DEVELOPMENT OF STEM CELL-BASED CANCER THERAPY STRATEGIES

Sumadi [1*], Rizki Zeillatul Warda [2]

[1]Faculty of Medicine, Universitas Jember, Indonesia

[2]Laboratory of Waste Management UPA and Integrated Laboratory, Universitas Jember, Indonesia

[*] Corresponding author : sumadifk@yahoo.com

ABSTRACT

Cancer remains one of the leading causes of death worldwide, with various treatment options available depending on the type and stage of the disease. Traditional therapies, such as surgery, radiotherapy, chemotherapy, and immunotherapy, have shown varying degrees of success, but each has its limitations. Recently, stem cell therapies have emerged as a promising alternative, offering more targeted treatments with fewer side effects. Stem cells, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and cancer stem cells (CSCs), have demonstrated potential in cancer therapy through mechanisms like tumor site targeting, paracrine signaling, and gene delivery. MSCs, in particular, are of interest due to their ability to migrate to tumor sites and release exosomes that can influence tumor growth, angiogenesis, and metastasis. Modified MSCs have been engineered to deliver anticancer agents or "suicide" genes, providing a more focused approach to tumor treatment. Moreover, MSCs have shown promise in addressing challenges like drug resistance and recurrence in cancer. However, their effectiveness depends on factors such as exosome composition and the tumor microenvironment. Despite the challenges, stem cell-based therapies, including MSC-derived exosomes, represent a novel strategy to enhance the specificity and efficacy of cancer treatments. This review explores current advances in stem cell-based cancer therapies, highlighting their potential, ongoing research, and the need for further studies to optimize these approaches for clinical application.

Keywords : Cancer treatments; mesenchymal stem cells; tumor; stem cell therapy

INTRODUCTION

Cancer is a highly deadly disease and one of the leading causes of death worldwide (Siegel et al., 2016). Cancer treatments vary depending on the type and stage of the disease, as well as the goals of the therapy. Surgery is commonly performed to remove tumors localized to a specific area. Additionally, radiotherapy works by destroying cancer cells through DNA damage, while chemotherapy uses chemical drugs to slow tumor growth. Immunotherapy, which involves techniques such as the use of monoclonal antibodies or cancer vaccines, has shown promising results in improving patient recovery. However, this therapy often lacks specificity for certain tumor locations, reducing its effectiveness and increasing the risk of recurrence. In contrast, stem cell therapy offers a more targeted approach to treating cancer. This method enhances the efficiency of other therapies by minimizing damage to healthy tissues. Currently, various stem cell-based strategies are being tested in laboratories and are considered promising, although they still face several challenges (Gomes et al., 2017).

In the past decade, the number of clinical studies utilizing MSCs, iPSCs, and CSCs for cancer therapy has steadily increased, with iMSC emerging as one of the latest additions. Although MSCs often spark

controversy in cancer research, these cells possess unique abilities, such as detecting tumor sites, communicating through paracrine signaling, and delivering exosomal miRNAs, enabling them to interact with cancer cells within the tumor microenvironment (Aldoghachi et al., 2023). On the other hand, iPSCs, now producible through safer, non-viral methods, provide a new source of stable pluripotent cells and their derivatives, including iMSCs (Aldoghachi et al., 2023). These iMSCs have the potential to serve as alternatives to traditional MSCs, addressing limitations like biological variability and challenges in large-scale production while retaining their therapeutic benefits. iPSCs have also been used to study cancer mechanisms, including treatment resistance (Aldoghachi et al., 2023). Furthermore, understanding CSC flexibility in tumor growth and metastasis, as well as the role of exosomal miRNAs in supporting cancer stem cells, paves the way for innovative non-cell-based anticancer therapies (Aldoghachi et al., 2023).

MATERIALS AND METHODS

This study employs a narrative review method to examine and analyze literature relevant to the research topic. This approach aims to provide a comprehensive understanding of concepts, theories, and previously published findings. The research process consists of several stages, including identifying literature sources, selecting relevant literature, analyzing the content, and compiling the narrative.

This study is based on a literature search from the PubMed and Google Scholar databases. The literature used includes English-language articles published between 2019 and 2024. To find relevant sources, keywords such as stem cells, cancer, cancer therapy, stem cell mechanisms, and cancer therapy updates were used. Articles were selected by reviewing the titles and full text, while additional searches were conducted manually to ensure the completeness of sources relevant to the research topic.

RESULT AND DISCUSSION

Types of Stem Cells for Cancer Therapy

Stem cells come from various sources, and each source has unique characteristics in terms of proliferation, mobility, and differentiation into other cell types. These differences are key factors in determining how these cells are utilized to treat tumors.

Pluripotent Stem Cells (PSC)

Embryonic stem cells (ESC) are taken from the inner part of an embryo that has not yet differentiated into specific cell types and have the ability to develop into almost any type of body cell, except for the cells that form the placenta. The use of ESC in research is limited due to ethical concerns related to embryo destruction. In 2006, Yamanaka discovered a method to transform ordinary body cells into induced pluripotent stem cells (iPSC), which have nearly the same capabilities as ESC (Takahashi &Yamanaka, 2006; Chu et al., 2020). However, iPSCs do not involve the destruction of embryos, thus reducing ethical issues. Currently, both ESC and iPSC are used to generate effective T cells and NK cells, as well as to create cancer vaccines (Knoor et al., 2013; Ruella & Kenderian, 2017).

Adult Stem Cells (ASCs)

Types of stem cells (ASC) that can develop into various specialized cells in the body and are often used in cancer treatment.

HSC (Hematopoietic Stem Cells) are stem cells found in the bone marrow and function to produce blood cells. The use of these cells from umbilical cord blood has been approved by the FDA for the treatment of

certain types of blood cancer (Copelan, 2006; Chu et al., 2020).

MSC (Mesenchymal Stem Cells) are found in various parts of the body and are important for repairing damaged tissues. These cells can develop into other types of cells, such as bone or fat cells, and are used in cancer treatment (Lin et al., 2019).

NSC (Neural Stem Cells) are found in the central nervous system and can produce new cells needed by the brain and nerves. These cells are also being tested in the treatment of cancers that affect various organs, whether localized or spread (Kanojia et al., 2015; Chu et al., 2020).

Cancer Stem Cells (CSC)

CSC are cells that are similar to stem cells or cells that are still young and not fully mature. These cells can arise due to genetic changes in normal stem cells or younger cells. CSCs are found in tumor tissue and play a role in helping cancer grow, spread to other organs, and cause the cancer to recur after treatment (Chang, 2016).

Tumor Treatment Using Exosomes from Mesenchymal Stem Cells (MSC)

Exosomes are small vesicles secreted by eukaryotic cells, formed within the endosomal compartment of the cell (Raposo & Stoorvogel, 2013). Exosomes and other types of vesicles are found in various tissues and body fluids, such as urine, blood, and cerebrospinal fluid. They contain various molecules, including microRNA (miRNA), proteins, and lipids that make up their outer membrane. Additionally, exosomes can carry other types of RNA, such as ribosomal RNA or long non-coding RNA, as well as DNA fragments (Guescini et al., 2010).

Research has shown that exosomes released by one cell can interact with other cells through specific proteins on their surface (Neviani & Fabbri, 2015). Mesenchymal stem cells (MSC) produce exosomes that can influence tumor growth by regulating new blood vessel formation (angiogenesis), tumor metastasis, and cancer cell proliferation (Ratajczak et al., 2006). These exosomes also function as intercellular communication tools, carrying molecular signals that either promote or inhibit tumor growth, depending on certain conditions.

One innovative therapeutic approach is using MSCs in prodrug "suicide" gene therapy. This gene, found in Escherichia coli bacteria or yeast, functions to convert the prodrug 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU), an anticancer drug that is toxic to tumor cells. In this therapy, MSCs are modified to carry genes or drugs that specifically target tumors (Choi et al., 2023). For example, MSCs derived from adipose tissue are engineered to express certain enzyme genes, such as thymidine kinase from the herpes simplex virus, used in combination with the drug ganciclovir (Matuskova et al., 2010). This combination allows MSCs to convert the prodrug into a toxic compound that kills tumor cells while remaining safe for healthy tissues.

Stem cells, such as MSCs derived from adipose tissue and clonal NSCs HB1.F3.CD, are engineered to express the CD gene (Gutova et al., 2019). Research shows that NSCs carrying this CD gene have been specifically used to treat malignant gliomas (a type of brain cancer). This approach aims to address the challenge of delivering anticancer drugs to tumors while also helping to repair damaged tissues. Additionally, other studies use a yeast variant of the CD gene, yCD::UPRT, to enhance the effectiveness of this therapy (Ko et al., 2003). Laboratory and real-world model studies have shown that this approach is safe and effective for cancer treatment. In addition to the CD gene, other enzymes, such as carboxyesterase, are also used in this therapeutic strategy. This enzyme converts the prodrug CPT-11 (irinotecan) into its active form, SN-38, which is highly effective in inhibiting topoisomerase I, an

enzyme essential for cancer cell growth (Danks & Potter, 2004; Choi et al., 2023). CPT-11 is often used in combination with other drugs to treat neuroblastoma and has shown promising results in clinical trials. NSCs engineered to produce this enzyme have demonstrated significantly higher abilities to activate CPT-11 compared to similar enzymes found in the liver. Another gene therapy strategy involves the thymidine kinase (TK) enzyme from the herpes simplex virus (HSV-TK) (Bhaumik, 2011). This enzyme works by converting the drug ganciclovir (GCV) into its active form, which can effectively kill cancer cells. The same NSCs, HB1.F3.CD, are used to produce this enzyme, allowing GCV to work more effectively in eliminating tumors (Wang et al., 2012).

Overall, MSC exosomes offer great potential to enhance the effectiveness of chemotherapy by specifically targeting tumors. However, the effects of MSC exosomes on tumors remain a topic of debate, as they can either support or inhibit tumor growth depending on the origin of the exosomes, their composition, and the type of tumor.

Cancer Treatment Using Mesenchymal Stem Cells (MSC)

Tumors require new blood vessels to obtain nutrients and oxygen for growth and metastasis (Jain et al., 2007; Aravindhan et al., 2021). This process of forming new blood vessels is called angiogenesis. One way to stop angiogenesis is by using modified mesenchymal stem cells (MSC) (Ghaedi et al, 2011; Aravindhan et al., 2021). MSCs naturally migrate to tumor sites and can deliver drugs or compounds that inhibit blood vessel formation, preventing the cancer from progressing further. However, administering anti-angiogenic drugs throughout the body often leads to side effects such as toxicity and disrupted blood flow, reducing the effectiveness of the treatment. In tumors, angiogenesis occurs due to an imbalance between factors promoting and inhibiting blood vessel formation, influenced by various elements in the tumor environment. Endostatin is a natural protein that can halt angiogenesis and has been widely used in cancer therapy. Research shows that MSCs modified to carry endostatin can be injected into mice. These cells successfully target the tumor, reduce its size, and decrease blood vessel formation without severe side effects (Zheng et al., 2012; Aravindhan et al., 2021). Additionally, MSCs produce exosomes, which are tiny particles that carry genetic messages. These exosomes can influence blood vessel formation in tumors by carrying specific microRNAs. When exosome activity is blocked, the levels of pro-angiogenic microRNAs decrease, demonstrating that exosomes play a crucial role in the interaction between MSCs and tumors.

Exosomes produced by MSCs can play a crucial role in communication between tumor cells and also help prevent the formation of new blood vessels (angiogenesis) by carrying molecules that can counteract angiogenesis. These exosomes contain miRNA, which can regulate gene expression and be used to stop molecules that stimulate angiogenesis, offering a new approach to halting tumor growth. On the other hand, inflammation occurring in tumors can attract MSCs to the site. During inflammation, certain substances are produced that can affect the properties and capabilities of MSCs, ultimately contributing to the formation of new blood vessels within the tumor. Research shows that TNF-α, a substance that triggers inflammation, can cause MSCs from the pancreas to produce VEGF. This VEGF increases the formation of new blood vessels in human endothelial cells. Overall, MSC exosomes can function to inhibit angiogenesis and tumor development, while inflammation within the tumor can influence how MSCs play a role in this process (Khiatah et al., 2019).

SUMMARY

Research on cancer therapy using stem cells highlights the potential of various stem cell types derived from different sources, each with unique properties that make them suitable for treatment. Pluripotent stem cells (PSCs), like embryonic stem cells (ESCs), can develop into nearly any body cell but raise ethical concerns. Induced pluripotent stem cells (iPSCs), which are reprogrammed from regular body cells, offer a less controversial alternative and are used in therapies such as cancer vaccines and T-cell therapies. Adult stem cells (ASCs), including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), also play significant roles in treating various cancers. For example, HSCs are used for blood cancers, MSCs help in tissue repair and cancer treatment, and NSCs are tested for brain cancer therapy. However, cancer stem cells (CSCs), which are found in tumors, contribute to cancer growth, spread, and recurrence, as they are resistant to treatments. An innovative cancer therapy approach involves MSCs producing exosomes, which can regulate tumor growth by affecting angiogenesis, or the formation of new blood vessels needed for tumor development. Modified MSCs can deliver therapeutic genes or drugs to tumors, such as using "suicide" prodrugs or enzymes to activate cancer drugs specifically at the tumor site. MSCs can also produce molecules like endostatin to inhibit angiogenesis, reducing tumor size without severe side effects. Despite the promising potential of MSCs in cancer treatment, the effectiveness of this therapy depends on factors like exosome composition and tumor conditions, which require further research to optimize its use.

BIBLIOGRAPHY

Aldoghachi, A. F., Chong, Z. X., Yeap, S. K., Cheong, S. K., Ho, W. Y. and Ong, A. H. K. (2023), “Stem Cells for Cancer Therapy: Translating the Uncertainties and Possibilities of Stem Cell Properties into Opportunities for Effective Cancer Therapy”, International Journal of Molecular Sciences, Vol. 24 No. 2, pp. 1012.

Aravindhan, S., Ejam, S. S., Lafta, M. H., Markov, A., Yumashev, A. V. and Ahmadi, M. (2021), “Mesenchymal stem cells and cancer therapy: insights into targeting the tumour vasculature”, Cancer Cell International, Vol. 21 No. 1, pp. 158.

Bhaumik, S. (2011), “Advances in imaging gene-directed enzyme prodrug therapy”, Current Pharmaceutical Biotechnology, Vol. 12 No. 4, pp. 497-507.

Chang, J. C. (2016), “Cancer stem cells Role in tumor growth, recurrence, metastasis, and treatment resistance”, Medicine, Vol. 95, pp. S20-S25.

Choi, Y., Lee, H. K. and Choi, K. (2023), “Engineered adult stem cells: a promising tool for anti-cancer therapy”, BMB Reports, Vol. 56 No. 2, pp. 71-7.

Chu, D., Nguyen, T. T., Tien, N. L. B., Tran, D., Jeong, J., Anh, P. G., Thanh, V. V., Truong, D. T. and Dinh, T. C. (2020), “Recent Progress of Stem Cell Therapy in Cancer Treatment: Molecular Mechanisms and Potential Applications”, Cells, Vol. 9 No. 3, pp. 563.

Copelan, E. A. (2006), “Hematopoietic stem-cell transplantation”, The New England Journal of Medicine, Vol. 354 No. 17, pp. 1813-26.

Danks, M. K. and Potter, P. M. (2004), “Enzyme-prodrug systems: carboxylesterase/CPT-11”, Methods in Molecular Medicine, Vol. 90, pp. 247-62.

Ghaedi, M., Soleimani, M., Taghvaie, N. M., Sheikhfatollahi, M., Azadmanesh, K., Lotfi, A. S. and Wu, J. (2011), "Mesenchymal stem cells as vehicles for targeted delivery of anti-angiogenic protein to solid tumors", The Journal of Gene Medicine, Vol. 13 No. 3, pp. 171-80.

Gomes, J. P. A., Assoni, A. F., Pelatti, M., Coatti, G., Okamoto, O. K. and Zatz, M. (2017), "Deepening a Simple Question: Can MSCs Be Used to Treat Cancer?", Anticancer Research, Vol. 37 No. 9, pp. 4747-58.

Guescini, M., Genedani, S., Stocchi, V. and Agnati, L. F. (2010), "Astrocytes and Glioblastoma cells release exosomes carrying mtDNA", Journal of neural transmission, Vol. 117 No. 1, pp. 1-4.

Gutova, M., Flores, L., Adhikarla, V., Tsaturyan L., Tirughana, R., Aramburo, S., Metz, M., Gonzaga, J., Annala, A., Synold, T. W., Portnow, J., Rockne, R. C. and Aboody, K. S. (2019), "Quantitative Evaluation of Intraventricular Delivery of Therapeutic Neural Stem Cells to Orthotopic Glioma", Frontiers in Oncology, Vol. 9.

Jain, R. K., di Tomaso, E., Duda, D. G., Loeffler, J. S., Sorensen, A. G. and Batchelor, T. T. (2007), "Angiogenesis in brain tumours", Nature Reviews. Neuroscience, Vol. 8 No. 8, pp. 610-22.

Kanojia, D., Balyasnikova, I. V., Morshed, R. A., Frank, R. T., Yu, D., Zhang, L., Spencer, D. A., Kim, J. W., Han, Y., Yu, D., Ahmed, A. U., Aboody, K. S. and Lesniak, M. S. (2015), "Neural Stem Cells Secreting Anti-HER2 Antibody Improve Survival in a Preclinical Model of HER2 Overexpressing Breast Cancer Brain Metastases", Stem Cells, Vol. 33 No. 10, pp. 2985-94.

Khiatah, B., Qi, M., Du, W., T-Chen, K., van Megen, K. M., Perez, R. G., Isenberg, J. S., Kandeel, F., Roep, B. O., Ku, H. T. and Al-Abdullah, I. H. (2019), "Intra-pancreatic tissue-derived mesenchymal stromal cells: a promising therapeutic potential with anti-inflammatory and pro-angiogenic profiles", Stem Cell Research & Therapy, Vol. 10 No. 1, pp. 322.

Knoor, D. A., Ni, Z., Hermanson, D., Hexum, M. K., Bendzick, L., Cooper, L. J. N., Lee, D. A. and Kaufman, S. (2013), "Clinical-Scale Derivation of Natural Killer Cells From Human Pluripotent Stem Cells for Cancer Therapy", Stem Cells Translational Medicine, Vol. 2 No. 4, pp. 274-83.

Ko, T., Lin, J., Hu, C., Hsu, Y., Wang, A. H. and Liaw, S. (2003), "Crystal structure of yeast cytosine deaminase. Insights into enzyme mechanism and evolution", The Journal Biological Chemistry, Vol. 278 No. 21, pp. 19111-7.

Lin, W., Huang, L., Li, Y., Fang, B., Li, G., Chen L. and Xu, L. (2019), "Mesenchymal Stem Cells and Cancer: Clinical Challenges and Opportunities", BioMed Research International, Vol. 2019.

Neviani, P. and Fabbri, M. (2015), "Exosomic microRNAs in the tumor microenvironment", Frontiers in Medicine, Vol. 2 No. 47.

Raposo, G. and Stoorvogel, W. (2013), "Extracellular vesicles: Exosomes, microvesicles, and friends", The Journal of Cell Biology, Vol. 200 No. 4, pp. 373-83.

Ratajczak, J., Miekus, K., Kucia, M., Zhang, J., Reca, R., Dvorak, P. and Ratajczak, M. Z. (2006), "Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery", Leukemia, Vol. 20 No. 5, pp. 847-56.

Ruella, M. and Kenderian, S. S. (2017), "Next Generation Chimeric Antigen Receptor T Cell Therapy: Going off the Shelf", BioDrugs, Vol. 31 No. 6, pp. 473-81.

Siegel, R. L., Miller, K. D. and Jemal, A. (2016), “Cancer Statistics, 2016”, CA: A Cancer Journal for Clinicians, Vol. 66 No. 1, pp. 7-30.

Takahashi, K. and Yamanaka, S. (2006), “Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors”, Cell, Vol. 126 No. 4, pp. 663-76.

Wang, C., Natsume, A., Lee, H. J., Motomura, K., Nishimira, Y., Ohno, M., Ito, M., Kinjo, S., Momota, H., Iwami, K., Ohka, F., Wakabayashi, T. and Kim, S. U. (2012), “Neural stem cell-based dual suicide gene delivery for metastatic brain tumors”, Cancer Gene Therapy, Vol. 19 No. 11, pp. 796-801.

Zheng, L., Zhang, D., Chen, X., Yang, L., Wei, Y. and Zhao, X. (2012), “Antitumor activities of human placenta-derived mesenchymal stem cells expressing endostatin on ovarian cancer”, PloS One, Vol. 7 No. 7.