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Cancer Stem Cells as a new promising approach of efficient oncological treatment - the review of literature

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Summary:

Introduction and purpose:

For many years a lot of research projects have been conducted with the aim to discover special cells, which are responsible for a neoplasm development. One of the theories concerns cancer stem cells (CSCs). This theory presumes the existence of original, undifferentiated cancer cells. These cells are capable of transform to all types of cells in neoplasm mass. The purpose of this study was to review the currently available data about the theory of CSCs and especially potential usage of this theory in oncological treatment. Pubmed and Scopus databases from the last 10 years were searched for phrase "cancer stem cells".

A brief description of the state of knowledge:

Impaired signaling pathways lead to an occurrence of CSCs which may contribute to the development of neoplasm eventually. It is proved, that gamma secretase inhibitors impede Notch signaling pathway, which leads to a decrease of tumour markers expression and consequently decline *in vivo* tumour growth. It is believed that epigenetic mechanisms, including DNA methylation, histones alteration and RNA orientation are pivotal regulators of CSCs. It was shown, that histone deacetylases (HDAC) modulate refractoriness on chemotherapy in haematological tumours. It is also evidenced that peculiar designed microRNA directly inhibit CD44 which suppresses prostatic cancer stem cells and its metastases. CSCs have high expression of programmed death-ligand 1 (PD-L1) including breast and colon cancer, which proclaims in favour of immunotherapy aimed on CSCs.

Conclusions:

Constantly growing knowledge about CSCs biology is creating new opportunities of detection, isolation and design of the therapies aimed on CSCs.

Key words: Cancer stem cells, elective treatment, chemotherapy, remission.

Introduction and purpose:

According to World Health Organization (WHO) predictions it is estimated that in 2040 over 29 million patients will suffer from cancer worldwide.

In comparison to number of patients diagnosed with cancer in 2018, it will be a surge of new cases approximately about 63,4% [1]. Thus, it is crucial to research and discover new mechanisms of carcinogenesis as well as a new potential treatments based on new types of targeted therapies in cancer.

Significant breakthrough in research about cells responsible for oncogenesis became cancer stem cells (CSCs). Results of this research abolished certain theory that tumours consisted with a group of homogeneous cells [2].

CSCs are a group of undifferentiated cells, which are part of solid tumours and haematological neoplasms as well. Due to expression of certain molecules and combinations of molecules which are called markers, those cells can be isolated *ex vivo*. Isolation of CSCs is based mainly on their surface markers, such as cluster of differentiation (CD) group, in particular CD133.

Concentration of cytoprotective enzymes, for instance aldehyde dehydrogenase (ALDH) or level of expression of ABC transporters are also taken into account when it comes to CSCs extraction. However, the universal CSCs' marker is still to be found. In comparison to normal cells, CSCs have specific properties – they have unlimited capability for self-regeneration. Hence, they account for growth, metastases and recurrence of tumour after initial treatment response [2,3]. Thanks to a diverse morphology they are seemingly responsible for metastases occurrence as well as refractoriness to typical chemotherapy [3].

CSCs are likely to become one of the crucial challenges for contemporary medicine. In our article, review of currently available data about actually revealed correlations between CSCs and cancer development was elaborated. Furthermore, we analysed clinical implications and forecast of usage this knowledge in the future.

State of the knowledge:

As far back as in 2016 Nassar D. and Blanpain C. in their research claimed, that heterogeneity amid cancer cells results from plenty of different mechanisms including genetic mutations, tumour microenvironment impact and existence of specific cancer cells which have increased capability of proliferation. Today, they are called cancer stem cells [4]. Those cells have been discovered in solid tumours, including breast, lung and colon cancer, but also in melanoma and brain tumours [1].

Metastases and refractoriness to commonly used chemotherapy are main hindrances which appear during cancer treatment. CSCs can be a new approach to those problems. CSCs are characterized by heterogeneous DNA repairing mechanisms. They can circumvent immune system and easily adjust to hostile environment. CSCs develop multidrug resistance (MDR) and to achieve efficient response, new drugs targeted on CSCs should be produced. Those drugs should modify the microenvironment and/or alter enzymes activity inside those cells [5]. Research focused on properties of somatic stem cells, which are accountable for intestinal epithelium regeneration were a first-step in discovery of CSCs in colon cancer. Since CSCs population existence was proven, they are assumed to be one of the main reasons of anticancer treatment failure in colon cancer. According to that, they should be considered as new, important therapeutic target. Hence it seems that proliferation pathways inhibitors with cytotoxic and CSCs differentiation-inducing medicaments can conceive more effective treatment in colon cancer [6].

Results of the research reveal that accumulation of epigenetic alterations can lead to occurrence of new mutations and genomic instability in cancer cells. CSCs can be modulated by epigenetic mechanisms. New drugs, targeted on these epigenetic pathways in CSCs might be useful. In many clinical trials focused on inhibitors of epigenetic modulating enzymes, histone deacetylases (HDAC) and DNA methyltransferases (DNMT) were analysed. It was proved, that the HDAC decrease resistance to chemotherapy in haematological neoplasms [7]. According to Zhang et al. HDAC inhibitors caused significant suppression of CSCs in chronic myeloid leukaemia (CML) after administration of imatinib [8]. Li et al. demonstrated that selective HDAC inhibition *in vivo* yielded decrease of CSCs number in CML, in the mechanism contingent on p53 [9].

Some authors suggest that microRNAs are important epigenetic regulators of CSCs as well. Liu et al. proved that microRNA miR-34a inhibits CD44 directly and it leads to suppression prostatic cancer stem cells growth and occurrence of metastases [10]. These correlations seemingly can be used in the future in new types of therapies.

Notch signaling pathway is activated by ligand-receptor interaction of Notch1 to Notch 4 receptors and Notch ligands – Delta 1, 3, 4 and Jagged 1, 2; it is important pathway in proliferation, differentiation and stem cells apoptosis. Activation of the mentioned pathway can be both oncogenic and can suppress oncogenesis. Notch signaling pathway is activated in malignant tumours, including breast cancer and glioblastoma. Impeding of this pathway by antibodies against Delta 4 or Notch1 ligands decrease the population of breast cancer stem cells. Its other advantage is that heterografts are more liable to taxanes therapy. Secretase gamma inhibitors block Notch signaling pathway and it yields decline of CSCs markers expression and subsequently *in vivo* stunt tumour growth [11].

PI3K/Akt/mTOR signaling pathway is another pathway, which have recently been profoundly analysed. Expression of this pathway correlates with CSC persistence and oncogenesis. Hisham F. Bahmad et al. assessed the efficiency of two different points of suppression in PI3K/Akt/mTOR signalling pathway in research based on human cells line U251 (glioblastoma) and SH-SY5Y (neuroblastoma) and their CSCs. It was proved, that drugs targeted on this pathway due to its impeding might limit migration ability of cells from both cells lines and can decrease CSCs number [12].

Wingless-related integration site (Wnt) signaling pathway is also a pathway crucial in cancer development. Wnt/beta-catenin (canonical pathway) is the best described pathway and collected evidences indicate that it is important factor in oncogenesis. Inhibitors of the above pathway can be divided into few groups: micromolecular inhibitors like nonsteroidal anti-inflammatory drugs (NSAID), molecularly targeted substances, like cAMP response element-binding (CREB) protein and beta-catenin antagonist ICG-001. Subsequent group are biological inhibitors, including antibodies, RNA interference and recombined proteins. Last reports suggest, that Wnt/beta-catenin signaling pathway modulate CSCs regeneration in CML and removal of beta-catenin leads to deprivation of residual CSCs in mice bone marrow after imatinib therapy. Latest pre-clinical research demonstrated, that combination of indomethacin (NSAID) with imatinib prolongs survival in CML model [11].

CSCs can easily adjust to environment, due to avoiding of immune system. One of the main mechanisms, which helps to circumvent immune system is high expression of programmed death-ligand 1 (PD-L1) in CSCs. High expression was detected in CSCs including breast and colon cancer. It can suggest potential beneficial impact of PD1/PD-L1 immunotherapy targeted on CSCs in a course of these cancers' treatment [13]. Chimeric antigen receptor-T cells immunotherapy can be optimal alternative for immunotherapy based on monitoring checkpoints inhibitors (monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or antibodies which bind with PD1 and PD-L1). In pre-clinical research Deng et al. in 2015 proved, that CAR-T cells targeted against CSCs EpCAM marker have significant anticancer properties in prostatic cancer. Hence, it can be a prospect of new therapeutic method based on tumour specific elimination [14].

The creation of specific microenvironment around CSCs which yields the status of immunosuppression is another mechanism to omit the immune system. Prostatic cancer stem cells in histopathological negative lymph nodes were detected in mice with prostatic intraepithelial neoplasia. It was perceived, that chemokine receptor type 4 (CXCR4) inhibitors *in vivo* prevented from occurrence of immunosuppressive microenvironment in examined lymph nodes. It can be evidence, that CXCR4 has the impact on development of CSCs in lymph nodes in prostatic cancer. Thus, it can participate in the creation of immunosuppressive microenvironment [15].

Conclusions:

Growing knowledge about CSCs' biology gives the opportunity to design tests for early detection and isolation of those cells. Development of algorithms in advanced cancer treatment, which consider identification and elimination of CSCs should avail to patients and give them longer period of life with decent quality of life.

Among a variety of mechanisms, HDAC inhibitors, microRNA modifications and alterations of certain signaling pathways seem to be most promising and may be useful in treatment in prospect of the future. Those signaling pathways take part in the proliferation of CSCs clones. Perhaps the most crucial factors are Notch and WNT/beta-catenin signaling pathways, which were mentioned in our article. Revelation of specific points in molecular mechanisms, which might be a target for a new kind of medicaments in cancer treatment is a main purpose of scientists. In prognosis of a predicted drastic surge of morbidity rate in oncology, new kind of treatment development seems to be a pivotal action.

The challenge will be to identify relevant clinical endpoints that could provide information on the specific impact of targeted therapy on patient's state and results of treatment. However, further research is needed to provide a scientific basis for introducing these methods into common hospital practice.

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