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Foreword: "Targeting signaling pathways in stem cells"

This special issue of Advances in Biological Regulation deals with significant advances that have been made in the past 10 years in the field of cancer initiating cells (CICs) also known as cancer stem cells (CSC) and leukemia stem/initiating cells (LSCs/LICs). CICs represent a reservoir that is believed to drive relapse and resistance to chemotherapy in many different types of cancers. CICs are the key cells in the tumor possessing the critically capacity for self-renewal. They can give rise to the generation of heterogeneous lineages of cancer cells that comprise the tumor. While the origins of CICs are not clear; it has been speculated that CICs can arise from stem, progenitor or even differentiated cells. CICs are often thought to be resistant to classical cancer treatments such as chemotherapy, radiation and surgery and persist after "standard" treatments or may evolve, or be selected for, after targeted therapeutic approaches. After therapy, CICs may repopulate the patient with a more aggressive, metastatic or drug resistant cancer. Thus it is essential to develop novel approaches to target CICs. The development of appropriate targeting techniques is a very active area of research.

CICs are normally quiescent and for this reason highly resistant to chemotherapy. This property often allows them to evade treatment and give rise to disease relapse. CICs may differ from the bulk of the tumor cells (BC) present in the cancer patient as the CICs have some properties of stem cells. CICs are normally dormant or slowly replicating and hence not as sensitive to anti-mitotic drugs as BCs. CICs may undergo asymmetric division to yield a cell with CIC properties which have certain stem cell properties and also produce a more differentiated BC cell. CICs can yield the differentiated cells present in the original cancer as well as therapy-resistant cells. Gene expression profiling experiments have demonstrated that CICs may exhibit patterns of gene expression more similar to stem cells than to the BCs. CICs often have elevated telomerase and DNA repair activities, as well as, membrane bound ATP-binding cassette transporters (ABC "drug" transporters) whose normal functions are to exclude xenobiotics.

The first cancer stem cells were observed and documented in acute myeloid leukemia approximately 20 years ago. Subsequently, CICs have been demonstrated in other types of leukemia as solid tumors. Initially CSCs were isolated and characterized by the phenotypes by the expression of certain constellations of cell surface markers, especially CD markers. CICs can also be identified by flow cytometry as the side population (SP). The SP are not stained by the Hoechst dye due to the expression of the ABCG2 transporter which is often elevated in CICs. ABCG2 is an ABC transporter that mediates the efflux of DNA dyes such as Hoechst and other compounds from the cell. More recently other markers such as aldehyde dehydrogenase have been shown to be expressed in CICs. Certain signaling pathways have been demonstrated to be important in various CICs, including Jak/STAT, PI3K/PTEN/Akt/mTORC1, NOTCH, NF-κB and others. Certain common drugs such as the anti-diabetes drug Metformin have been shown to be potentially effective against certain CICs. The papers presented in this special issue of Advances in Biological Regulation will discuss CICs present in various cancers as well as the

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roles of certain signal transduction pathways and the ability to target some of these signaling pathways.

In the manuscript by Martelli and colleagues, the presence of LIC in acute lymphoblastic leukemia (ALL) is critically discussed as well as the importance of the PI3K/PTEN/Akt/mTORC1 and NOTCH signaling pathways. The critical role of silencing of PTEN by mutations and epigenetic mechanisms and the effects of downstream activation of this PI3K/PTEN/Akt/mTORC1 pathway in concert with NOTCH mutations in ALL is also evaluated. This manuscript critically discusses the expression of various CD markers on the various ALL-LICs subsets. The prospective of targeting the NOTCH and PI3K/PTEN/Akt/mTORC1 pathways to improve the therapy of ALL is also evaluated. The possibilities of combining targeted therapies with chemotherapy including glucocorticoids were also discussed in this review.

Drs Fragoso and Barata discussed in detail the key role of PTEN in leukemia LICs. In particular, their review summarized the critical contributions of various mouse genetic models in elucidation of various LICs and signaling pathways. They reviewed the key observations that PTEN regulates LICs and hematopoietic stem cells (HSCs) through different mechanisms. These differences make it is possible to identify pathways that differentially affect LICs and HSCs and should allow the discovery of novel approaches to selectively target the LICs. While PTEN mutations are not as frequent in blood cancers as in solid tumors, functional PTEN activity may be suppressed by epigenetic, posttranscriptional and posttranslational mechanisms. Suppression of PTEN can lead to aberrant activation of the PI3K/PTEN/Akt/mTORC1 pathway in leukemia. Normally PTEN maintains HSCs in a quiescent state. However, loss of functional PTEN activity results in HSC cycling which leads to their exhaustion. The proliferating HSCs with defective PTEN may acquire other mutations which results in leukemogenesis and LICs. However, these LICs with defective PTEN display activated PI3K/PTEN/Akt/mTORC1 pathway and should be sensitive to effective PI3K, Akt and mTORC inhibitors. The PI3K, Akt and mTORC inhibitors should sensitize the PTEN mutant LICs to chemotherapy but leave the normal HSC alone.

Active-site mTOR kinase inhibitors, which target both mTORC1 and mTORC2, have been shown to promote the death of CD34+/CD7-/CD4- cells in human T-ALL, a subset described as being enriched in leukemia-initiating potential in human T-ALL. mTOR kinase inhibitors were also demonstrated to sensitize the CD34+/CD7-/CD4- T-ALL cells to dexamethasone, a chemotherapeutic drug commonly used in the treatment of T-ALL These and other results indicate the important of the PI3K/PTEN/Akt/mTORC1 pathway in T-ALL LIC.

The roles of the STAT transcription factors in LICs and CICs were discussed in the review by Dorritie and co-authors. The key roles of STAT5 in the regulation of normal HSCs and LICs were evaluated. STAT3 also plays important functions in HSC stem cell self-renewal and B-cell development. The regulation of STATs in various cancers by JAKs and other molecules including negative regulators such as suppressors of cytokine signaling (SOCS) family members is covered in detail. Novel potential JAK and STAT inhibitors and their uses in hematopoietic leukemia and solid cancer CICs are also evaluated.

Chronic myeloid leukemia (CML) CICs may not be BCR-ABL-dependent for their proliferation and survival. This may make certain BCR-ABL CML CICs resistant to tyrosine kinase inhibitors (TKIs) such as imatinib and nilotinib. In some imatinib/nilotinib resistant CML CICs, the cells proliferate due to activation of the JAK2/STAT5 pathway. Inhibition of JAK2 eliminated TKI resistance.

The JAK/STAT pathway also plays key roles in solid tumors CICs. The SP subset of breast cancer cells, including those present in established cell lines such as MCF-7, is enriched in CICs. Some studies have shown that treatment with the STAT3 inhibitor IS3 295 or knockdown of STAT3 with short hairpin RNA (shRNA) resulted in a decrease in SP fraction and suppressed tumor initiating ability.

STAT3 activation was also observed in colon CICs. Inhibition of STAT3 with small molecule inhibitors or shRNAs suppressed colon CIC xenograft growth. Likewise, glioblastoma CICs may also rely on JAK/STAT signaling for growth and self-renewal. Clinical studies also demonstrated that elevated JAK1 and STAT3 expression correlated with higher grade tumors and a decrease in overall survival. Clearly the JAK/STAT pathway is critically involved in CICs and developing inhibitors to selectively target this pathway in CICs but leave normal stem cells alone is essential.

The roles of CICs in solid cancers including pancreatic (Fitzgerald & McCubrey), prostate (Bertrand and colleagues), and breast cancers (McCubrey and colleagues) were discussed. The markers for identification of identification of pancreatic cancer stem cells include: CD133, ALDH, side population cells and the triplet combination CD4+, CD24, ESA were discussed in the review by Fitzgerald &