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Original Research Article

Vitamin D Controls Cancer by Regulating Telomere and Telomerase

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ABSTRACT

Deficiency of vitamin D in the body may cause many disorders and diseases including cancer. Vitamin D receptors are one of the most important nuclear receptors responsible for transcription and cellular proliferation and thus affects telomere and telomerase. Telomerase enzymes is responsible for transcription and copies the telomere. The process of telomere copying leads to absence of cell death and thus causes the cellular proliferation of cells within the body. If maintained at normal level, vitamin D regulates and controls the processes of cellular replication and proliferation leading to control and regulation of rate of secretion of telomerase which in turn maintains the appropriate telomere length. Since telomerase is one of the primary factors of cancer spread, telomerase regulation and control can lead to cancer control. Therefore, by maintaining normal vitamin D level in the body DNA can be protected from damage.

Keywords: Cancer, Vitamin D, Vitamin D receptors, Telomere, Telomerase

INTRODUCTION

There are different sources of vitamin D, but the sun is the main source of vitamin D in the body, which is not limited to maintaining the health of teeth and bones only but affects many of the functions of the body[1]. Vitamin D receptors are one of the most important nuclear receptors responsible for reproduction and cell proliferation. It is also responsible for maintaining the immune system. Vitamin D receptors are found in almost all the types of cells in the body. Therefore, vitamin D deficiency is responsible for many disorders and diseases including cancer[2]. Cancer is the second leading cause of death in the world[3]. There are several different treatments of cancer such as strategies of radiation therapy, chemotherapy, immune therapy and the vitamin D supplements. Treatment by vitamin D is one of the most important treatments on which many studies have been done[4-6]. The telomerase is 90% active in cancer cells and therefore affects telomere length which is responsible for cell proliferation and death i.e., cells immortality. Vitamin D affects the telomerase and thus can control the cancer cells by controlling the regulation of telomerase and telomere.

Vitamin D

The sun is the main source of vitamin D. When the ultraviolet light drops on the human skin, the vitamin D starts to form in the body. Vitamin D is also found in very few foods, such as some fish and fish oil, in addition to a very minimal quantity in liver and fungus. It is also available in the form of Vitamin D fortified

products, such as milk, and in form of capsules[1]. The deficiency of vitamin D may lead to several complications and diseases. Its deficiency may cause loss of bone density that contributes to fractures and osteoporosis. Other disease includes diabetes, blood leukemia, rectal diseases, colon cancer, prostate cancer and other cancer[7-9].

Vitamin D is soluble in fat. Vitamin D3 is formed in the skin when ultra-violet (UV) rays interact with 7-Dehydrocholesterol, a type of cholesterol[8]. The compound 25-hydroxyvitamin present in the liver turns into 1,25-dihydroxyvitamin (calcitriol), active form of vitamin D, in the kidney[9]. Vitamin D increases the intestinal absorption of phosphorus, magnesium and calcium thus it affects the health of bones and teeth significantly. Vitamin D deficiency also weakens the muscle strength[7,9].

Vitamin D Receptors

Most of the cells contain receptor for vitamin D. Vitamin D receptors (also called as calcitriol receptor) belongs to the superfamily of steroid/thyroid hormone nuclear receptor, which are located mainly in the nuclei of target cells. Calcitriol allows the vitamin D receptors to act as a transgenic agent that regulates the gene expression of the vector proteins which are involved in calcium absorption in the intestine. Vitamin D receptors are produced by the cells in most of the organs such as brain, heart, skin, gonads, prostate and breast. The activation of vitamin D receptors in the intestine, bone, kidney, and thyroid cells helps to maintain the calcium and phosphorus levels in the blood with the help of thyroid hormone and calcitonin[10-12]. The vitamin D receptors are expressed in the natural killer cells, B and T lymphocytes, and monocytes. By the down-regulation of cytokine and other pro-inflammatory factors, vitamin D imparts major anti-proliferative and anti-inflammatory effects, which may influence the leukocytes turnover. So, vitamin D supplements will be able to protect against immune diseases and decrease vitamin D deficiency[7,9,11].

Cancer

Cancer is a group of disease that are described by genetic events in which normal cells acquire genomic instability and thus obtained the potential to replicate indefinitely. It cannot be controlled with its ability to invade neighboring and distant tissues and destroy them. When the tissues are aggressive in nature, it is called malignant tumor, which is the opposite of the benign tumor. In benign tumor growth is limited and does not have the ability to move to different places in the body and is not a sign of cancer[13,14]. But sometimes the benign tumor may convert to malignant tumor. More than 100 types of cancer are classified. Cancer can affect all the stages of human body including the fetus, but the risk increases as the person progresses in age[7].

Four factors play an important role in the carcinogenesis i.e., the environment, reproductive life, diet and smoking. These factors may turn normal cells into cancerous cells when changes occur in the genetic material such as a randomized error, a mutation in the DNA version of cell division, or inheritance of this mutation from the mother cell. All these factors affect cellular processes and enzymes within the body. One of the most important of these enzymes is telomerase, which restores the length of the telomere, which causes the absence of cell death[7].

Telomere and Telomerase

Telomere is a group of consecutive nucleotides sequence (TTAGGG) which are nucleoprotein in nature. Telomere is made up of polymerase and telomerase and other enzymes. The telomere protects the end of chromosomes from erosion and disappearance of genetic information (DNA preservation) after each cell division. Each chromosome contains two telomeres and a total 92 telomeres in the diploid human cell[15-17]. Telomerase is an enzyme that works to repair ribosome nuclear protein to maintain telomere length but does not prevent its depletion completely. Telomerase is largely present in stem cells, white blood cells and fetal cells[15]. Telomerase is active

in 90% of cancer and tumors. The action of telomerase can be sub-divided into three different steps. The first step involve binding of 3'matrix end of chromosome of short telomere with the RNA domain. The second step, direct addition of nucleotide leading to elongation. The last step includes the translocation that enables repeated use of the same binding site[16,17].

Relationships between Vitamin D and Cancer

Some studies have shown that colon, prostate, and breast cells contain the enzyme required for producing 1,25- dihydroxy vitamin D[18]. A study was conducted on the growth of cancer cells and found that on average tumor was 80% bigger in mice that were deficient in vitamin D as compared with vitamin D-sufficient mice. Vitamin D is one factor that causes the high rate of cancer than many cancers including breast cancer[19]. Low serum level of 25-hydroxyvitamin D were reported to be associated with greater risks of breast cancer[7,20]. Studies of tumors and cancer cells in mice showed that vitamin D have many activities which may slow down or prevent cancer development, including decreasing cancer cell growth, promoting cellular differentiation, reducing tumor blood vessel formation and stimulating cell death[21]. The author Hisatake *et al.*, conducted a study on mice and found that cell inhibition of breast and prostate cancer was obtained by 40% in three days with increased vitamin D concentration[22]. The author Liu et al., studied the relation between relative leukocyte telomere length and vitamin D by using plasma 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D biomarkers. He found that high plasma level of 25-hydroxyvitamin D might be related with longer telomeres, and this association may be modified by calcium intake[23].

The ovarian cancer is one of the major causes of death in the United States. The study by Zhang and others showed the effect of vitamin D receptors in tumor suppression in mice. He found that multiple ovarian cancer cell lines responded to active form of vitamin D, for growth suppression. Also, they identified vitamin D regulated genes with known function in ovarian tumorigenesis as mediators for growth suppression. He concluded that vitamin D receptor which mediate the anti-tumor effects may represent the novel molecular target for developing new therapeutics for the ovarian cancer. This implies that future of vitamin D might become the new goal of treating ovarian cancer[24]. Furthermore, some studies have shown the relationship between Vitamin D and the cancer injury i.e., the decrease in vitamin D level increases the risk of cancer[18]. Current research suggests that vitamin D is one of the factors that inhibit growth and helps in differentiation and apoptosis through many molecular targets. As there is receptors of vitamin D in cytoplasm in the active form of 1,25-hydroxyvitamin D, it recognizes vitamin D response element in the gene promoter region and thus regulates the transcription of target gene[7].

Relationship between Telomere and Telomerase with Cancer

After several divisions, cells attain the stage of cellular aging due to a lack of telomere length at each split and these vital processes lead to cell death[25]. In normal cells there is a balance between the telomerase secretion and the telomere length. If the telomere is short, telomerase secretion is increased, and if telomere is long, telomerase secretion is decreased[12]. But in case of cancer cells there is continuous division and reproduction and thus the cell does not reach ageing stage because of increase in telomerase enzyme in it[26,27]. Telomerase is found in around 90% of all the type of malignant tumors[28,29]. The systematic review by the author Popli and others investigated the relationship between increased protein the human telomerase revers transcription (hTERT) and increased oral squamous cell carcinoma (OSCC)[25]. A study was conducted on the growth of bladder cancer cells by inhibiting catalytic subunit of telomerase (hTERT) which were found to cause remarkable long- and short-term effects on the growth of bladder cancer cells[26]. In human, clinical studies has also been done for hTERT immunotherapy strategies[30]. The study by Jerry

et al. on telomerase found that inhibitors have an effective role in the treatment of patients with cancer and thus looks forward to use telomerase as a global cancer treatment goal[26].

Effect of Vitamin D on Telomere and Telomerase

Telomere is found on the ends of the chromosome. With each division of cell, it decreases in length until the cell reaches the stage of aging i.e., there is a decrease in its activity, and it stop functioning followed by cell death. But when telomere is reduced or shortened, it may stimulate the secretion of telomerase inducing the cell's immortality, increase its activity, and transform it into a cancer cell. Also, when telomeres are longer than normal it indicates that the cell may turn into a cancer cell due to increased activity of telomerase[25]. A randomized clinical trial with seventy African Americans participants having serum 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L were treated with vitamin D3 supplements or placebo. The results suggests that vitamin D3 supplements may slow down the Horvath epigenetic aging as it increases telomerase activity[31]. There is an early onset of aging in white blood cells of dialysis patients due to the reduction in telomere length. A retrospective study was done with 62 hemodialysis patients and 60 healthy individual and the role of active vitamin D treatment on the telomere length in peripheral mononuclear cells (PBMC) was measured. It was measured in PBMC by southern blot and the hemodialysis patients treated with active vitamin D were found to have longer telomere length as compared to untreated individual[2,32].

Suramin is used as an alternative treatment in some cancers. A study found that Suramin reduces the alkaline-phosphatase secretion upto 50% after stimulating by 1,25-dihydroxy-Vitamin D (3) and reduces the telomerase activity by approximately 40% in human osteosarcoma cells[33]. There is a direct effect of vitamin D on white blood cells and C-reactive protein (CRP). CRP protein is a sign of the presence of inflammation in healthy people with chronic inflammatory diseases. CRP reduces telomere length in white blood cells leading to impaired immunity. It indicates that there is an inverse relationship between vitamin D and CRP. A study found that vitamin D reduces inflammation and affects white blood cells increasing telomere length which leads to immune strength[12]. According to a study conducted on 1424 Caucasian women, there is a relationship between the increase of vitamin D in plasma and increase in the length of telomere in white blood cells (leukocyte) as measured using both plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D[23]. In a study seventy African Americans were divided into four groups at random and they were given serum 25-hydroxyvitamin D< 50 nmol/L. Each group took a different concentration of 25-hydroxyvitamin D <50 nmol/L for 16 weeks. In the group that dealt with the concentration of 4000 units, the international ratio decreased aging by 1.85 years. This indicates that the activity of telomerase increased resulting in decreased aging which thus means increasing telomere length because taking vitamin D supplements[31]. Taking enough vitamin D preserves DNA and reduces oxidation in cells, clinical trial results showed the effect of vitamin D supplementation on oxidative reduction in colon and rectal cells. Decreased oxidation of chromosomes and chromosomal aberrations were observed on different cell types in animals after taking vitamin D supplementation. This shows that vitamin D has a role in preventing DNA damage by regulating cell growth rate by preventing telomere shortening and inhibition of telomerase activity[2,34].

CONCLUSION

Vitamin D is one of the most important vitamins whose deficiency in the body may cause many disorders and diseases including cancer. Vitamin D receptors are one of the most important nuclear receptors they are responsible for transcription and cellular proliferation and the gene encoding the human vitamin D receptors is located on the long arm of chromosome 12. This indicates that vitamin D affects telomere and telomerase. Telomerase is one of the enzymes

responsible for transcription. It copies the telomere which is the end of the chromosome. The process of telomere copying leads to absence of cell death and thus causes the cellular proliferation of cells within the body. If maintained at normal level, vitamin D regulates and controls the processes of cellular replication and proliferation, and this leads to the regulation and controls of the rate of secretion of telomerase which in turn maintains the appropriate length telomere. If the telomere is short the body secrete telomerase at the appropriate quantity, the telomere will reach the appropriate length. Whereas if the telomere long there is less telomerase secretion and thus telomere will return to its proper length. Since telomerase is one of the primary factors of cancer spread, telomerase regulation and control can lead to cancer control and by maintaining the normal vitamin D level in the body, it keeps DNA from damage.

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