THE INVOLVEMENT OF DIFFERENT VITAMIN TYPES IN ASSISTING THE ACTIVATION OF STEM CELLS: A REVIEW

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ABSTRACT

Recent research indicates that vitamins play a key role in regulating cellular processes, especially in stem cells. Stem cells are undifferentiated cells with the potential to develop into various cell types and regenerate themselves. The article selection process followed predetermined inclusion criteria and spanned from March 18, 2024, to March 31, 2024, lasting one month. Articles were searched using specific keywords, and those meeting the criteria were selected. Six articles were collected for review, primarily focusing on assessing the role of each vitamin in stem cell survival. Most vitamins studied have shown similar functions in enhancing the viability of stem cells by promoting their differentiation. However, recent research has revealed a unique role for vitamin E in relation to stem cells. Vitamin E acts as a facilitator for mesenchymal stem cells, inhibiting dendritic cells and enhancing their immunomodulatory effects. All these vitamins are pivotal in preserving the wellbeing and functionality of both stem cells and bodily tissues.

Keywords : Vitamin; activation; stem cells

INTRODUCTION

Vitamins are natural organic substances that play a crucial role in maintaining the physiological functions of the body in the minimal required amounts. The human body cannot synthesize them on its own or produce sufficient amounts to meet physiological needs normally (Combs, 1992; Godoy-Parejo et al., 2019). Vitamins play a crucial role in various cellular processes and can cause serious symptoms in humans if vitamin intake is not met, and in some situations, can even lead to death. The discovery of vitamins first occurred in 1912, with the first identified vitamin being vitamin A. Since then, a total of 13 types of vitamins have been successfully identified, each recognized for its crucial role in maintaining human health (Semba, 2012; Godoy-Parejo et al., 2019). Typically, vitamins can be obtained through food consumption, but the administration of vitamin supplements is also often practiced in healthcare. The latest findings indicate that vitamins play a role in regulating processes at the cellular level, particularly in stem cells (Blaner, 2013; Godoy-Parejo et al., 2019).

Stem cells are cells that have not yet specialized in the human body. They have the capacity to transform into various types of cells within the organism and have the ability to regenerate themselves. Stem cells can be found in both embryos and adult bodies (Zakrzewski et al., 2019). There are two natural variants of stem cells: first, pluripotent stem cells which can be found in culture, also known as embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs); and second, tissue-specific stem cells responsible for replacing specific tissue types in the bodies of mammals and other animals (Slack, 2018). The main principle in using iPSCs for cell therapy is that firstly, iPSCs are directed to differentiate into the desired cell types, then the resulting tissue-specific cells are transplanted into the patient as a cell suspension or more complex tissue structure (Moradi et al., 2019). The majority of stem cell research and applications utilize cell culture systems where the cell culture system can support the life of stem cells because the culture medium provides various important components for the cells (Godoy-Parejo et al., 2019).

Cell culture is the process in which cells from humans, animals, or plants are transferred or placed into a controlled medium suitable for cell growth (Khumairoh and Puspitasari, 2016). Cell culture contains various important components that support cell life. These components are contained within the cell culture medium, which includes water, carbon, nitrogen, energy, purines and pyrimidines, amino acids, and vitamins (Bonnet et al., 2020). In cell culture, the vital role of vitamins becomes evident in their everyday use, both in basic research and their application in clinical practice (Godoy-Parejo et al., 2019). This article will outline the roles of each vitamin (Vitamin A, B, C, D, D3, E) in stem cell activation.

MATERIALS AND METHODS

This type of study is a narrative review. The researcher conducted 2 stages in the process of article selection and extraction.

Article Selection Process

This type of study is a narrative review. The article selection process is based on a combination of keywords: “role” OR “vitamin” OR “stem cells” OR “vitamin A” OR “vitamin B” OR “vitamin C” OR “vitamin D” OR “vitamin E” through the Google Scholar databases.

The article selection process is based on predetermined inclusion criteria. The inclusion criteria for article selection include, among others:

1. The article is open access
2. The article was published between the years 2019-2024
3. The article is indexed in Scopus Q1-Q3

Data Extraction

The article search process was conducted for 1 month, from March 18, 2024, to March 31, 2024. The article search process involved searching for article titles using keywords and selecting them one by one based on inclusion criteria. A total of six articles were successfully collected by the researcher for review. The main focus was on evaluating the role of each vitamin in the survival of stem cells.

The analysis technique used in this review is descriptive analysis because the researcher did not conduct hypothesis testing. The process of selecting and extracting articles for research materials is conducted according to Figure 1.

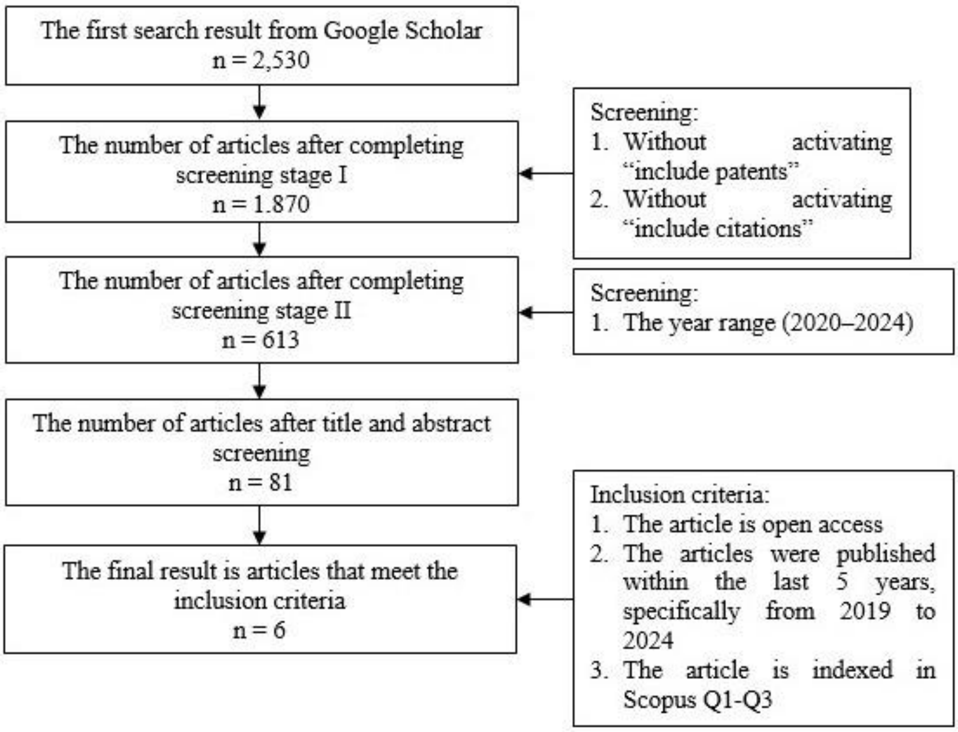

Figure 1. Flow Diagram of Literature Search

RESULT AND DISCUSSION

Vitamin A

Vitamin A was the first type of vitamin discovered, consisting of a group of compounds known as retinoids (retinol, retinal, and retinoic acid). Compounds in vitamin A can be found in animal food sources, while its precursor (carotenoid) can be found in plant food sources. Humans have the ability to produce vitamin A from carotenoids such as β-carotene, which is a fat-soluble pigment that gives bright colors to plants (Duester, 2008; Godoy-Parejo et al., 2019).

Members of the vitamin A family have different roles in stem cell culture. Recent findings indicate that one compound from vitamin A, namely retinoic acid, can influence specific lineage differentiation. Retinoic acid plays a central role as a guide for both hair follicle stem cells and epidermal stem cells. When the human body experiences an open wound, only a portion of the skin stem cells will immediately work to help and grow into new epidermis to cover the wound, while the rest are performed by hair follicle stem cells so that they reveal transcription factors from both stem cells, hair follicle stem cells, and epidermal stem cells. Therefore, retinoic acid is used as bait to lure stem cells to differentiate into either hair cells or epidermal cells (Tierney et al., 2024).

Retinoic acid governs the capacity of stem cells to transition into pluripotency and differentiate into specialized cell types by regulating the expression of mRNA and microRNA (Tagliaferri et al., 2020). This modulation affects the functioning of genes by altering various cellular processes such as DNA methylation, histone acetylation, and histone methylation (Maleknia et al., 2023). In human embryonic stem cells (hESCs), exposure to retinoic acid leads to an elevation in overall levels of DNA methylation, thereby facilitating cell differentiation (Chehelgerdi et al., 2023). Furthermore, retinoic acid impacts histone modifications like acetylation on H3, H4, and H3K in both hESCs and mouse embryonic stem cells (mESCs), subsequently driving the process of cell differentiation (Coradin et al., 2022). In instances involving mESCs and neuroblastoma, retinoic acid inhibits methylation on H3K27 while promoting methylation on H3K4, both of which are mechanisms that encourage cell differentiation (Cheng et al., 2019).

Vitamin B3

Vitamin B3 or niacin plays a vital role in cellular metabolism, particularly in the Krebs cycle, which is a key part of the aerobic respiration pathway, as well as in the formation of several crucial molecules in the body. Chemically, vitamin B3 is known as nicotinic acid, while its amide form is known as nicotinamide. Both molecules act as precursors to two important coenzymes in metabolic reactions and are involved in DNA repair processes. Food sources rich in vitamin B3 include meats (such as chicken and beef), fish, and plant-based products like nuts, grains, and legumes (Bayram-Weston et al., 2024).

In the context of its role in stem cells, vitamin B3 is involved in promoting the differentiation of pancreatic cells derived from human embryonic stem cells (hESCs) (Zhang et al., 2021). Human embryonic stem cells (hESCs) have pluripotent properties that allow them to differentiate into various types of cells in the body (Wang et al., 2020; Ahmed et al., 2020; Salehi-Pourmehr et al., 2020; Koster et al., 2020; Zhang et al., 2021).

The role of Vitamin B3 is demonstrated by supporting the formation of pancreatic progenitor cells from human embryonic stem cells (hESCs) by inhibiting the activities of CK1 and ROCK. Nicotinamide regulates the differentiation process by inhibiting CK1 and ROCK. We found that CK1 suppression triggers the formation of pancreatic progenitor cells expressing PDX1/NKX6.1. Experiments with CK1α and CK1ε inhibition via shRNA knockdown show that this facilitates pancreatic progenitor differentiation. Moreover, nicotinamide accelerates pancreatic progenitor differentiation by suppressing ROCK. Additionally, RNA-seq analysis indicates that CK1 and ROCK suppression result in pancreatic gene expression similar to nicotinamide treatment (Zhang et al., 2021).

Vitamin B12

The B-complex vitamins offer a hopeful option for restoring a variety of tissues and cells linked with different organs. These vitamins oversee particular biological functions within tissues, including cellular metabolic reactions, intercellular communication, and the upkeep of stem cells (Dai and Koh, 2015; Bhanothu et al., 2021). The B-complex vitamins consist of vitamin B1, B2, B3, B5, B6, B7, B9, and B12. Sources of B-complex vitamins can be found in animal or plant products.

Recent research indicates that vitamin B12 plays a role in tissue regeneration and cellular reprogramming processes. Cellular reprogramming is a condition in which cells lose their identity so they can revert to a pluripotent state. Once cells reach a pluripotent state, they can undergo specialization and differentiation into various cell types. Cellular reprogramming is considered a preliminary step in the tissue repair process (Kovatcheva et al., 2023).

Vitamin C

The discovery of ascorbic acid was first made during the outbreak of scurvy that occurred during the exploration period. This background prompted scientists to conduct research by isolating ascorbic acid in 1928, and research on ascorbic acid continues to be studied to this day (Fu et al., 2020). Ascorbic acid, commonly known as vitamin C, is a water-soluble vitamin due to its structure resembling sugar. Ascorbic acid can be produced endogenously in plants and most animals (Linster and van Schaftingen, 2007; Godoy-Parejo et al., 2019).

Ascorbic acid plays different roles for each stem cell. The role of ascorbic acid in the field of stem cells derived from dental tissues is as a growth and differentiation factor for dental stem cells. Therefore, dental healthcare professionals can develop a therapy called regenerative endodontic therapy (Diederich et al., 2023). In the study conducted by Diederich and colleagues, it was found that STRO-1 positive stem cells derived from both types of cells, namely Dental Pulp Cells (DPC) and the cells of the apical papilla (CAP), responded to 0.1 mM ascorbic acid. The response exhibited by these dental stem cells was indicated by an increase in the expression of dental stem cell markers and an enhancement in proliferation capability (Diederich et al., 2023).

Ascorbic acid deficiency is associated with various orthopedic medical conditions, such as increased risk of developing degenerative intervertebral disc disease in the elderly, bone dysplasia, osteoporosis, and progression of osteoarthritis (Hung et al., 2017; Lai et al., 2017; Yi et al., 2022; Chen et al., 2024). Therefore, further studies are conducted regarding the role of ascorbic acid in the field of orthopedics. Ascorbic acid (AA) promotes cell growth by accelerating DNA synthesis and directing mesenchymal stem cells to differentiate into various types of cells, including adipocytes, osteoblasts, myoblasts, and chondrocytes (Takamizawa et al., 2004; Fulzele et al., 2013; Chen et al., 2024). Chen and colleagues conducted the latest experiments in the field of stem cells. They modified the test by performing Microfracture (MFX) stimulation on ascorbic acid to be injected into an animal model. Recent studies on the role of ascorbic acid in bone marrow mesenchymal stem cells have shown cartilage repair in the animal model. MFX treatment combined with ascorbic acid can induce key factors in cartilage stem cell differentiation (Chen et al., 2024).

In addition to its role in dental stem cells and cartilage stem cells, ascorbic acid also plays a role in cancer stem cells. The latest findings indicate that cancer stem cells play a strong role in initiating the cancer process and its metastatic spread (Gillberg et al., 2018; Fu et al., 2020). Ascorbic acid has the potential to regulate the cancer epigenome by maintaining a balance between pro-apoptotic and anti-apoptotic genes through the preservation of DNA hypomethylation. Additionally, ascorbic acid is capable of controlling the metastatic spread of cancer by regulating the growth and transformation of cancer stem cells, the quantity and stability of collagen, extracellular matrix restructuring, immune response to cancer, and microenvironmental conditions influenced by hypoxia (Fu et al., 2020). The schematic diagram illustrating the role of ascorbic acid in cancer metastasis is described in Figure 2, adapted from the research findings of Fu et al., 2020.

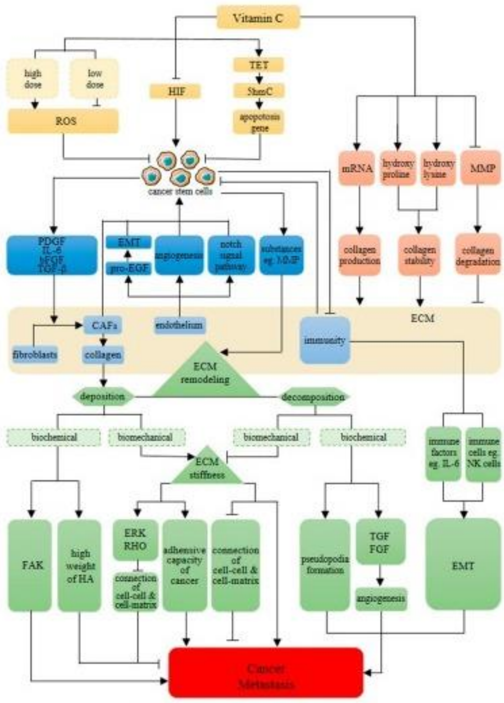

Figure 2. The Schematic Diagram Illustrating the Role of Ascorbic Acid in Cancer Metastasis

Vitamin D3

Vitamin D3, also known as cholecalciferol, is renowned for its role in regulating the balance of calcium and phosphorus in the body, which is crucial for maintaining bone homeostasis and strength. In addition to aiding the absorption of these minerals in the intestines and reducing their excretion through the kidneys, vitamin D3 also strengthens bone calcification and stimulates various osteoblast functions, such as differentiation, proliferation, as well as the expression of various specific proteins and growth factors. The production of vitamin D3 occurs in the skin from the precursor 7-dehydrocholesterol through a process requiring exposure to ultraviolet (UV) radiation, but it can also be obtained through food or supplements (van Driel and van Leeuwen, 2017; Borojević et al., 2022).

Vitamin D3 has been proven to play a crucial role in supporting the survival of stem cells. Recent research indicates that vitamin D3 can enhance development, show expression of pluripotency markers (NANOG, SOX2, and Oct4), and activate differentiation potential towards bone formation in Bone Marrow Mesenchymal Stem Cells (BM-MSC). Additionally, vitamin D3 also demonstrates potential to reduce the aging process in BM-MSCs (Borojević et al., 2022). The research findings analyzed by Borojević and colleagues examined the effects of Vitamin D3 on osteogenic differentiation of BM-MSCs using ALP and Alizarin Red staining. From the analysis, it was found that there was a significant increase in early and late osteogenesis of BM-MSCs maintained in osteogenic medium enriched with Vitamin D3 (Borojević et al., 2022). The analysis of the research results is depicted in Figure 3, adapted from Borojević et al., 2022.

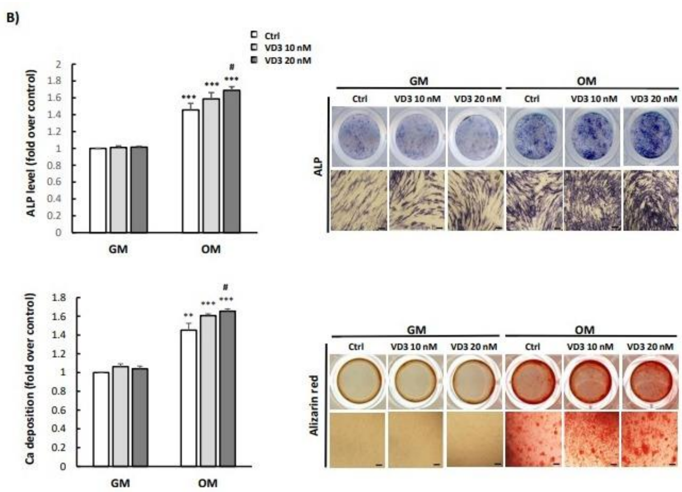

Figure 3. The Osteogenic Cell Growth of BM-MSCs was Evaluated in Growth Medium (GM) or Osteogenic Medium (OM), Both With and Without the Presence of Vitamin D3

Vitamin E

Vitamin E refers to a group of fat-soluble compounds, consisting of tocopherols and tocotrienols. As an antioxidant, this vitamin helps protect cell membranes from oxidation-reduction (redox) processes (Cardenas and Ghosh, 2013; Ghasemi et al., 2021).

Based on the research conducted by Ghasemi and team, it was found that the administration of vitamin E and selenium helps mesenchymal stem cells to inhibit dendritic cells and enhance their immunomodulatory effects. These findings are consistent with the research analysis, which indicates that MSC CM can increase CD40 on myeloid dendritic cells. The administration of vitamin E and selenium in MSC CM has been shown to reduce CD40 and increase the concentration of IL-10 in dendritic cells (Ghasemi et al., 2021).

SUMMARY

All of these vitamins play a key role in maintaining the health and function of stem cells and body tissues. Almost all types of vitamins that have been studied have a similar role in supporting the survival of stem cells by promoting their differentiation. However, previous research has found a different role for vitamin E in stem cells. Vitamin E acts as a supporter of mesenchymal stem cells to inhibit dendritic cells and enhance immunomodulatory effects.

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