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RESEARCH ARTICLE

Do Cancer Stem Cells propel tumour growth, mediating chemo resistance and radioresistance?

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Abstract

The origin and nature of cancer stem cells (CSC) still remains questionable. In addition not much is known about the reason for their resistance to various treatments and relapse in cancer patients after long treatments of chemotherapy and radiotherapy. To answer all these questions, various researchers have proposed cancer stem cell hypothesis which have two separate but related components. First hypothesis states that CSC originates by tissue stem cells through dysregulation of the normally tightly regulated process of self-renewal. However the second hypothesis states that CSC contains a cellular subcomponent that retains key stem cell properties. These two hypotheses are useful to understand of carcinogenesis and tumour cell biology. The cancer stem cell model suggests that it may be necessary to alter the current thinking in CSC treatment. Eradication of cancers may require the targeting and elimination of cancer stem cells. Thus, one must devise strategies that can selectively kill these cancer stem cells while sparing normal stem cells.

Introduction

Cancer in general is known as a dreadful disease to the public however they remain unaware of the process through which it originates. Researchers have conducted various studies on cancer stem cells (CSC) which has given rise to new discoveries which show immense potential towards developing successful therapeutic strategies for cancer treatment. However to understand these studies better we need to understand the basic biology of CSC.

CANCER STEM CELL (CSC)

Cancer stem cell (CSC) is a cell type which consists of a unique subpopulation of neoplastic cells within tumours that is highly tumourigenic and relatively resistant to standard therapies. CSCs have been identified in multiple malignancies, including leukaemia and various solid cancers (Chen et al., 2013). These CSCs maintains the growth of cancer cells through its possession of stem cell properties and these CSCs have the capacity of self-renewal, the ability to differentiate, active telomerase expression, activation of antiapoptotic pathways, increased membrane transporter activity and the ability to migrate and metastasize. Cancer stem cells were first documented in haematological malignancies patients like acute myeloid leukaemia (AML) where a small subset of cancer cells capable of forming new tumours (Wicha et al., 2006; Spillane and Henderson, 2007; Visvader and Lindeman, 2008).

CANCER STEM CELL HYPOTHESIS AND RELATED CONTROVERSIES

Currently, there is debate going on between groups of researchers about the origin and nature of CSCs. The CSCs may hold answers to some of the questions related to cancer growth. In an attempt to figure out the role of CSCs, researchers have come up with two theories/ hypotheses. These hypotheses have two separate but related components (Chen et al., 2013).

The first hypothesis explains about the cellular origin of tumours. According to this component stem cells (SC) are a natural source of cancer stem cells (CSC) since stem cells have a long time survival capability and hence genetic changes can accumulate continuously which are required for malignant transformation (Fábián et al., 2009). During normal development symmetric stem cell self-renewal causes stem cell expansion; a process is tightly regulated by components of the stem cell niche. Stem cells differentiate into a transient amplifying population that undergoes further proliferation and causes cell migration, terminal cell differentiation and apoptosis of fully differentiated cells. In the event, when stem cells divide asymmetrically one of the daughter cells remains a stem cell (Wicha et al., 2006; Sell, 2004). Aberrant differentiation of cells generates tumour heterogeneity and any further mutations or epigenetic changes in the daughter stem cell may be responsible for carcinogenesis. The major problem with this hypothesis is that it believes stability within the tumour does not consider the cancer stem cell phenotype. However, several studies have demonstrated that more differentiated cancer cells can acquire mutation or activate a transcription factor like FOXC2 and then get converted into cancer stem cells (Shipitsin and Polyak 2008).

More than 40 years ago, it was believed that tissue-specific stem cells are the cells of origin of cancer while some other research groups have proposed that cancer represents a maturation arrest of stem cells (Wicha et al., 2006; Till and Mc, 1961; Alberts et al., 2008). Stem cells are long lived in nature so accumulation of multiple mutations within cells makes them susceptible to carcinogenesis after some period of time. The women of Hiroshima and Nagasaki exposed to the atomic bomb radiation developed breast cancer approximately 20 to 30 years after exposure (Liu et al., 2005). Currently a number of studies are being carried out wherein researchers have discovered that deregulation of Wnt, Notch and Hedgehog pathways in rodent models as well as in humans leads to tumourgenesis. Defects in the Wnt signalling pathway are seen early in lung, head, neck, melanoma cancer carcinogenesis while alterations in Hedgehog signalling causes human basal carcinomas of the skin, pancreatic, gastric, prostate and breast carcinomas. Alterations in Notch signalling have been observed in human T-cell acute lymphoblastic leukemia, cervical cancer and breast cancer (Liu et al., 2005; Wicha et al., 2006; Tu et al., 2002; Dontu et al., 2003; Shackleton et al., 2006).

Second hypothesis argues that tumours are driven by cellular components that display stem cell properties. Cancer stem cells undeniably exist in many tumour types. Normal stem cells and cancer stem cells share numerous properties like self renewal, expression of cell surface markers, quality of being long lived, allowing multiple mutations over time and increasing the rate of differentiation (Jablons and He, 2006). Self-renewal property is responsible for tumourgenesis while differentiation contributes to tumour phenotypic heterogeneity. The concept of cancer, which suggests that the tumour arises from a rare population of cells with stem cell properties, is more than 150 years old. According to, *in-vitro* clonogenic assays, subpopulations of tumour cells can give rise to new tumours when transplanted into immunodeficient animals (Wicha et al., 2006; Beachy et al., 2004; Reya et al., 2001; Diehn and Clarke, 2006). The origin of CSC remains controversial. The inflammatory cells in bone marrow recruited to gastric epithelium which primary targets for mutagenesis and hence cancer stem cells are responsible for an epithelial malignancy (Houghton et al., 2004).

Transgenic mouse models provide considerable advances in understanding of the pathogenesis and development of human cancers. However, transgenic mouse systems are not able to reproduce human cancers in many conditions. This concept gained generous experimental support with the development of animal models which have stem cell properties of tumour cell subpopulations. Although xenotransplantation models are useful for explaining the hypothesis, these models have received a lot of criticism. According to some researchers mouse is a foreign environment for human cancer cells and therefore they will have full tumourigenic potential with stromal elements and cytokine signalling. In several studies, the required number of tumour cells drastically drops as compared to xenografting and transplantability of the malignancy was no longer confined to a subset of cells. This highlights the issue contemplating whether the ability of cells to adapt in new conditions rather than their absolute tumourigenic capabilities plays a major role in xenograft growth. A recent study showed that IL-4 has a significant role in colon cancer signalling. The ability of CSCs to resist cell death is mediated by IL-4, whose production is seen in the colon cancer cells. Breast, thyroid and lung cancers also produce IL-4 (Fábián et al., 2009).

According to John Dick *et al.,* (1970) experiment, when human leukaemia cells are transferred into severe combined immunodeficient (SCID) mice, small population of cancer stem cells showed that the CD34+ CD38- fraction was highly enriched for leukaemia initiating activity in transplanted recipients, while both the CD34-CD38- and CD34- fractions did not initiate leukaemia (Spillane and Henderson, 2008; Hope et al., 2004; Tan et al., 2006).

Clarke and Diehn performed an experiment on human breast cancers using the same model. In this study, using flow cytometry techniques and same model breast cancers were divided into subgroups of similar cells according to their cell surface markers. Tumour cells which contain CD44+CD24- negative lineage were separated from the main tumour mass. When CD44+CD24- negative lineage was injected into the severe combined immunodeficiency disease mice, they developed breast cancer. This experiment was repeated several times with the same breast cancer cell line to verify the results. This proved that CD44+CD24-lineage negative cells were identified as cancer stem cells (Wicha et al., 2006).

Al-Hajj et al., (2003), also obtained matching results when they isolated tumourigenic cells from human breast carcinoma by using FACS. In their experiment, they implanted fractionation of samples into the mammary pads of NOD/ SCID mice and reached the conclusion that only the CD44+CD24- lineage cells were responsible for tumour initiating activity while even a 100- fold more cell dosage from the CD44+CD24+ or CD44- did not form tumours (Al-Hajj et al., 2003).

According to Singh *et al.*, (2003) when glioblastoma stem cells were transplanted into NOD/SCID mouse brains they developed a tumour with the phenotype of CD133+ cells. However, when these CD133+ cells were compared with CD133- cells they could not form CNS tumours. These data support the hypothesis for a cancer stem cell origin for CNS tumours (Singh et al., 2003).

CHEMO-RESISTANCE AND RADIO-RESISTANCE OF CANCER STEM CELLS

Medicine and science have proposed multiple agents for the treatment of cancer. Most cancer patients experience a relapse of cancer irrespective of prolonged treatments. Why do tumours fail to respond to treatments or reoccur after successful remission by chemotherapy and radiotherapy? These days researchers are getting closer to unlock these mysteries. These and many other raised questions are answered by the new concept of Cancer Stem Cells. According to the theory, most current therapies like radiation and chemotherapy kill the most rapidly dividing cells in tumour. In contrast, CSC usually divide at very slow rate which may increase their resistance to treatments. This resistance to chemotherapy maybe acquired by a range of mechanisms like mutation or over expression of the drug target, inactivation of the drug or elimination of the drug from the cell (Dean et al., 2006).

In addition to that, the effectiveness of chemotherapy can be minimized by drug delivery via poor absorption, excessive metabolism, environmental changes or poor penetration of sites but the main cause of failure of chemotherapy is the resistance of CSC against anticancer compounds is known as drug resistance. The ability of cells to acquire resistance to multiple compounds is known as multidrug resistance. This resistance is mainly caused by the increased expression of multidrug efflux transporters which are localized chiefly in the plasma membrane (Shipitsin and Polyak, 2008; Reya et al., 2001; Gottesman and Ambudkar, 2001; Cervenak et al., 2006; Leonard et al., 2003; Ishikawa et al., 2007; Robey et al., 2009; Gottesman et al., 2002). In 1970, it was proposed that there should be mechanism present that protects stem cells from mutations and epigenetic changes. There are many mutations that arise during DNA replication and these mutations can be repaired by stem cells during each division of stem cells. If this is also the case for CSC, then CSC mat become resistant to many treatments that kill other tumour cells but not actual CSC. The most striking example is gastrointestinal stromal tumour which is resistant to imatinib treatment and this treatment inhibits c-kit gene (Alberts et al., 2008; Van der Zwan and Dematteo, 2005).

Several investigators have provided evidence that Abl tyrosine kinase inhibitor termed imatinib may be relatively or even completely resistant to the CML stem cells. The CML stem cells that survived imatinib treatment regenerated the tumour providing evidence in support of the important role played by cancer stem cells in the progression of the disease (Michor et al., 2005).

CML stem cells may share biological properties with their normal counterparts that would make them inherently poor targets for imatinib. This is caused by high expression of the multidrug resistance-1 gene which encodes an efflux pump protein. This efflux pump is capable of transporting imatinib out of cells and may also limit the cellular uptake of imatinib (Jones et al., 2004). A recent study investigated the expression of MDR transporter ABCG2 and stem cell markers in therapeutically naïve cancer cells isolated from lung, breast, ovarian and gastric cancers. According to this study 58% fraction of cancer stem cells tested positive for ABCG2 (Romano, 2006). Such a finding indicates a subpopulation of chemo-resistant cancer stem cells expressing the MDR transporter ABCG2. The CSCs existence has intense implications for cancer biology and therapy because eradication of CSCs is important in achieving cure.

Quiescent CSCs are thought to be "more resistant to chemotherapy" and targeted therapy. The study by Ishikawa et al., (2007) supported the concept that certain CSCs enter a quiescent state and allow the majority of human leukaemia stem cells to remain in the G_0 phase of the cell cycle when they are xenotransplanted into mice (Ishikawa et al., 2005).

According to Williams *et al.,* (1987) and Donohue *et al*., (1994) when testicular cancer patients were treated with platinum-based chemotherapy, they often left residual masses behind. These masses had to be removed surgically but if there were any immature cancer cells in the tumour observed, the patients had to be treated with more chemotherapy or else they had a substantial chance of relapsing. On the other hand, if the tumour contained only mature teratoma then such patients did not require further therapy and they were often cured (Williams et al., 1987; Donohue et al., 1994).

Ionizing radiation represents the most effective therapy for glioblastoma which is one of the most lethal forms of human malignancies. Patient suffering from glioblastomas survive less than 12 months because of resistance to radiation and other treatments (Legler, 1999). Numerous experimental and clinical findings provide evidences that tumours after radiotherapy originate from at least one surviving cancer stem cell and permanent tumour control requires inactivation of all cancer stem cells. Large number of cancer stem cells can not be killed by low radiation doses, however after a threshold dose, local tumour increases sigmoidally with increasing radiation dose (Baumann et al., 2008).

Phillips *et al.* (2007) and Bao *et al.* (2006) provide evidence that breast and glioblastoma stem cells are radioresistant when they are compared with these respective mature cancer cells. These researchers studied xenografts from primary glioblastoma multiforme specimens regarding established cell lines. CD133+ cells were identified as the tumourigenic population in primary glioblastoma multiforme specimens but Bao *et al.* (2006) found that CD133+ cells were radioresistant when compared with CD133− tumour cells. CD133+ cells were accumulated after irradiation *in vitro* and *in vivo* xenografts models. They observed that the CD133+ cells activated the DNA damage checkpoint response more effectively than CD133– cells in human glioma xenografts and primary glioblastoma specimens. Therefore, this CSC population has evolved a more efficient DNA damage repair system than the bulk of the tumour which confers resistance to radiation treatment. As a result, the percentage of CD133+ derived cells after irradiation increased more than fourfold than CD 133-. This confirms that CD133+ tumour cells have greater radioresistance than CD133- cells *in vitro* (Diehn and Clarke, 2006; Bao et al., 2006; Phillips et al., 2007; Bao, 2006).

Conclusions

Research has been indicating in recent years that malignant tumours are initiated and maintained by a population of cancer stem cells which share similar biological properties to normal adult stem cells. Self-renewal and differentiation potential are classical features of stem cells. Cancer stem cells can self-renew and produce cancer cells instead of normal cells. However, the origin of the cancer stem cell remains elusive. Cancer stem cells undoubtedly exist in many tumour types. Cancer stem cells are caused by genetic or epigenetic events in multipotential stem cells like MSCs, tissue-specific stem cells, progenitor cells, mature cells and cancer cells as well as tumours are driven by cellular components that display stem cell properties. Besides the current development of cancer therapeutics based on tumour regression may produce agents that kill differentiated tumour cells while CSC becomes resistance to all treatments. Therefore development of more effective cancer therapies requires targeting this important cell population.

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