

Chemoresistance is a complex mechanism, involving various biological pathways. Also, chemoresistance is a major cause of cancer treatment failure. Cancer stem cell (CSC) in solid cancer has recently identified, but its role in solid organ tumour is not clearly documented. However, research data supported that CSC may involve in carcinogenesis, invasion and metastasis, as well as resistance to various form of chemotherapy. Understanding more how CSCs involve in chemoresistance would enhance our knowledge and thus would lead us to the possibly newly developed cancer treatment.

2. Stem cells and clinical relevance to therapy

Stem cells are a small and distinct population of cells in living body. Stem cells can divide, and can produce progeny of differentiated cells with specific functions, therefore, have two major key characteristics: 1) capacity for asymmetric division or self-renewal and 2) generate a quiescent stem cell that can produce "progenitor" cells, which can differentiate into more mature and differentiated cells.

Self-renewal is a characteristic process of stem cells, thereby, ensuring that the stem cells survive a long time. All stem cells must regulate the balance between self-renewal and differentiation. The self-renewal and differentiation of stem cells is regulated by many signalling pathways, and some pathways are associated with carcinogenesis including Notch, Shh, BMI 1 and Wnt signalling pathways [Jordan, 2004]. In fact, some of these proteins (eg. Wnt) has become therapeutic target [Takahashi-Yanaga and Kahn, 2010].

In general, human stem cells can be classified broadly into embryonic, foetal and adult stem cells. Adult stem cells have limited potential for differentiation into different cell types of their tissue of origin whereas embryonic stem cells can differentiate into all cell phenotypes [Bellantuono and Keith, 2007]. Most adult tissue-specific stem cells are traditionally believed to be multipotent, but not pluripotent. However, recent data has documented that adult stem cells can show plasticity, and that the adult tissue-restricted stem cells may develop into cells resembling pluripotent stem cells [Askenasy et al., 2006;Kiger et al., 2000;Bellantuono and Keith, 2007].

Recently, stem cell research has been expanding rapidly, not only in basic scientific research but also in clinical research. Treatment of many complex diseases with stem cell is more widely used in various types of haematologic diseases, including thallasemia, aplastic anemia and other hematologic malignancies. As well, stem cell has increasing roles in the

treatment of other non-haematologic diseases including heart failure, liver dysfunctions and neurodegenerative diseases [Chang and Appasani, 2006;Dimarakis et al., 2005;Gordon et al., 2006;Burt et al., 2008].

Better understanding about stem cells has started from the studies of haematopoietic tissues. In the haematopoiectic system a wide variety of blood cells in the circulation appear to originate from the same precursors [Huntly and Gilliland, 2005]. With this observation, later identification of haematologic stem cells was achieved. The rapid further advancement in haematopoietic stem cell knowledge has later made haematopoietic stem cell transplantation become a standard treatment for various haematologic diseases, with a good and safe outcome [Ikehara, 2003]. Therefore, approval of stem cell therapy is limited primarily to haematologic diseases. Treatment of other degenerative diseases with stem cell therapy is possibly only in the research area, but with a potential expand to clinical practice in the near future. For example, recent published data has used human CD34+ adult bone marrow stem cells for the treatment of chronic liver disease and has shown an impressive outcome [Gordon et al., 2006;Levicar et al., 2008]. Haematopoietic stem cells have also being used in many clinical (Phase I) trails in the treatment of ischaemic heart disease, diabetes and other neurodegenerative diseases with an impressive preliminary outcome [Balsam and Robbins, 2005;Dimarakis et al., 2005;Levicar et al., 2007]. However, long-term outcome clinical data has still to be documented and carefully evaluated.

3. Cancer stem cells: a small population in tumours

Most cancer cells grow and divide rapidly and indefinitely, as well as stem cells. This observation has led to the possible link between cancer cell and stem cell. In fact, knowledge about cancer stem cell (CSC) become widely accepted following the work of John Dick and his colleagues in 1994 who described the presence of CSCs in haematologic malignancies [Lapidot et al., 1994]. The concepts of CSCs arose from the observations of the capacity to and comparability of self-renewal between stem cells and cancer cells. As a result, CSCs are believed to be involved in carcinogenesis, as well as in local invasion and in the metastatic process [Glinsky et al., 2005; Spillane and Henderson, 2007]. As well, there is also accumulating data supported that stem cells play an important role in chemo- and radiotherapy resistance [Dean et al., 2005].

In the seminal experiment in 1960, patients had their own tumour cells injected into their body subcutaneously. A low success rate of tumour growth occurred at the injection site (14.3%), with a large number of cancer cells (at least 1×10^6 cells) required in order to induce a tumour growth at the autotransplantation site [Southam and Brunschwig, 1960]. At that time, the explanation as to why cancer cells isolated from malignant tumours could not regenerate on reinjection was unclear. However, with the recent knowledge about CSC, an explanation for the results of the experiment may be the small percentage of CSCs in the tumour inoculations. Out of the 1×10^6 cells that implanted into his patients, less than 0.5% consisted of CSCs. This small population of stem cells was able to induce growth and form a tumour at the injection site. Thus, the reason as to why at least 1×10^6 cells were required for the implantation in order to generate a new tumour.

4. Breast cancer stem cells

The success to identify CSCs in haematologic malignancies has led to the discovery of stem cells in solid tumours, which later has enhanced our knowledge of cancer biology. Amongst

the study of CSC in solid organ malignancies, breast CSC is one of the most widely investigated. In normal breast epithelium, there are two main cell types, known as luminal epithelial and myoepithelial cells. The stem cell populations reside in the luminal, but not in the myoepithelial compartment [Gudjonsson and Magnusson, 2005]. As a result of mutations in the stem/progenitor cells, normal breast stem/progenitor cells are transformed into breast CSCs/progenitor cells [Beier et al., 2007;Ricci-Vitiani et al., 2007].

Previously, identification and isolation of stem cells in solid organ tumour was not possible. Until recently, identification and isolation of CSCs from the other cell populations was succeeded due to development of newly discovered cell surface biomarkers and advancement of biomolecular technology (ie. flow cytometery). Stem cells identified from solid tumours express organ-specific cell surface markers. For example, EpCAM(high)/CD44(+)/CD166(+) is a specific marker for the human colon CSCs [Dalerba et al., 2007] and CD133 is the specific stem cell marker for human central nervous system cancers [Beier et al., 2007]. Breast CSCs were first identified by Al-Hajj *et al* (2003) who established that the CD44(+)/CD24(-) was the surface phenotypic profile of breast CSCs [Al-Hajj et al., 2003]. A small number of CD44(+)/CD24(-) cells (as few as 200 cells) were able to give rise to new tumours after injection into the mammary fat pad of NOD/SCID mice [Al-Hajj et al., 2003]. These findings have been confirmed subsequently by other research [Ponti et al., 2005].

CD44 is a 37 kDa cell adhesion molecule expressed in most cell types, including putative breast CSCs [Goodison et al., 1999]. CD24 was originally found during the early stage of B cell development and is highly expressed in neutrophils, but not in normal T cells or monocytes [Balic et al., 2006]. The gene studies of CD44+ cells, extracted from human breast tissues, have shown the expression of genes associated with self-renewal, including hedgehog signaling pathway-related genes – Gli1 and Gli2 [Shipitsin et al., 2007]. As well, the TGF-β signalling pathway, known to be important in human embryonic stem cells and promoting invasion and angiogenesis, was found to be activated in CD44(+) breast cancer cells [Shipitsin et al., 2007]. These findings have suggested that CD44 (+) expressing cells that are CD24(-) are CSCs and have supported the probable role(s) of CSCs in determination of biological aggressiveness and invasive behaviour.

In addition, recently, aldehyde dehydrogenase 1 (ALDH 1) has been used as another marker to identify breast CSCs. ALDH1 is a detoxificating enzyme responsible for the oxidation of intracellular aldehydes [Duester, 2000]. As few as 20 breast cancer cells with $CD44^+/CD24^-/ALDH^+$ were able to generate tumours in NOD/SCID mice [Ginestier et al., 2007].

Success in identifying and isolation of CSC in breast cancer is probably a breakthrough in cancer research and that make scientist can study further the roles of CSC in cancer biology more easily.

5. Anti-cancer chemotherapy resistance

Nowadays, treatment of cancer consists of various modalities, including surgery, radio-, chemo-therapy and others. However, in order to achieve the maximum systemic control, one of the most crucial modalities is chemotherapy. Therefore, resistance to chemotherapy is a major cause of failure in the treatment of solid organ malignancies. Mechanisms involved to resistance process are complex and not fully understood. The following mechanisms are proposed to be involved in chemotherapy resistance.

5.1 ABC transporters and multidrug resistance

Chemotherapeutic drug resistance includes the efflux/influx of drugs via the adenosine triphosphate-binding cassette (ABC) transporters. These cell membrane proteins include 3 main types – P-gp (ABCB1/multi-drug resistance (MDR) 1), MDR-associated protein (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2). The ABC transporter system has been conserved across the phylogenic spectrum, from bacteria to mammals, and through evolution. The main function of ABC transporters is to excrete toxins from the liver, kidneys and gastrointestinal tract. In addition, ABC transporters act as a filter for toxins which enter certain vital structures such as the brain, placenta and testes. ABC transporters are thought to play a crucial role in chemotherapeutic agent resistance mechanisms by effluxing drugs out of tumour cells. Consequently, intracellular drug concentrations may fluctuate and be low. To date, more than 40 ABC transporter genes have been discovered and are classified into 8 subfamilies: ABCA through ABCG and ANSA (arsenite and antimonite transporter) [Mahadevan and List, 2004].

ABC transporter subfamily A (ABCA) gene consists of 13 members that have various roles in the cell membrane. ABC transporter subfamily B, also known as MDR, comprises 11 members. The best characterised is P-gp (MDR1/ABCB1), a 170 kDa glycoprotein encoded by the *MDR1* gene. The ABC transporter subfamily C is also known as MRP, with currently at least nine members (MRP1-9) having been identified and related closely to chemoresistance mechanisms [Hopper-Borge et al., 2004]. BCRP is another protein associated with chemoresistance mechanisms. It is a member of the ABC transporter subfamily G. It is named "BCRP" because it was originally isolated from the MCF-7 breast cancer cell line; it is not only found in breast cancer, but is also detected in various types of chemoresistant malignancies.

In cancer cells, over-expression of P-gp correlates with resistance to anthracyclines, vinca alkaloids, colchicines, epipodophyllotoxins and taxanes [Avendano and Menendez, 2002]. Over-expression of P-gp is associated with many chemoresistant cancers including lymphoma, acute leukaemia, breast cancer, ovarian and head and neck cancer [Sauna et al., 2001]. A study of more than 400 tumour specimens of colon, renal, adrenal, liver and pancreas, showed that patients with increased levels of MDR1 RNA tended to be more resistant to chemotherapy [Goldstein et al., 1989]. A meta-analysis review by Trock *et al* (1997) indicated that the proportion of breast tumours expressing P-gp of the various studies was 41.2%. Moreover, the same study claimed that breast cancer patients who had tumours expressing P-gp were three times more likely to be chemoresistant [Trock et al., 1997].

In the human normal cell, BCRP can be detected in the heart, ovary, kidney and foetal liver [Allikmets et al., 1998]. Cell lines selected for resistance to mitoxantrone, topotecan, doxorubicin, SN-38 (the active metabolite of irinotecan), flavopiridol and indolocarbazole topoisomerase I inhibitors, all over-expressed BCRP. However, typical substrate of P-gp such as vinca alkaloids, paclitaxel and verapamil are not transported by BCRP [Allen and Schinkel, 2002]. Expression of BCRP was seen in all tumour types, but was more common in adenocarcinomas of the GI tract, endometrium, lung, and melanoma [Diestra et al., 2002].

5.2 Detoxification enzyme involving in chemotherapy resistance

Three phases of drug detoxification are responsible for excretion of toxic substances from the cell. Phase I detoxification is usually mediated by cytochome P450 and results in

eliminating OH forming free radicals. Phase II is generally involved in converting metabolites to less toxic agents. During phase II, toxic substances will conjugate with glutathione, glucuronic acid or sulphate, which will be catalyzed by glutathione S-transferase, uridine diphosphate-glucuronosyl transferase, and sulfatase. Finally, exporting the toxic drug with its metabolites out of the cells via transmembrane efflux pumps is the main activity that occurs during phase III detoxification. Therefore, impairment of detoxification process is directly linked to impairment of chemotherapeutic agent activation, thus involves to chemotherapy resistance.

5.3 Inactivation of apoptosis

The deregulation or inactivation of apoptosis in a cell is crucial to the subsequent development of cancer in that cell. This malfunction of the apoptotic process may predispose the cell to resistance to chemotherapeutic agents, as induction of apoptosis is a key element of drug-induced cancer cell death. The apoptosis is thought to be mediated by the tumour-suppressor protein p53. It prevents tumourigenesis by acting as a cellular-stress and DNA-damage sentinel. As a result of DNA damage, hypoxia or proliferating signals, p53 stabilizes causing cells to undergo cell cycle arrest (checkpoint function) temporarily or permanently, or apoptosis and death [Levine, 1997].

Most human cancers have either mutations in p53 or defects in p53 regulated pathways [Lowe et al., 1994; Vousden and Lu, 2002]. p53 null mice are very prone to developing cancers [Attardi and Donehower, 2005]. Most cancer therapies are DNA-damaging agents, thus, if the cancer cells have a disabled/deregulated apoptotic pathway (p53 mutation or over-expression of BCL-2 protein), this will prevent death of the cancer cell through drug-induced apoptosis. Therefore, there probably is a non-apoptotic dependent pathway of cell death. Clonogenic survival assays in mice have failed to reveal any differences between rates of cell death of normal and malignant cells to ionising radiation, implying that there are other pathways for cancer cell death. This suggests that those cancers carrying the Tp53 allele or over-expressing the anti-apoptotic protein BCL-2 should be more resistant to cancer drug therapy than tumour cells with intact apoptotic pathways (presence of wild type 53, low levels of BCL-2). This has not been shown to be the case for non-haematological malignancies.

In a recent review, there was no clear evidence that either the apoptotic index or levels of p53, BCL-2 or other homologous proteins are predictive of the response of solid tumours to chemotherapy or radiotherapy [Schmitt and Lowe, 1999;Brown and Wilson, 2003]. Apart from apoptosis, cells can be eliminated following DNA damage by necrosis, mitotic catastrophe (giant or multinucleated cells), autophagy (self-cell digestion) with intracellular vacuoles containing ribosomes, and premature senescence.

The precise pathway of cell death as a result of drug treatment is difficult to determine and is dependent on a range of factors, including tumour cell type and volume, drug combinations and doses used as well as activated anti-cancer host defences.

6. Role of cancer stem cells in chemoresistance

One characteristic of CSCs that differentiates them from other normal cells in the tumour is that CSCs have high levels of ABC transporter proteins. These transporter molecules are responsible for protecting cells from drug damage via the efflux pumping mechanisms. Thus, CSCs, as a result of these biological properties, are resistant to drug treatment, including chemotherapeutic drugs [Dean et al., 2005].

In clinical practice, optimal chemotherapy treatment can kill most cells within solid tumour. However, a small fraction of cells (CSCs) are drug resistant, possibly because of enrichment of ABC transporter proteins. This small fraction of CSCs remain quiescent in the G0 phase. Over a period of time and due to stimuli associated with tumour cell death, these quiescent stem cells give rise to progenitor cells and subsequently become new mature tumour cells with a chemoresistant phenotype. This is the postulated model of acquired chemoresistance in breast cancer observed in the clinic [Dean et al., 2005]. Patients at this stage will develop recurrent tumours and fail to be responsive to further chemotherapy treatment.

The high expression of ABC transporter protein in tumour stem cells results in exclusion of the fluorescent dye Hoechst 33342 and Rhodamine 123, and can be detected by flow-cytometry. The cells that are able to efflux Hoechst 33342 as detected on flow-cytometry are known as the "side population" (SP) cells. However, some drug resistant non-stem cells have these properties as well. Stem cells also have an active DNA repair capacity and a resistance to apoptosis.

In addition, as previously evidenced, CSCs are believed to have overexpression of ALDH1, a detoxification enzyme [Lugli et al., 2010;Neumeister et al., 2010]. However, ALDH1 alone is not specific marker for stem cells [Neumeister and Rimm, 2010]. For example, in a study of breast CSC, as few as 500 ALDH1 positive cells can generate a new tumour; whist as few as 20 CD44+/CD24-/lin-/ALDH1+ cells can induce a new tumour [Ginestier et al., 2007].

The linkage between CSCs and chemoresistance is an interesting and challenging area of research. The ability to identify CSCs in tumours and perhaps to kill these cells is a therapeutic strategy designed to overcome cancer chemoresistance. However, the knowledge and evidence regarding the contribution of CSCs to chemoresistance is still embryonic and requires further careful evaluation.

7. Strategies to overcome chemoresistance by targeting cancer stem cells

If the chemoresistant cells are CSCs, targeting treatment at these cells would be the way forward to overcome the chemoresistance and could improve the outcome of breast cancer treatment. The traditional approach of changing chemotherapeutic regimens, after tumours develop resistance to one chemotherapeutic regimen, may not be useful in chemoresistant breast cancers. Most current chemotherapeutic drugs are targeted on rapidly dividing cells within the tumour, but tend to spare the slowly dividing and inherently resistant CSCs and, thus, may not lead to long-term cures [Hellman et al., 2008].

CSCs may be eliminated by selectively targeted therapies against various self-renewal signalling pathways including Notch, Shh, BMI 1 and Wnt signalling pathways [Massard et al., 2006]. However, if normal stem cells and CSCs share the same pathways to maintain their self-renewal, it would be more complex to selectively target at self-renewal pathways of CSCs without any side-effects to normal stem cells. Fortunately, it appears that CSCs are more likely to be more dependent on certain putative pathways [Pardal et al., 2003].

CSCs may be protected from external toxic agents via the over-expression of ABC transporter proteins. Therefore, targeting at this protein may be an alternative strategy and, thus, a way to overcome chemoresistance. Recently, an *in vitro* study have shown the benefit of gefitinib (Iressa, AstraZeneca), a tyrosine kinase inhibitor, in reversing chemotherapy resistance in multidrug resistant breast cancer cells expressing ATP transporters [Yang et al., 2005]. Also, gefitinib has been recently reported to successfully overcome SN-38-resistance in small-cell lung cancer cells *in vitro* [Takigawa et al., 2007].

Moreover, instead of killing tumour cells with chemotherapy, biological therapy with monoclonal antibodies targeted against specific cellular surface molecules or receptors should be considered. Targeting at the apoptotic pathway could be an alternative. Cell death is generally programmed by apoptosis, including that regulated by CSCs [Baguley, 2006]. The elimination of CSCs may be feasible by increasing the ratio of pro-apoptotic to anti-apoptotic proteins and signal pathways, perhaps targeting at pro-apoptotic members of the Bcl2 family [Thompson and Thompson, 2004]. Alternatively, targeting CSCs at the niche endothelium would be a possible therapeutic strategy. CSCs niches are likely to be well endowed with a blood supply by angiogenesis [Baguley, 2006]. Therefore, blockage of action of VEGF signalling with anti-VEGF, bevacizumab (Avastin, Genetech), could be an alternative.

However, all the strategies proposed above are speculative. Published data, so far, has not yet confirmed the benefit of these approaches in chemoresistant patients where CSCs are believed to be the predominant factor. If CSCs are key molecules responsible for chemoresistance, there is an urgent need to enhance both experimental and clinical studies to support the use of these biological therapies in chemoresistant breast cancers. It is likely that additional agents, following chemotherapy, may be needed to eradicate CSCs, if a good long-term outcome is to be achieved.

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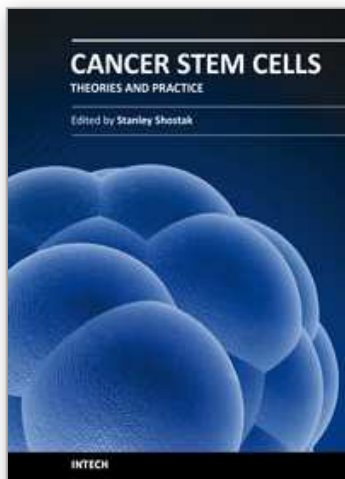
Cancer Stem Cells Theories and Practice

Edited by Prof. Stanley Shostak

Cancer Stem Cells Theories and Practice does not 'boldly go where no one has gone before!' Rather, Cancer Stem Cells Theories and Practice boldly goes where the cutting edge of research theory meets the concrete challenges of clinical practice. Cancer Stem Cells Theories and Practice is firmly grounded in the latest results on cancer stem cells (CSCs) from world-class cancer research laboratories, but its twenty-two chapters also tease apart cancer's vulnerabilities and identify opportunities for early detection, targeted therapy, and reducing remission and resistance.

How to reference

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