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The Link Between Stem Cells and Neoplasia

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Abstract: Stem cells and cancer have been found to be amazingly closely intertwined with one another in such a way that they form a meshwork that can help to explain the genesis of cancer and more importantly lead the way to an effective cure to this dreaded disease. In this study, the link between stem cells and neoplasia is bridged and novel therapies for cancer are reviewed.

Key words: Stem cells, neoplasia, cancer, disease

INTRODUCTION

It is interesting that one establishes links between stem cells and cancer and highlight the parallels and overlaps between these two fields.

Stem cells and cancer have been found to be linked tightly to each other such that at the heart of every tumor, some researchers believe, lie a handful of aberrant stem cells that maintain the malignant tissue (Wade, 2006).

In fact, supporting this hypothesis lie a number of findings which all resulted in the discovery of cancer stem cells in several types of neoplastic growth.

Identification of cancer stem cells: The first identification of cancer stem cells by John Dick and his collaborators at the University of Toronto was in certain types of leukemia. It is quite understandable that stem cells were first detected in leukemia as opposed to solid tumors since the latter were impossible to distinguish by means of their surface-protein, a technique which was nonetheless established for hematopoietic progenitor cells. However, since the first discovery in 1997, Dr. Michael Clarke (2003), tracked cancer stem cells in breast tumors. Cancer cells with stem-like properties have also been found in human brain tumors in 2004 by Dr. Peter Dirks of the University of Toronto and later they have been identified in bone cancer by Dr. C. Parker Gibbs of the University of Florida (Wade, 2006).

In fact, it seems that cancer cells with stem-like properties reside in every neoplastic growth and this is supported by Dr. Gary Gilliland of Harvard stating that these types of cells have been reported in every malignant growth examined so far (Wade, 2006).

What is an interesting finding is the fact that the majority of cancer cells within a tumor are unable to proliferate further. The malignancy of a tumor is due to a limited number of cells which have these stem-like properties and which thus confer the ability to cancer cells to divide uncontrollably and colonize secondary areas. This finding creates a new paradigm of the underlying concepts involved in carcinogenesis.

One can conclude thus, that not all the cells within a neoplastic growth are equally malignant. An experiment conducted in 1961 where cells extracted at random from a tumor are injected at a different site further solidifies this conclusion. If all the cells extracted had the ability to proliferate, another neoplastic growth would soon be established at the new site. However, it was reported that if a small sample is used, the probability is that no tumor forms. In fact, it requires more than a million cell for a tumor to be induced at a secondary site. This backs the concept that the bulk of cells within a tumor are not malignant and only a minor population supports the proliferation of the cancer, indicating the functional heterogeneity of cancer cells. The rest of the cells may be supportive tissue, acting as a scaffold, providing mechanical support to the other cells (Department of Health and Human Services, 2005).

The identification of cancer stem cells in several tumors examined may raise certain questions such as Is neoplasia the result of aberrant changes in the cell cycle of the cells making up the organ itself such as brain cells, for example, or is it the consequence of abnormal divisions of the stem cells that reside in that organ?

In fact some hypotheses suggest that cancer stem cells may arise from a mutation in their DNA and thus self-renewal fails to be tightly regulated as happens under

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normal conditions. Moreover, these mutations in the stem cell population may have time to accumulate. Another possibility is that when a stem cell divides into another stem cell and a progenitor cell, the latter, instead of differentiating, acquires the property of self-renewal. All in all, cancer stem cells seem to originate from failure of control of the stem cell pool which is usually kept under scrutiny (Wade, 2006).

Cancer stem cells derived from a wider spectrum of tumors throws more light on the role of these stem cells in the overall pathogenesis of the tumor. In order to grasp better the pathogenesis of tumors at all levels, cancer stem cells derived from a wider spectrum of tumors should be examined as well as focusing on the genetic, molecular and biochemical mechanisms as well as the stem-cell niche that all have vital roles in controlling stem cell renewal and differentiation (Wade, 2006).

IMPLICATIONS OF THE PRESENCE OF STEM CELLS IN TUMORS

An interesting aspect that emerges from the notion of cancer stem cells is that assessment of the percentage of cancer cells that have the potential to initiate the tumor and thus are responsible for its proliferation may be related to the rate of spread of the cancer and thus throws light to its degree of malignancy. The number of stem cells responsible for carcinogenesis varies from one type of cancer to another. For example, in acute myeloid leukemia only one out of million cells examined had the ability to maintain proliferation, representing a frequency of 0.1-1%. On the other hand, mammary tumor stem cells make up 2% of the total population while cancer stem cells in brain may account for 0.3-25% of the tumor cells (Department of Health and Human Services, 2005).

Conducting these types of experiments in a wider spectrum of types of cancer can throw more light on the role of these stem cells in cancer malignancy.

Another promising area to be investigated is that of delving into the control of these stem cells at the molecular and genetic level and try to grasp what goes wrong in the cell cycle of the previously normal stem cells residing within a particular tissue. What are the intrinsic and extrinsic factors that trigger stem cells to start dividing abnormally or cause the progenitor cell to renew itself instead of differentiating?.

Needless to say, it is crucial to identify the genes and proteins that govern the processes of self-renewal both in embryonic and adult stem cells.

The polycomb gene *Bmi-1* and *Wnt* seem to be vital for the cell fate and for controlling self renewal and thus are probable to be involved in supporting and tuning the cancer stem cells' population. The polycomb gene *Bmi-1* is crucial for embryogenesis, control of the cell cycle and lymphopoiesis acting as repressor of transcription of certain genes. In fact, deletions of this gene in mice leads to a gradual loss of hematopoietic lineages because the stem cells are unable to self renew (Department of Health and Human Services, 2005).

In an interesting experiment, genes known to cause leukemia were introduced in mice lacking the *polycomb* gene. Leukemia was indeed induced in these mice but the cancer was unable to spread to other areas, thus highlighting the need of this gene for stem cells to be able to maintain themselves and self-renew (Department of Health and Human Services, 2005).

The Wnt signal pathway has also been implicated in hematopoietic malignancy and colon carcinoma and is believed to be essential for controlling the balance between self-renewing cells and others that differentiate. In fact, it is believed to switch off genes in certain cells to prevent them from self-renewing and thus undergo differentiation. Mutations in genes involved in this cascade of events fail to switch off or silence certain genes, resulting in a continuously transcriptionally-active state. This, obviously, disrupts the control of the stem cell population (Department of Health and Human Services, 2005).

Hedgehog activity is also implicated in certain lung, brain, esophagus, skin and other types of cancers. Experiments have shown that suppressing hedgehog activity results in killing cancer stem cells which need it for maintaining the cancer in a proliferative state. This means that targeting the pathways involved, by means of chemotherapeutic drugs, is highly promising although side effects to other healthy tissues may be inevitable. Hedgehog together with Wnt are crucial for stem cell proliferation in circumstances of organ damage and this may explain how malignancies tend to appear after chronic irritation to an organ such as alcohol damaging the liver or chronic acid reflux damaging the epithelium of the esophagus.

Such experiments that are currently being conducted and their results raise high hopes for the future of cancer research and are essential to guide us through a better understanding of the pathogenesis of cancer at the molecular and genetic level, with the goal of establishing much more effective and specific therapies. In fact, based on the knowledge that cancer stem cells are responsible for the proliferation of the tumor, one may target chemotherapeutic agents specifically to these cells which are actually the engine of metastasis rather than the entire bulk of the tumor.

The weak point of current chemotherapeutic agents is that they try to destroy the major part of the cells making up the tumor without specifically targeting the cancer stem cells which are the main threat and which represent a very small minority of the entire tumor. In fact, without being dramatic, one can say that the quest for cancer is so close, yet so far away (Stanford University, 2004; Wade, 2006).

This is highlighted in treatment of chronic myelogenous leukemia using the anticancer drug Gleevac which does not result in complete regression of the disease. This may be the result of failure of this drug to attack specifically cancer stem cells that are ultimately responsible for cancer proliferation and are the engines of metastasis (Wade, 2006). In the account that follows, promising cancer therapies are discussed, depicted by the use of two main examples, namely chronic myelogenous leukemia and breast tumor which is a solid tumor. Using these types of cancer as an example, helps one to grasp the essence that lies in destroying cancer stem cells rather than focusing on killing all tumor cells randomly.

If this reasoning is viable, a stumbling block is the elimination of these cancer stem cells without killing the otherwise healthy stem cells. One way of circumventing this hurdle may be based on the fact that cancer stem cells are more energy-consuming than other stem cells and thus drugs that inhibit normal cell processes and result in a depletion of useful metabolites affect much more cancerous stem cells than normal ones (Wade, 2006).

CANCER STEM CELLS IN CHRONIC MYELOGENOUS LEUKEMIA

Sean J. Morrison from University of Michigan's Center for Stem Cell Biology claims to have conducted studies that propose means of distinguishing healthy stem cells from cancerous ones (University of Michigan, 2006). In a study in the journal *Nature*, Morrison's team explained how they not only unraveled distinguishing characteristics of the two types of stem cells but also established drugs that result in different behaviour between the two types. Thus, these differences can be therapeutically exploited to ensure efficient cancer cure (University of Michigan, 2006).

It was found that deletion of the *Pten* gene from adult hematopoietic stem cells in mice induces leukemia as a result of the production of leukemic stem cells, the latter having the ability to proliferate and thus are capable of regenerating the tumor at secondary sites. Apart from enhancing leukemic stem cells, deletion of the *Pten* gene also led to depletion of the healthy stem cell pool. The significant observation was that while the *Pten* gene is crucial for survival of the healthy stem cells, cancer stem cells can endure without this gene (University of Michigan, 2006).

Needless to say, this is very promising for the demarcation between normal and cancer stem cells and provides a way of establishing drugs that target specifically cancer stem cells. This goal can be achieved by using drugs that act on the metabolic pathway in which *Pten* acts. Cancer and normal stem cells should respond differently to such a chemical. The team used the drug rapamycin which suppresses this metabolic pathway and is usually used to transplant rejection. The results showed that administration of this drug leads to a regression of leukemic stem cells while enhancing normal stem cells. In fact, delivering this drug in mice immediately after deleting their *Pten* gene inhibited leukemia to develop whilst those mice that already had leukemia lived longer while put on the drug (University of Michigan, 2006).

These findings depict the importance of unraveling the factors regulating the control of the normal stem cell pool so that more specific therapies with less toxic side-effects are produced. However, Morrison underlines the fact that these results are limited to mice and are not yet applied to humans. More trials need to be conducted to verify the effectiveness of such drugs in humans as well.

Jamieson and her team together with other collaborators at Stanford, the University of Toronto, discovered that the cancer stem cells that were responsible for the flourishing of the tumor resembled hematopoietic progenitor cells namely the granulocyte-macrophage progenitors. This meant that the cancer stem cells were derived from the hematopoietic progenitor cells in the bone marrow that started renewing themselves uncontrollably rather than from healthy stem cells (Stanford University, 2004).

A distinguishing characteristic between cancer stem cells and their progenitors was Beta-catenin, a protein typically present in embryonic stem cells, conferring their property of self-renewal. This protein was also present in the nucleus of cancer stem cells accounting for their ability to divide uncontrollably. What is interesting is the fact that many patients who did not respond to the anti-cancer drug Gleevec, possessed large amounts of this protein, thus confirming the relation between this protein and cancer endurance (Stanford University, 2004).

Beta-catenin forms part of a cascade of events triggered by Wnt protein which, under normal conditions, is active in cells that are continuously dividing such as embryonic or stem cells. Those adult stem cells that do not produce Wnt have a limited number of divisions. The

team revealed that inhibiting the abnormal activity of these proteins prevents stem cells from proliferating uncontrollably. It follows therefore, that at the root of several types of cancer lie mutations in proteins constituting the Wnt pathway. In fact, mutations in any protein of the Wnt pathway which result in activation of the cascade of events are theoretically potent to trigger neoplastic growth (Stanford University, 2004).

It is only when drugs are produced that inactivate these proteins that efficient cancer therapy will have legs to stand on.

Recently, it has also been found that stem cells from bone marrow can be used as a vehicle to deliver anti-tumor proteins such as interferon-beta and interferon-alpha to the site of neoplasia thus providing a means to inhibit progression of chronic myeloid leukemia (Stanford University, 2004).

This is a very promising aspect of oncology that can lead to suppress cancer proliferation by targeting the cells responsible for the seedling and colonization of tumor at secondary sites.

CANCER STEM CELLS IN BREAST TUMOURS

Apart from leukemia, solid tumors were also found to contain cancer stem cells. In fact, Michael F.Clarke and Max S.Wicha together with their collaborators at the University of Michigan have detected these stem cells in breast tumors (Touchette, 2003). Cells from nine human breast tumors and metastases were examined and the researchers managed to classify the tumor cells into 2 different categories based on their markers. The distinction became clear when they transplanted these two types of cells into mice. The type with the ability to proliferate resulted in carcinogenesis even if small number of cells were injected. This was opposed to the cells which lacked the ability to colonize which even when relatively large quantities were used, no tumor developed (Touchette, 2003).

A crucial goal is to unravel what renders the cancer stem cells distinct from the rest of the other cells. This can be identified at the genetic level by using DNA microarrays to detect genes that are only active in cancer stem cells and thus are the culprits for the colonizing properties of the tumor.

An important milestone towards a better understanding of cancer stem cells has been their actual identification from the other bulk cells forming the tumor. This was possible by analyzing the cell surface markers using specific antibodies and flow cytometry to isolate heterogeneous cancer cells. A particular group of cells

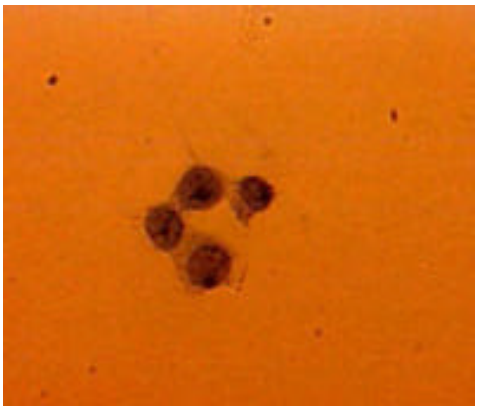

Fig. 1a: Cancer stem cells isolated from human breast cancer lost the ability to Arbor (2003)

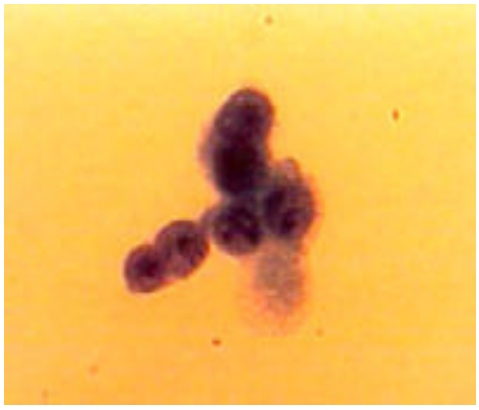

Fig. 1 b: Cells from human breast cancer that have spread and form tumor (Arbor, 2003)

was found to express the protein marker CD44 but had low levels, if any, of CD24. These cells had the ability to seed new tumors at secondary sites which had the same composition of cells as the original tumor and more significantly, were common to all but one of the tumors they were sampling. The overall consistency of the markers in the majority of the tumors is a very promising lead (Arbor, 2003).

Figure 1 (a and b) are images portraying the two main groups of different cells in a breast tumor and how they stain differently with cell surface markers.

CONCLUSION

Research on cancer stem cells is being conducted at an extremely great pace. Science and medicine will have championed an important milestone if the stem cells

responsible for cancer metastasis are understood at the molecular, biochemical and genetic level. This knowledge will be the key to opening doors that lead to effective chemotherapeutic drugs, targeting to destroy the cells that ultimately pose the major threat. Hopefully, if this is achieved, cancer therapy will no longer be science-fiction but a concrete aspect of medicine based on molecular and genetic basis.

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