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Editorial

Role of Cancer Stem Cells in Hepatocellular Carcinoma in Albino Rat

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Cancer stem cells (CSCs) are cancer cells found within tumors that carry the same characters of normal stem cells, especially the capability to give rise to all cell linage found in a particular cancer sample and the potential to proliferate extensively [1].

Cancer stem cells (CSCs) were first hypothesized in the past 40 years, but only in the past years these cells were found to have role in hematological malignancies. More recently CSCs were found to play a pivotal role in some solid tumors such as liver, prostate, breast, brain, and colon [2].

For the last decades, the most acceptable theory explaining cancer initiation and progression was that cancer derives from serials of genetic mutations occurring in the normal somatic cells. These mutations resulted in enhanced proliferation, inhibition of differentiation, and reduced capacity to undergo apoptosis [3]. Moreover they added that each mutation would result in progressive "dedifferentiation" so that the tumor cells would continually lose their mature, tissue-specific functions but as the differentiated cells have limited life spans. It would be difficult for any given cell to acquire all the mutations necessary to become transformed, thus explaining the relatively uncommon occurrence of transformation.

It has been suggested that the origin of these cells that have the ability to divide progressively carrying these oncogenic mutations can be normal stem cell transformed into cancer cells, and then cancer cells would proliferate indefinitely and form a tumor [4].

Histological evidence of progenitor cell proliferation can be seen in much liver pathology including hemochromatosis, alcoholic liver disease, and viral hepatitis. Each of these diseases carries with it an increased risk of hepatocellular carcinoma (HCC) development [5].

CSCs have been characterized in solid tumors using a variety of stem cell markers, including cluster of differentiation 90 (CD90) or (Thy-1) expressed mainly in leukocytes and is involved in cell-cell and cell-matrix interactions. CD90 is also expressed by bone marrow-derived mesenchymal stem cells and hepatic stem/progenitor cells (HSPCs) [6].

CD90 is expressed by hepatic stem/progenitor cells during liver development, but infrequently in the adult liver. $CD90^+$ cells exhibit stem cell like properties [7].

Another marker is CD133 which is a trans-membrane glycoprotein; CD133 was first identified as a human hematopoietic stem cell marker. It has since been shown to identify stem cells and tumors from several tissues. CD133 is marker of circulating endothelial progenitor cells (EPCs) in HCC. CD133 is also a valuable marker and is expressed in 1% to 5% of human HCC [8].

CD44 is a cell surface adhesion molecule mediating multiple signaling pathways which has been used as a CSC marker in leukemia, head or neck cancer and pancreatic tumors [9].

$CD90^+$ and $CD44^+$ cells also may serve as a sensitive and specific marker for cancer stem cell in hepatocellular carcinoma; CD44 modulates the biological activity of the $CD90^+$ CSCs [7].

Identification of the markers for liver tumor cells with stem-like properties affords the possibility to isolate and study liver cancer at its root. Such studies may lead to the development of therapies with the potential to bring liver cancer stem cells back under control, or eradicate them entirely.

Our work was designed to identify the markers for liver tumor cells with stem-like properties. Also to assess whether liver cancer stem cells are the source of initiation and progression of hepatocellular carcinoma through examining their tissue specificity i.e. CD markers: CD90, CD133, CD44. Also to track the progression of cancer stem cell during different stages of liver injury such as early and late cirrhosis and finally cancer.

The quick development of the CSC field, combined with genome-wide screening techniques, has allowed for the identification of essential new CSC markers and pathways, and these discoveries have added to one of the most significant developments in cancer treatment. However, several important issues still remain to be determined.

Normal stem/progenitor cells also share most of the major pathways important to CSCs development and differentiation and drugs targeting these pathways could have an unfavorable effect on normal cells. For example, scanty information is known about CSC directed therapies (e.g. targeting CD133 in $CD133^+$ liver CSCs).

Initial results are favorable, but its potential short- and long-term side effects of these therapies are still uncertain. Such non-specific therapies will lead to tissue and/or organ damage due to the exhaustion of the reserve/regenerative stem cells.

Such treatment with unknown targets may lead to acute and irreversible organ failure due to targeting the wrong cells. Therefore, it is serious in demarcating the molecular differences between CSCs and their tissue specific stem cell equivalents, to prevent damage to normal somatic stem cells and to safeguard selectively targeting CSCs. This growing knowledge base should have the potential to clearly identify candidate genes and pathways that are important for CSC survival and propagation but are not important for normal stem

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cell function.

It worth to mention that; CSCs obviously have a multifactorial pathogenesis rather than being regulated by a single signaling pathway, and hence targeting single molecules or pathways may have a limited profit in treatment.

On the other hand use of combinations of therapies may be needed to overcome the complicated network of signaling pathways, and eventually inhibit the signaling that controls tumor growth and survival. However, use of more than one regimen can lead to tolerability and drug-drug interaction problems, and consequently an alternative approach is to target multiple factors through the use of molecularly targeted agents.

It is sensible to understand which combination regimen is the most efficient for impeding CSC survival and propagation with the least impact on normal stem cell function. This requires more investigations CSCs markers, when a sufficient number of CSC markers become available and an ideal combination therapy identify, CSC-specific therapies might be developed that preserve healthy stem cells and thus diminish side effects and maintain regenerative tissue capacities.

Findings made in the CSC field will have a feed back into other zones of stem cell research because many marker gene products found in CSCs also share with the normal stem cell population. It is also predictable that a better understanding of the processes that control autonomous growth, differentiation and cell migration will contribute to novel regenerative-medicine-based treatments that will transform therapeutic strategies and bring renewed hope to cancer patients.

Targeting CSCs using nanotechnology can be also an interesting topic for further study in the future. Early elimination of the disease could be possible through targeting certain cells and can be of great value to predict and treat HCC.

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