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Stem Cells, Cancer and Cancer Stem Cells

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Abstract—*Stem cell biology has been reached to a newer level.It has been found that stem cell exist in haematopoitic system. HSC arise from mice and humans and have been shown tobe responsible for the generation and regemration of the blood forming and immune system. Perhaps most important and usefull property of stem cells is that of self renewal.Cancer stem cells -rare cells with indefinite potential for self renewal the derive tumorigenesis. Property of stem cells self renewal is been very usefull. And the study of mechanims of this self renewal have given a possibility that tumor cell might rise from normal cells.*

1. INTRODUCTION

This article is mainly based on how stem cells prolifirate with there ability to regenerate themselves into the mass of cells. It is been found that normals cells evolute themselves into stem cells which is leading its way to the cancer stem cells.Into the mass of this cancer cells only few have the ability to divide and increase thier mass while some cells act as a normal stem cells.

2. RESEARCH PAPER:STEM CELLS CANCER AND CANCER STEM CELLS

Stem cells can also be defined as cells that have the ability to divide themselves through self renewal and to generate mature cells of a particular tissue through differentiation. In most tissues, we can hardly find a stem cells.stem cells can only be found at speicific parts of the body such as during the formation of embryo which are called as embronic stem cells,in bone marrow etc.

As a result study of stem cells should be done carefully in order in order to observe there properties. Although it seems reasonable to propose that each tissue arises from a tissue-specific stem cell, the rigorous identification and isolation of these somatic stem cells has been accomplished only in a few instances. For example, haematopoietic stem cells (HSCs) have been isolated from mice and humans1–4, and have been shown to be responsible for the generation and regeneration of the blood-forming and immune (haematolymphoid) system Stem cells from a variety of organs might have the ability to be used for therapy in the future, but HSCs — the vital elements in bone-marrow transplantation — have already been used extensively in therapeutic settings . The recent discovery that bone marrow6–8, as well as purified HSCs9,10, can give rise to non-haematopoietic tissues suggests that these cells may have greater differentiation potential than was assumed previously. Definitive experiments are needed to determine whether the cells from the bone marrow that are capable of giving rise to different non-haematopoietic lineages are indeed HSCs or another population. If further studies support the idea of HSC plasticity, this will undoubtedly open new frontiers for understanding the developmental potential of HSCs, as well as expand their therapeutic application. As the characteristics of HSCs, their differentiation potential and clinical applications have been covered in earlier reviews, here we discuss emerging evidence that stem cell biology could provide new insights into cancer biology. In particular, we focus on three aspects of the relationship between stem cells and tumour cells: first, the similarities in the mechanisms that regulate self-renewal of normal stem cells and cancer cells; second, the possibility that tumour cells might arise from normal stem cells; and third, the notion that tumours might contain ‘cancer stem cells’ — rare cells with indefinite proliferative potential that drive the formation and growth of tumours. Through much of this review we focus on the haematopoietic system because both normal stem cells and cancer cells from this tissue are well characterized. Moreover, cancers of the haematopoietic system (that is, leukaemias) provide the best evidence that normal stem cells are the targets of transforming mutations, and that cancer cell proliferation is driven by cancer stem cells.

Self-renewal of haematopoietic stem cells One of the most important issues in stem cell biology is understanding the mechanisms that regulate self-renewal. Self-renewal is crucial to stem cell function, because it is required by many types of stem cells to persist for the lifetime of the animal. Moreover, whereas stem cells from different organs may vary in their developmental potential, all stem cells must self-renew and regulate the relative balance between self-renewal and differentiation. Understanding the regulation of normal stem cell self-renewal is also fundamental to understanding the regulation of cancer cell proliferation, because cancer can be considered to be a disease of unregulated self-renewal. In the haematopoietic system, stem cells are heterogeneous with respect to their ability to self-renew. Multipotent progenitors constitute 0.05% of mouse bone-marrow cells, and can be divided into three different populations: longterm self-renewing HSCs, short-term self-renewing HSCs, and multipotent progenitors without detectable self-renewal

potential2,11. These populations form a lineage in which the long-term HSCs give rise to short-term HSCs, which in turn give rise to multipotent progenitors11. As HSCs mature from the long-term self-renewing pool to multipotent progenitors, they progressively lose their potential to self-renew but become more mitotically active. Whereas long-term HSCs give rise to mature haematopoietic cells for the lifetime of the mouse, short-term HSCs and multipotent progenitors reconstitute lethally irradiated mice for less than eight weeks.

The stem cell niche is composed of a group of cells in a special location that functions to maintain stem cells.

The niche is a physical anchoring site for stem cells, and adhesion molecules are involved in the interaction between stem cells and the niche and between stem cells and the extracellular matrix.The niche generates extrinsic factors that control stem cell number, proliferation, and fate determination. Many developmental regulatory signal molecules, including hh, Wnts, bone morphogenetic proteins (BMP), fibroblast growth factors, and Notch, have been shown to play roles in controlling stem cell self-renewal and in regulating lineage fate in different systems.

The niche controls normal asymmetrical division of stem cells. This has been shown in invertebrates; whether it is conserved in the mammalian system is still an open question.

Normally, at least in the hematopoietic, intestinal, and hair follicle systems, the niche maintains stem cells primarily in a quiescent state by providing signals that inhibit cell proliferation and growth as evidenced by the ability of stem cells to retain bromodeoxyuridine labeling for a relatively long period of time (20–24). Only upon receipt of a stimulating signal does the stem cell become activated to divide and proliferate . Therefore, stem cell proliferation depends on dynamic niche signaling. Maintaining a balance between the proliferation signal and antiproliferation signal is the key to homeostatic regulation of stem cells, allowing stem cells to undergo self-renewal while supporting ongoing tissue regeneration (25). Any genetic mutation that leads stem cells to become independent of growth signals, or to resist antigrowth signals, will cause the stem cells to undergo uncontrolled proliferation and possible tumorigenesis . In this review, we will use recent studies of signaling regulation of stem cells in bone marrow, intestine, and skin to show the importance of this balanced control of stem cells by both growth-promoting and growth-inhibiting signals.

3. CANCER STEM CELLS AND ORGANOGENESIS

A tumour can be viewed as an aberrant organ initiated by a tumorigenic cancer cell that acquired the capacity for indefinite proliferation through accumulated mutations. If one views a tumour as an abnormal organ, then the principles of normal stem cell biology can be applied to understand better how tumours develop (reviewed in ref. 45). In fact, many observations suggest that analogies between normal stem cells and tumorigenic cells may be appropriate. Both normal stem cells and tumorigenic cells have extensive proliferative potential and the ability to give rise to new (normal or abnormal) tissues. Both tumours and normal tissues are composed of heterogeneous combinations of cells, with different phenotypic characteristics and different proliferative potentials46–49. Because most tumours have a clonal origin50–52, tumorigenic cancer cells must give rise to phenotypically diverse progeny, including cancer cells with indefinite proliferative potential, as well as cancer cells with limited or no proliferative potential. This suggests that tumorigenic cancer cells undergo processes that are analogous to the self-renewal and differentiation of normal stem cells. Although some of the heterogeneity in tumours arises as a result of continuing mutagenesis, it is likely that heterogeneity also arises through the aberrant differentiation of cancer cells. It is well documented that many types of tumours contain cancer cells with heterogeneous phenotypes reflecting aspects of the differentiation that normally occurs in the tissues from which the tumours arise. The variable expression of normal differentiation markers by cancer cells in a tumour suggests that some of the heterogeneity in tumours arises as a result of the anomalous differentiation of tumour cells. Examples of this include the variable expression of myeloid markers in chronic myeloid leukaemia, the variable expression of neuronal markers within peripheral neurectodermal tumours, and the variable expression of milk proteins or the oestrogen receptor within breast cancer. In other words, both normal stem cells and tumorigenic cells give rise to phenotypically heterogeneous cells that exhibit various degrees of differentiation. Thus, tumorigenic cells can be thought of as cancer stem cells that undergo an aberrant and poorly regulated process of organogenesis analogous to what normal stem cells do. It is perhaps not surprising that tumorigenic cells behave in ways that are analogous to normal stem cells given that cancer cells tend to display functional and phenotypic attributes of the normal cells from which they are derived.

4. THE IMPLICATIONS OF SOLID CANCER STEM CELLS

If the growth of solid cancers were driven by cancer stem cells, it would have profound implications for cancer therapy. At present, all of the phenotypically diverse cancer cells are treated as though they have unlimited proliferative potential and can acquire the ability to metastasize. For many years, however, it has been recognized that small numbers of disseminated cancer cells can be detected at sites distant from primary tumours in patients that never manifest metastatic disease. One possibility is that immune surveillance is highly effective at killing disseminated cancer cells before they can form a detectable tumour. Another possibility is that most cancer cells lack the ability to form a new tumour such that only the dissemination of rare cancer stem cells can lead to metastatic disease. If so, the goal of therapy must be to

identify and kill this cancer stem cell population. If solid cancer stem cells can be identified prospectively and isolated, then we should be able to identify more efficiently new diagnostic markers and therapeutic targets expressed by the stem cells. If tumour growth and metastasis are driven by a small population of cancer stem cells, this might explain the failure to develop therapies that are consistently able to eradicate solid tumours61. Although currently available drugs can shrink metastatic tumours, these effects are usually transient and often do not appreciably extend the life of patients. One reason for the failure of these treatments is the acquisition of drug resistance by the cancer cells as they evolve; another possibility is that existing therapies fail to kill cancer stem cells effectively. Existing therapies have been developed largely against the bulk population of tumour cells because they are often identified by their ability to shrink tumours. Because most cells with a cancer have limited proliferative potential, an ability to shrink a tumour mainly reflects an ability to kill these cells. It seems that normal stem cells from various tissues tend to be more resistant to chemotherapeutics than mature cell types from the same tissues. The reasons for this are not clear, but may relate to high levels of expression of anti-apoptotic proteins or ABC transporters such as the multidrug resistance gene. If the same were true of cancer stem cells, then one would predict that these cells would be more resistant to chemotherapeutics than tumour cells with limited proliferative potential. Even therapies that cause complete regression of tumours might spare enough cancer stem cells to allow regrowth of the tumours. Therapies that are more specifically directed against cancer stem cells might result in much more durable responses and even cures of metastatic tumours.

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