Editorial

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Self-renewal and pluripotency have been initially attributed to normal stem cells that posses the ability to give rise to all cell types in the adult organism. Seminal findings by John Dick in acute myeloid leukemia in the late 1990s led to the identification of cancer stem cells (CSCs). Since then, they have been an intense focus of cancer research. CSCs have been identified in most if not all the hematological malignancies as well as the solid tumors. CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. These cells are proposed to resist various forms of chemotherapy and radiotherapy and cause relapse and metastasis by giving rise to new tumors. Here, in the series of the review articles, we aim to draw parallels between epigenetics, molecular circuits and phenotype between normal pluripotent stem cells and cells with the stem cell like phenotype that propel tumor growth.

Development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease. Stem cell paradigm in hematopoietic malignancies has been thoroughly described by **Zagożdżon and Gołąb**. The authors describe in detail the phenotype and molecular features of CSCs as well as their oncogenic pathways that can be targeted by novel therapies.

Next, focusing on the regulation of breast cancer stem cell features (also named tumor-initiating cells), the review by **Czerwińska and Kamińska** provides a comprehensive overview of the pathway dependencies (Wnt/β-catenin, sonic hedgehog (Shh), Notch and BMP/TGFβ signaling) that contribute to the self-renewal properties of stem and/or progenitor cells. Adding to this complexity are emerging epigenetic and MicroRNA-based mechanisms that control pluripotency and stemness through regulating transcriptions factors such as Oct3/4, Nanog or Sox2. As discussed by these authors, this cross-talk between epigenetics and canonical signaling pathways opens up for exciting therapeutic opportunities as inhibition of DNA methylation, histone methyltransferases and histone deacetylases may directly impact some of the cell signaling pathways that controls stemness, tumorigenesis and metastatic potential. Therapeutic approaches to cancer have traditionally focused on 'chemotherapy' and on targeting oncogenic signaling and mechanisms intrinsic to cancer cell proliferation and survival. Along these lines, **Klimczak** discusses the core transcription factors that are expressed in many tumor types and are common with human pluripotent cells including embryonic stem cells and induced pluripotent stem cells. Recent findings have shown that tumor suppressor p53 plays significant role in maintenance of self-renewal of many types of stem cells that has profound implication for cancer biology and treatment. **Kulcenty and colleagues** describe in greater detail molecular mechanisms of cellular reprogramming that allows for generation of pluripotent cells (iPSc) from terminally differentiated somatic cells. The growing body of evidence suggests that the changes in molecular circuits during induced reprogramming are analogous to those observed during oncogenesis. Initially random changes in cellular signaling lead to more deterministic process that results in formation of undifferentiated cells that shares molecular features with CSCs. However, in contrast to cancerogenesis, the cellular reprograming is not initiated or facilitated by genetic changes and is purely induced by overexpression of specific transcription factors that in effect lead to profound changes of the cellular epigenome. **Gładych and co-workers** follows the story of the induced pluripotency and discuss changes in epigenetic landscape that occurs during the reprogramming process. Both, DNA methylation and histone modifications are involved in resetting the differentiated state of the somatic cells and forcing them towards acquisition of stem cell-like phenotype. The epigenetic changes during dedifferentiation lead to sequential expression of pluripotency genes, whilst expression of tissue-specific genes is being turned off. Importantly, the new epigenetic landscape plays important role in stabilization of the acquired phenotype and secures the self-renewal of newly born stem cells. Further research of these fascinating molecular and epigenetic mechanisms might shed new light on the oncogenesis and pave the way for novel therapeutic approaches targeting self-renewal of CSCs.

However, as reviewed by **Collet and co-workers**, it is now appreciated that the tumor microenvironment (e.g. cytokines, extracellular matrix, immune and endothelial vascular cells) critically contributes to the metastatic potential of cancer cells and to therapy resistance. By focusing on the tumour as a 'neo-organ', the authors describe how hypoxia, directly (i) regulates the expression of specific stem cell-like markers, (ii) induces angiogenesis, and (iii) controls the expression of regulatory microRNAs. Hence, the hypoxic niche, which is a hallmark of cancer,

serves as a master regulator of tumorigenesis. **Matak and colleagues** expand on this concept of "cancer stem cells" (or tumor-propagating cells) focusing on kidney renal cell carcinoma (RCC) as an example. They provide an operational definition of the term based on a detailed review of current markers (CD105, CD133, ALDH1, CXCR4, CD44, NCAM, CAIX) some of which hold prognostic value and represent promising candidate therapeutic targets. Again, consistent with the importance of hypoxia and the tumor microenvironment for disease progression, many of these stem cell-like markers are regulated by chemokines, cell adhesion, stroma- and matrix-induced signaling.

Along the similar lines, **Kwiatkowska-Borowczyk and co-workers** describes immunotherapeutic strategies that target CSCs. The immune system can be effectively activated to eradicate CSCs through a number of promising approaches. For example, dendritic cells can by engaged to present CSCs-specific antigens and early-stage clinical trials are already ongoing to validate this hypothesis. On the other hand embryonic stem cells (ES) or induced pluripotent stem cells are being currently used as cellular vaccines in a number of preclinical studies. Finally, application of monoclonal antibodies specific for stem cell antigens like CD44, CD133 or EpCAM is also being tested to activate the immune system against CSCs and the outcomes of preclinical studies and clinical trials are encouraging.

Lenera *et al.* show data that microelements likes selenium can be used as biomarkers for stratification of patients with high risk for development of aggressive types of tumors including: breast, prostate, colorectal, bladder, and lung adenocarcinomas.

Hibner and Gregoire provide historical account of discovery of oncogenic viruses and discuss mechanisms underlying the infectious causes of cancer. They describe strategies that these viruses employ to ensure virus propagation and oncogenic transformation along with acquisition of stem cell phenotype. They suggest that a useful way of analyzing the convergent characteristics of viral infection and cancer is to examine how viruses affect the hallmarks of cancer as originally described by Hanahan and Weinberg.

Tomczak *et al.* and **Shah *et al.*** focus on two different aspects of cancer molecular profiling carried out by the Cancer Genome Atlas consortium that has catalogued alterations at epigenetic, genomic, transcriptomic and proteomic levels and for more than 10000 patients for more than 20 tumor types. In the first half of their review, **Tomczak *et al.*** provide an overview of the organization of the TCGA network, data generation platforms, and tools generated for analysis and visualization of these data. In the later part they summarize major discoveries announced in consortium articles that analyzed single cancer types as well as carried out pan-cancer analyses. Shah *et al*., delineates major steps and methodological aspects of processing sequencing read information to derive alteration information from tumor molecular profiles. They provide comprehensive lists of software that are currently available to process this data.

In summary, we hope that lessons learned from studying adult and embryonic stem cells as well as the molecular and epigenetic mechanisms that control induced pluripotency may shed new light on the biology of CSCs and thus pave the ways for novel treatments targeting drivers of the stem cell-like phenotype in cancer.