

PROTECTING SECOND VICTIMS FROM WORK PERFORMED WITHOUT PASSION



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WHO IS A SECOND VICTIM?

A patient is obviously the first victim of harm. The person blamed for the harm is a second victim, such as a nurse who is the last person in a chain of harmful events in the process or a care giver who made an inadvertent mistake that should have been mitigated in the system. According to Beth Boynton's book *Confident Voices*, 80-97 percent nurses experience verbal abuse which is another way of blaming such second victims. The next issue is why the system problems are not recognized, and not mitigated? The reason usually is that there is very little effort invested by management in designing out the harm through robust changes in the system or planting safeguards and barriers. Blaming an individual is the easiest thing to do to avoid system accountability. In other words many managers manage risks without passion to prevent harm.

HOW DOES ONE START OUT WITH PASSION AND LOSE IT?

The Gallup organization defines a worker/manager without passion as a disengaged and unengaged employee. According to a Gallup pole nationally, engaged employees made up only 29% of the work force (an engaged employee is one who is willing to go the extra mile to help the organization do the right things). The remaining employees were either not-engaged (56%) or actively disengaged (15%). Not-engaged and actively disengaged employees tend to work in a substandard manner. Most important, disengaged managers are often responsible for disengaged and un-passionate safety culture.

Most employees are excited when they find the job of their choice. But they lose the excitement over time. There are at least two reasons. We can call

the first reason as "boiling frog phenomenon." James Kilts in his book *Doing What Matters* has this advice for new employees: Usually in your first day on a new job you spot a number of things that don't make sense. Some seem inefficient and ill conceived. Two weeks later wrong things seem perfectly fine because your experienced peers are OK with this stuff. You are in a pot that has been heating slowly and you don't know that you are being cooked. It is like the situation of a frog. If you put it into boiling water, it will not tolerate it. If you put it into cool water and slowly raise the temperature, the frog gets cooked before it knows what is happening. The second reason is the so-called "organizational silence." It is a result of punitive or "blame" culture in which employees choose self-censorship because they are afraid to speak up. In addition, they choose silence to fit into the norms of the organization and be a part of the group think. They are rewarded if they go along with the group in the name of team work.

HOW CAN WE MITIGATE HARM IN THE SYSTEM?

Dr. James Reason, through his Swiss cheese model on harm causation, has earned high respect for explaining why a single event by a nurse or any care giver cannot cause harm. Harm is always a result of hidden hazards in the system and a trigger event such as a human error. Hazard can be prevented either by preventing the system from being vulnerable or by preventing humans from making mistakes. History tells us that we can reduce human errors but cannot eliminate them entirely. Therefore the wise choice is to work with a passion to prevent system vulnerability.

But people without passion for zero harm are not ready to listen. To listen, hospitals first must create

an organization that empowers employees to do the right things including reporting on abusive employees. Ritz Carlton hotel system is such an example, where employees are expected to respect each other and authorized to go out of their way to give outstanding service to customers and improve the quality of service. This strategy protects the service providers from compromising quality and safety. They create passion for ultrahigh quality.

For employees to work with passion, hospitals must create meaningful work, capable and similarly committed colleagues, and respectful and respected managers who will welcome investment in safety as a business strategy instead of a necessary cost. The meaningful work includes work that can be done with normal effort. This is not the choice the nurses usually have with constant interruptions, real alarms, false alarms, sudden worsening of the patient condition, inadequate hand-offs, and a lot of wasted effort in looking for proper forms and supplies. Hospitals must evaluate the adequacy of work load with the help of industrial engineers who are trained to design a suitable work load that allows enough rest too. Rest is important for mental efficiency as well as physical efficiency. Some industrial organizations have a dedicated time for a nap after lunch. Hospitals need to decide whether they want efficiency with more people or chaos with less people. Savings from an increase in efficiency can often justify hiring more nurses.

About Dev Raheja

A respected and sought out expert on hospital and medical device safety, author Dev Raheja draws on his 25 years of experience as a risk management and quality assurance consultant to provide hospital stakeholders with a systematic way to learn the science of safe care. He uses evidence-based safety theories and tools taken from the aerospace, nuclear, medical, and chemical industries to identify the combination of root causes that result in an adverse event. He applies analytical tools that can effectively measure hospital efficiency, establish evidence between Lean strategies and patient satisfaction. His focus is on using various types of innovation including accidental, incremental, strategic, and radical, and establish a culture conducive to high return on investment.

HOW CAN NURSES HELP?

What can nurses do to prevent blame on their profession? My recommendation for them would be to band together as a team, create a name like Nurses Council on System Thinking, develop system improvements (especially on how to prevent employee disrespect against a fellow employee, find a high level manager (not a dictator), who believes in listening and convince the manager, as a team, on the solutions. The solutions should include eliminating wasted time for nurses such as finding forms, walking constantly for medications stored outside the patient rooms, supplies stored in remote places, working with poor quality medical devices, looking for batteries for failed instruments, and dealing with work environmental frustrations. Examples of work environment frustrations can be: bureaucratic procedures, unresponsive physicians, unsupportive supervision, missed breaks, expediting pharmacy delays, waiting to access the automated medication dispensing systems that are often unreliable, sloppy co-workers, and frustration of seeing many mistakes being made. Management is more open to implementing right things if the whole team believes in the solution with passion.

The nursing council can elect volunteer leaders, meet periodically during lunches to discuss ideas, and even invite managers during discussions. Convince management on *Primum non nocere*. It stands for *First, do no harm*. Including the harm to nurses!

EXPLORING THE ROLE OF STEM CELLS IN CANCER THERAPY

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ABSTRACT

The conventional methods for cancer treatment used so far are radiotherapy and chemotherapy. But, the drawbacks of these procedures are that most chemotherapy drugs and radiation techniques target the normally growing healthy cells of the body. They target the normal tissue as well, while being unable to completely destroy the cancer stem cells which are highly resistant to these techniques. Solid tumors such as breast cancer and colon cancer possess a minor population of tumorigenic cells termed cancer stem cells (CSCs) or tumor initiating cells (TICs). A recent approach to deal with these problems is by making use of stem cells. Stem cells are generally defined by an ability to differentiate into multiple cell lineages and self-renew. These stem cells have a number of utilities. They contribute to not only organogenesis but also help in regeneration in response to the injury of tissues and organs. Several studies conducted in the biology of stem cells have allowed for their identification and characterization in a variety of tissues and organs. This review makes an attempt to explore the behaviour and potential of stem cells in cancer treatment alongside the traditional methods of chemotherapy, radiation therapy and surgical removal of tumour.

Key words: Cancer, Stem cell, Therapy

INTRODUCTION

For a considerable period of time now, cancer has been causing distress and death in the world. Environmental stress and increasing amount of carcinogens circulating freely in the environment due to technological advances strangled hold of cancer. Despite recent advances in the treatments of cancer, the clinical outcome is yet far from expectation. The conventional methods for cancer treatment used so far are radiotherapy and chemotherapy. But, the drawbacks of these procedures are that they affect both normal and cancerous tissue while being unable to completely destroy the cancer stem cells which are highly resistant to these techniques (Moserle et al. 2010). A recent approach to deal with these problems is by making use of the array of cells, the stem cells. Stem cells are generally defined by an ability to differentiate into multiple cell lineages and self-

renew. They contribute to not only organogenesis but also regeneration in response to the injury of tissues and organs (Millera et al. 2005). Advanced studies in the biology of stem cells have allowed for their identification and characterization in a variety of tissues and organs. It has also been documented that in solid tumors such as breast cancer and colon cancer, there exists a minor population of tumorigenic cells which can generate new tumors in xenograft transplantation (Houghton et al. 2009). Cancer stem cells (CSCs) or tumor initiating cells (TICs) can be defined as cells with a tumour initiating potential (Wang & John 2005). They comprise a very small population in tumours and are known as tumorigenic cells, or tumor-initiating cells (TICs) (Chiba et al. 2009). These cancer stem cells possess stem cell-like properties, contributing to a hierarchical structure containing varied progenies in a similar fashion to normal stem cells.

Normal stem cells are characterized by three main properties:—

- (1) the presence of an extensive capacity for self-renewal, which allows maintenance of the undifferentiated stem cell pool over the lifetime of the host;
- (2) strict regulation of stem cell number; and
- (3) the ability to undergo a broad range of differentiation events to clonally reconstitute all of the functional elements in the tissue (*Clarke 2005*).

Two conceptual models of tumor growth have been proposed (*Martin et al. 2008, Krishnamurthy et al. 2004*). In the older, stochastic model, all cells in the tumor have a high proliferative capacity. A growth fraction of <1 still occurs due to individual cell loss and non-reproduction, the result of constraints of the microenvironment such as focal lack of nutrients or oxygen, and age. However, in many cancers a stem cell model of tumor reproduction probably takes place. As in normal tissues, only a small percentage of the tumor population (i.e., the CSCs) maintain the capacity for long-term proliferation, while most cells proceed forward in a process of aberrant terminal differentiation.

Stem cells can be divided into three main categories: embryonic, germinal, and somatic. Embryonic stem cells (ESCs) originate from the inner cell mass of the blastocyst. ESCs are pluripotent and have indefinite replicative life span, which can be attributed to their telomerase expression. Germinal stem cells are derived from primary germinal layers of embryo. They differentiate into progenitor cells to produce specific organ cells. Somatic/adult stem cells (ASCs) are progenitor cells as they are less totipotent i.e. have less replicative life span than ESCs. They exist in mature tissues such as haematopoietic, neural, gastrointestinal and mesenchymal tissues. ESCs are derived from 5-day old pre-implantation human embryos while ASCs can be obtained from a number of tissues like bone, synovium, brain, adipose tissue, blood vessels, blood and umbilical cord blood. Owing to reasons that are both ethical and legal, the use of ESCs is restricted in research and clinical fields, making ASCs the main supplement for the stem cells. More than two thirds of cancer patients currently receive either chemotherapy or radiotherapy, which in many

cases have beneficial effects and can improve quality of life and survival. In spite of the broad use of these therapies, there still remain many unresolved issues regarding the mechanisms that determine remission or the subsequent relapse of the tumor.

OBJECTIVE

The objective of this present review is to understand the role of stem cells in the treatment of cancer. This study explores the problems associated with the conventional therapies of cancer and the prospects of stem cells as a complementary therapy in addition to the traditional techniques of chemotherapy, radiotherapy and surgery. The origin, characteristic and application of stem cells has been highlighted.

STEM CELLS AND CANCER

The subject of stem cells in malignancy is one that still remains obscure today as compared with their role in normal tissue turnover. Tumors are composed of a heterogeneous mixture of tumor cells at various levels of differentiation. Only a small population of cells within a tumor possess self-renewal capacity (*Daniel & Brunschwig 1961, Harrington 2004*). Several studies have suggested, that while all cells within a tumor are equal, at any given time, only a small fraction of cells is in an appropriate state or is stimulated by appropriate external signals to form a new tumor. On one side, a predetermined population of cells exists with the “cancer stem cell” phenotype, enabling this cell to perpetuate the tumor, while on the other side, cells of the same tumor are incapable of self renewal. In order to prove the latter, prospective isolation of this population is required. John Dick and his group demonstrated that cells capable of establishing a human AML phenotype in a recipient mouse were isolated only within the cell fraction expected to contain the hematopoietic stem cells which is defined by the CD34+ CD38- phenotype (*Vormoor et al. 1994*). These cells could be passed from animal to animal and maintain the AML phenotype (*Dick 1996*), confirming the property of self-renewal. As a result for the first time, it was triumphantly demonstrated that there are cells within the tumor which have properties similar to stem cells, i.e., they possess the capacity to reconstitute the tumor when transplanted into an

appropriate recipient (differentiation) through several rounds of transplantation (self-renewal). A similar approach has led to the identification of subpopulations of tumor cells with stem cell properties within breast tumors (*Al-Hajj et al. 2003*), gliomas (*Singh et al. 2003, Singh et al. 2004, Sanai et al. 2005*), melanoma (*Fang et al. 2005*), prostate cancer (*Collins et al. 2005*) and osteosarcoma (*Gibbs et al. 2005*). Thus, the result of these observations is the "cancer stem cell hypothesis" (*Reya et al. 2001*). This hypothesis postulates that within a tumor, a small proportion of cells with unlimited proliferative capacity drive tumor growth. The observation that most cancers comprise a heterogeneous population of cells that have undergone varying degrees of differentiation leads to this model. The origin of CSCs has been quite obscure. For a long time, there has been conflicting beliefs of CSCs originating from normal (somatic) stem cells or from non-stem progenitors or differentiating cells. However, recently conducted studies that have been emphasize a progenitor cell origin for many types of leukaemic stem cells along with the stem cell origin (*Lobo et al. 2007*). In solid tumors too, it is most likely that not only somatic stem cells but also differentiating progenitor cells are capable of becoming CSCs (*Yang & Chang 2008*). Rapp et al. proposed a model of oncogene-induced plasticity for CSC origin by demonstrating reprogramming events triggered by a specific combination of oncogenes. *Li et al. 2009*, suggested that genomic instability is a driving force for transforming normal stem cells to CSCs and, in CSCs, a potential mechanism for cancer cell heterogeneity.

CANCER STEM CELL NICHE

The concept of stem cells existing in a unique microenvironment was first proposed by *Schofield 1978 (Schofield 1978)*. The stem cell niche comprises the microenvironment surrounding normal and cancer stem cells. It plays several roles including providing a mechanical anchorage for the stem cells and in cross-talk communication mediated by direct contact and/or indirect extracellular factors. Wnt ligands are produced and released from both stem cells and niche cells, BMP and Sonic hedgehog (Shh) are released from niche cells and epithelial cells respectively, and Notch signaling is transmitted between neighboring cells. The microenvironment may also provide signaling via the

cell receptor integrin as suggested by its expression in prostatic CSCs (*Collins et al. 2005*) and its co-expression with AC133 (CD133) in the epidermal basal cells (*Yu et al. 2002*). The concept of a CSC niche is a matter of debate (*Li et al. 2009*). Several possible models were proposed to clear this debate (*Sneddon & Werb 2007*). CSCs are capable of surviving the normal stem cell niche, a distinct CSC niche is necessary for activation, CSCs may be capable of providing signals that instruct an otherwise quiescent niche to become activated ("hijacking the niche"), CSCs could amplify an already existent activated niche, CSCs may be niche-independent, that is, they themselves acquire the ability to maintain its activity, and there may be a discrete niche that is inhibitory for CSC maintenance. No particular single model fits all the different types of cancer. Further research is required to set up a CSC niche theory that can be universally accepted.

CANCER STEM CELL MARKERS

Several specific markers are utilized to detect and isolate CSCs from among the innumerable cancer cells and stromal cells occupying the entire tumor tissue (*Yang & Chang 2008, Hirschmann-Jax et al. 2004*). This is primarily because CSCs constitute a very small fraction of the cancer cell population. Some of the markers include CD34 in several kinds of leukemia and CD44 in breast cancers, colorectal cancers, pancreas cancers, prostate cancers, head/neck cancers and some bone sarcomas.

Some of the important cancer stem cell markers are elaborated below.

CD34

CD34 was reported to be expressed in common acute lymphoblastic leukemia cells in 1987. It was suggested that CD34-positive leukemic cells may represent a less differentiated phenotype form than CD34-negative ones (*Ryan et al. 1987*). CD34 which is a heavily glycosylated type I transmembrane molecule can be phosphorylated by a variety of protein and tyrosine kinases. It is a confirmed to be a sialomucin (*Lanza et al. 2001*). In contrast to the high endothelial venules for which CD34 serves as a ligand for I-selectin, CD34 is not the ligand for I-selectin in hematopoietic stem/progenitor cells. Ligands for hematopoietic CD34 remain to be identified (*Lanza et al. 2001*).

CD44

CD44 which is originally described as a leukocyte-homing receptor, is made up of a family of glycoproteins encoded by a single gene, which vary in size due to alternative splicing. It functions as a pleiotropic factor and is important for tissue remodeling, cell-to-extracellular matrix adhesion, and cell migration. CD44 is the major receptor of hyaluronan (previously known as glycosaminoglycans), carbohydrate polymers of the extracellular matrix (Stern 2008). CD44 has been utilized as a CSC marker not only for leukemia but also for a variety of solid cancers.

CD133

A broad spectrum of malignant tumors including brain tumors, colorectal cancers, pancreatic cancers, breast cancers, prostate cancers, ovarian cancers and some lung cancers have CD133 as a specific marker of CSCs (Eramo et al. 2008). CD133 was first reported as a novel marker for human hematopoietic stem and progenitor cells (Yin et al. 1997). It was later found in some types of leukemic cells (Martin et al. 2008). CD133 expression has been detected in human central nervous system stem cells (Uchida et al. 2000), human trophoblasts (Pötgens et al. 2001), human lymphatic/vascular endothelial precursor cells (Salven et al. 2003), and human prostatic epithelial stem cells (Richardson et al. 2004). The CD133 antigen is a 120 kDa five-transmembrane domain glycoprotein, and its chromosomal location (4p16.2-p12) and amino acid sequence have been resolved (Piechaczek 2001). CD133 is actually detected by its glycosylated epitope, AC133, and it is likely that AC133, not CD133, is a more reliable CSC marker (Mizrak et al. 2008). A number of other studies have emphasized that the use of CD133 expression as a marker for CSC should be critically evaluated (Bidlingmaier et al. 2008). Such reports may explain the inconsistency observed in the results from different studies.

RESISTANCE TO CHEMOTHERAPY

It has been suggested experimentally that side population (SP) and CSC have higher resistance to chemotherapy than the bulk of cancerous cells. Hirschmann-Jax et al. first demonstrated that neuroblastoma SP cells were less sensitive to

mitoxantrone (Hirschmann-Jax et al. 2004). Szotek et al. 2006 states doxorubicin could not inhibit the SP fraction of ovarian cancer, unlike non-SP cells showed similar results. The fact that this drug preferentially kills non-SP cells (Chua et al. 2008) is further reinforced by the fact that the SP of human malignant glioma cell lines and primary glioblastoma was shown to increase following treatment with temozolomide. A number of studies conducted on CD133+ brain tumor stem cells disclosed a survival advantage compared to CD133- cells to temozolomide, carboplatin, paclitaxel and etoposide (Eramo et al. 2008).

One key property is resistance to apoptosis (Moserle et al. 2010). Stem cells are programmed to be long-lived, in order to maintain the progenitor pool from which differentiated cells derive. For this purpose, stem cells activate some protective mechanisms that shield them from senescence and cellular stress. These mechanisms include: (I) activation of some self-renewal pathways, such as TGF- β , Sonic Hedgehog (SHH), Wnt/ β -cat or BMI-1; (II) expression of anti-apoptotic proteins like BCL-2; (III) enhanced capability to repair DNA damage after genotoxic stress; (IV) generation of autocrine loops through the production of growth factors like epidermal growth factor (EGF); and (V) over-expression of drug-effluxing pumps and metabolic mediators, that allow the cell to rapidly eliminate or degrade toxic compounds and radical oxygen species (Moserle et al. 2010). A point of great importance is that it appears that resistance to apoptosis, which can be limited to CSC initially, is often rapidly acquired also by the bulk of tumor cells at relapse. This might be attributed to the genetic instability which distinguishes tumor from normal cells. The result is that chemotherapy invariably causes bone marrow toxicity due to its effects on trans-amplifying, progenitor and even more differentiated cells. Although tumors may initially show regression, they inadvertently become completely resistant to chemotherapy. After apoptosis, a second key property is expression of certain pumps, namely ABCC1, ABCG2 and MDR1. These are the principal mediators of multidrug-resistance identified so far. They transport both hydrophobic and hydrophilic compounds, helping the cell to extrude several drugs including vinblastine, paclitaxel, mitoxantrone, doxorubicin, topotecan, methotrexate and imatinib mesylate (Yin et al. 1997). Although the exact physiological role of these pumps is still

under scrutiny, it is known that they are involved in cellular protection against exogenous products and in resistance to hypoxic stress, mediated by an increased ability to consume hydrogen peroxide (*Martin et al. 2008*) and a reduced accumulation of toxic heme metabolites (*Krishnamurthy et al. 2004*). In normal stem cells these pumps play a role in the repression of cellular differentiation and are generally turned off in committed progenitors and mature cells. The enhanced expression of these pumps in SP may explain their particular drug resistance and their tolerance to hypoxic conditions and as a result, make these proteins ideal targets for cancer therapy. Cancer stem-like cells were separated by the SP fraction method from hepatoblastoma cells. The *in vivo* experiment by *Hayashi et al. (2011)* proved that SP fraction cells inoculated into mice were self-replicated, and also identified the existence of cancer stem-like cells (*Anderson et al. 2005*).

RESISTANCE TO RADIATION THERAPY

Radiation therapy is a traditional method of cancer treatment. Normal tissues are subjected to multiple doses of radiation therapy over a number of weeks to minimize damage to normal tissues and achieve therapeutic effects to the optimum. However, this method of giving interspersed radiation doses can be linked with accelerated repopulation, leading us to believe that a subset of radiation-resistant cells undergo proliferation. Experimental data from breast or brain cancer models indicate that CSC are endowed with resistance to radiation and suggest that CSC numbers in a tumor can affect relapse after radiotherapy (*Yin et al. 1997*). It was demonstrated in a glioblastoma model that the CD133+ fraction, enriched in CSC, is more resistant to radiation-induced apoptosis than its CD133- counter-part. The percentage of CD133+ cells following irradiation was increased both *in vitro* and in tumors (*Bao et al. 2006*). Experimental studies conducted with other groups showed in breast cancer cell lines a similar enrichment for the progenitor cell-containing SP after irradiation (*Chen et al. 2007*). An example of CSCs being provided with very efficient mechanisms of DNA damage repair, giving them the ability to activate DNA damage check points more readily than the rest of the cancerous cells is provided in glioblastoma cell lines. Here, the CD133+

subpopulation displays a basal activation of some proteins involved in the DNA damage check point, such as the checkpoint kinases Chk1/2. Inhibition of these kinases with a small molecule inhibitor disabled radioresistance of CSC-enriched cells (*Bao et al. 2006*). This efficient DNA damage repair is just one of many mechanisms that account for the particular resistance of CSC to radiation therapy.

OVERCOMING CSC AND SP RESISTANCE TO CANCER THERAPEUTICS

According to the CSC hypothesis, CSC are more resistant to therapy than non-CSC. Thus, changes in tumor volume after therapy, which are governed by modification of the total burden of cancer cells, may not serve as an indicator of tumor eradication. It is absolutely essential to get rid of the sub-population of rare CSCs in order to effectively control certain tumours. As a result, fundamental optimization of cancer therapies is required in order to target CSC.

CSC and SP within a tumor can be targeted using two possible strategies:

- (i) introducing treatments able to target molecular pathways which are specifically over-activated in malignant stem cells
- (ii) sensitizing CSC to standard therapies by blocking those mechanisms which cause these cells to survive and as a result, lead to their resistance to cancer therapeutics.

STEM CELLS FOR CANCER THERAPY

Source:

The ideal choice of the source of stem cells for therapeutic purposes is ESCs. This is due to their higher totipotency and indefinite life span as compared to ASCs (adult stem cells), which have lower totipotency and restricted life span.

But, the use of ESCs have limitations which are mostly ethical in nature. As a result, their application in therapy and research is not without restrictions. Another cause for concern is that the stem cells with higher totipotency have been shown to be more tumorigenic in mice (*Serakinci et al. 2004*). This is why, due to their greater ease of availability and fewer ethical constraints, ASCs are the stem cells with wider

research and therapeutic applications. ASCs are also more easily accessible as compared to ESCs making them the preferred choice. The most commonly studied stem cells are ASCs from bone marrow (HSCs & MSCs) : MSCs support HSCs in the bone marrow and have the ability to differentiate both in vivo and in vitro into the different mesenchymal cells such as bone, cartilage, fat, muscle, tendon and marrow stroma (Simonsen et al. 2002).

ESCs are obtained from 5-day old pre-implantation human embryos. ASCs can be obtained from many tissues including bone, synovium, deciduous teeth, adipose tissue, brain, blood vessels, blood and umbilical cord blood (Awad et al. 2004, Lee et al. 2004). While ethical and legal reasons restrict the use of ESCs in research and clinical fields, ASCs constitute the main source for the stem cells. These ASCs are mostly derived from the bone marrow and peripheral blood. One of the most common procedures performed to obtain ASCs is the bone marrow (BM) aspiration, but it is associated with morbidity in the form of wound infection and sepsis complications (Pittenger et al. 1999). ASCs can also be obtained from adipose tissues such as abdominal fat and infra-patellar fat (Huang et al. 2004). This is a less invasive and less morbid option than the bone marrow aspiration. Biological studies conducted have shown that there is no significant difference in the cell growth kinetics, cell senescence, gene transduction of adherent stromal cells and yield from stem cells obtained from bone marrow or adipose tissues (De Ugarte et al. 2003). The peripheral blood also provides a safe and easily accessible route for Another procedure involving minimal morbidity is by using ASCs through peripheral blood. The use of ASCs through peripheral blood has shown to induce more T and NK (Natural Killer) cells compared to bone marrow ASCs (Talmadge et al. 1997).

CHOICE OF TYPE OF STEM CELL : BONE MARROW OR PERIPHERAL BLOOD

The most commonly used stem cell sources are the bone marrow and the peripheral blood. The disadvantage of the bone marrow aspiration procedure lies in the fact that it is invasive and is associated with the potential possible complications which consist of fracture, wound infection and sepsis. On the other hand, the procedure for PBSCs isolation is not as invasive.

A greater number of CD4 T and NK cells are induced by PBSCs as compared to stem cells obtained from the bone marrow (Talmadge et al. 1997). As a result, the stem cells from peripheral blood are considered the preferred source of stem cells. However, it has been noted that the occurrence of graft versus host reaction varies with PBSCs compared to BM stem cells (Couban et al. 2002). Double stem cell transplantation has been documented to improve overall survival compared to single stem cell transplantation (Attal et al. 2003). It has been reported that Granulocyte-colony stimulating factor (G-CSF) helps in proliferation and differentiation of haematopoietic progenitor cells (Szyper-Kravitz et al. 2003). G-CSF has also been reported to mobilise autologous peripheral blood stem cells and to preserve and increase the length of telomerase (Szyper-Kravitz et al. 2003). A number of agents which are shown to enhance the G-CSG activity in mobilising stem cell are paclitaxel and docetaxel (Danova et al. 2000), recombinant human thrombopoietin (Somlo et al.1999), lithium (Canales et al.1999) and recombinant methionyl human stem cell factor (r-metHuSCF) (Prosper et al. 2003).

STEM CELLS IN TISSUE REGENERATION AND AS DELIVERY VEHICLES

Stem cells from haemopoietic tissues have dazzling properties that enable them to switch between haematopoietic and non-haematopoietic lineages, exhibiting an unexpected degree of developmental or differentiation potential. Needless to say, theoretically, this allows HSC to be used to regenerate any non-haematopoietic tissue (Martin-Rendon & Watt 2003). The applications of this technique lies in bone tumours as the reconstruction of bone following chemotherapy and surgery is always a problem that has to be dealt with efficiently. For instance, the stromal stem cells derived from bone marrow have been used in the cell-based bone reconstruction following chemotherapy and surgery in osteosarcoma and Ewing sarcoma (Beccheroni et al. 2003). The regeneration of osteoblasts from the survived mesenchymal progenitor cells following COSS-96 (the cooperative osteosarcoma study) polychemotherapy in vitro and its potential in vivo use has been shown by Jager et al. (2005). A number of clinical trials showing role of the stem cells in the regeneration of myocardial tissue following

myocardial infarction have been conducted (*Klein et al. 2007*). Systematic drug delivery or gene therapy are techniques showing promise, but is several factors such as immune detection, non-specific accumulation in normal tissues and poor permeation pose constraints to this procedure. It can also be said, that the effects of many anticancer agents are restricted due to either their toxicities or their short half lives such as interferon β , which shows anti-proliferative and pro-apoptotic activities in vitro, but has shown restricted effects on human malignancies in vivo (*Chawla-Sarkar et al. 2001*). A solution that can be proposed for these would be the cell-based carriers that may target the desired site.

The concept of use of stem cells as delivery vehicles owes its origin to the fact that tumors, acting like injuries, send out chemo-attractants such as the vascular endothelial growth factor (VEGF) to recruit MSC to form the supporting stroma of the tumor, and pericytes for angiogenesis. This MSC which is transduced with an adenoviral expression vector carrying interferon- β gene has been demonstrated to increase the production of interferon- β at the local site (*Studený et al. 2004*). This in vivo function of MSC is dependent to an extent on signals from the target tissue microenvironment. An example that can be cited here is that the tissues such as skin would have high cell turn over where there would be more signals for MSC compared to connective tissues where the high cell turnover is apparent only during healing process (*Studený et al. 2004*). In a similar fashion, MSC engineered to release interferon- β has been reported to create high local interferon- β levels in the mice glioma (*Nakamizo et al. 2005*). The neural stem cells have been reported as the delivery vehicles for the gene therapy for CNS disorders (*Muller et al. 2006*). *Liu et al. (2010)* demonstrated high-dose therapy/ autologous stem cell transplantation can improve cure rate and prolong survival time significantly in patients with nasopharyngeal T cell lymphomas (*Muller et al.*

2006). There also seems to be promise in the future for the use of the endothelial progenitor cells as the delivery vehicles for gene therapy because of their attraction towards the site of angiogenesis rather than the quiescent vasculature (*Anderson et al. 2005*). Stem cells can also be made to deliver immune-activating cytokines and other secreted proteins to brain and breast tumors (*Hayashi et al. 2011*).

CONCLUSION

As our understanding of stem-cell behaviour rapidly increases, more and more reports suggest that use of stem-cell therapy will extend well beyond regenerative medicine in the near future. The traditional therapies of chemotherapy and radiotherapy often lead to initial shrinkage of tumours but, eventual development of metastatic drug-resistant disease in the treated patients. As a result, the use of stem cells in immuno-modulation or reconstitution is one of the most important methods in cancer therapy. Due to their inherent tumortropic migratory properties, stem cells can serve as vehicles for the delivery of effective, targeted treatment to isolated tumours and to metastatic disease. In vitro, stem cells can readily be engineered by inserting specifically tailored transgenes with antitumour effects to create tumour-seeking therapeutic vehicles. Transgene effects include direct tumour-cell killing, promotion of local immune responses, oncolytic virus production, and prodrug activation schemes. Stem cell transplants can be from the bone marrow, the peripheral blood and in case of children and young adults, from the umbilical cord blood which is stored and frozen. The battle against cancer rages stronger than ever before. Advanced studies and new insights into avenues for stem-cell sourcing have shortened the probable time to realize the long awaited victory against cancer and to rescue millions of patients, their hopes and dreams from its curse.

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