Vol 5|Issue 3| 2015 |212-216.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

A COMPREHENSIVE REVIEW ON TREATMENT OF CANCER USING RETINOIC ACID RECEPTORS

D. Sireesha*, P. C. Jayanth, P. Rajasekhar, M. Niranjan Babu

Department of Pharmacology, Seven Hills College of Pharmacy, Tirupati-517501, Andhra Pradesh, India.

ABSTRACT

A tumor or neoplasm occurs when abnormal cells form within the brain. There are two main types of tumors they are malignant or cancerous tumors and benign tumors. Brain cancer can have a wide variety of symptoms including seizures, sleepiness, confusion, and behavioral changes. A brain tumor is a mass or growth of abnormal cells in or close to your brain, which can be noncancerous (benign) or cancerous (malignant). Tumors can begin in your brain (primary brain tumors), or cancer can begin in other parts of your body and spread to your brain (secondary, or metastatic, brain tumors). The current article gives an idea about the pathogenesis, various causes, diagnosis and the latest methods of treatment available for cancer using vitamin A through the retinoic acid signaling pathway.

Key words: Seizures, Confusion, Tumors, Metastatic, Retinoic acid signaling pathway.

INTRODUCTION

Cancerous tumors can be divided into primary tumors that started within the brain and those that spread from somewhere else known as brain metastasis tumors, this article deals mainly with primary tumors. All types of brain tumors may produce symptoms that vary depending on the part of the brain involved these may include headaches, seizures, problem with vision, vomiting, and mental changes. The headache is classically worst in the morning and goes away with vomiting [1, 2]

Pathophysiology

Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in *many* genes are required to transform a normal cell into a cancer cell [3].

Causes of cancer

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control.

Carcinogens

Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer. Tobacco, asbestos, arsenic, radiation such as gamma and x-rays, the sun, and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to carcinogens, free radicals are formed that try to steal electrons from other molecules in the body. Theses free radicals damage cells and affect their ability to function normally.

Genes - the family type

Cancer can be the result of a genetic predisposition that is inherited from family members. It is possible to be born with certain genetic mutations or a fault in a gene that makes one statistically more likely to develop cancer later in life.

Chemical Carcinogens

A carcinogen is something (chemical, radiation, etc) which can damage a cell and make it more likely to

*Corresponding Author **D. Sireesha** E mail: Jayanthpharmacy@gmail.com

turn into a cancerous cell. As a general rule, the more the exposure to a carcinogen, the greater the risk. Well-known examples include:

Tobacco**,** If you smoke, you are more likely to develop cancer of the lung, mouth, throat, oesophagus, bladder and pancreas. Smoking is thought to cause about 1 in 4 of all cancers. About 1 in 10 smokers die from lung cancer. The heavier you smoke, the greater the risk. If you stop smoking, your risk goes down considerably.

Workplace Chemicals**,** such as asbestos, benzene, formaldehyde, etc. If you have worked with these without protection you have an increased risk of developing certain cancers.

Age

The older you become, the more likely that you will develop a cancer. This is probably due to an accumulation of damage to cells over time. Also, the body's defences and resistance against abnormal cells may become less good as you become older. For example, the ability to repair damaged cells, and the immune system which may destroy abnormal cells, may become less efficient with age. So, eventually one damaged cell may manage to survive and multiply out of control into a cancer. Most cancers develop in older people.

Radiation

Radiation is a carcinogen. For example, exposure to radioactive materials and nuclear fallout can increase the risk of leukemia and other cancers. Too much sun exposure and sunburn (radiation from UVA and UVB) increase your risk of developing skin cancer. The larger the dose of radiation, the greater the risk of developing cancer. But note: the risk from small doses, such as from a single X-ray test, is very small.Infection

Some germs (viruses and bacteria) are linked to certain cancers. For example, people with persistent infection with the hepatitis B virus or the hepatitis C virus have an increased risk of developing cancer of the liver. Another example is the link between the human papillomavirus (HPV) and cervical cancer. Most (possibly all) women who develop cervical cancer have been infected with a strain (subtype) of HPV at some point in their life. Another example is that a germ (bacterium) called *Helicobacter pylorus is* linked to stomach cancer [3].

Classification scheme for brain tumours

Diagnosis

Tests that examine the brain and spinal cord are used to detect (find) adult brain tumor. The following tests and procedures may be used:

CT scan

A procedure that makes a series of detailed pictures of are as inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.

MRI (Magnetic Resonance Imaging)

A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of the brain and spinal cord. A substance called gadolinium is injected intothe patient through a vein. The gadolinium collects around the cancer cells so they show up brighter in the picture. This procedure is also called nuclear magnetic resonance imaging (NMRI).Adult brain tumor is diagnosed and removed in surgery. If a brain tumor is suspected, a biopsy is done by removing part of the skull and using a needle to remove a sample of the brain tissue. A pathologist views the tissue under a microscope to look for cancer cells. If cancer cells are found, the doctor will remove as much tumor as safely possible during thesame surgery. An MRI may then be done to determine if any cancer cells remain after surgery [4].

Treatment

There is no single treatment for cancer - doctors have a range of options available and must decide which is best for each patient. They will often combine several types of treatment for greater effect, taking into account all sorts of factors.

For example, the patient's age, history and lifestyle are very important in deciding on the best treatment. Doctors will involve the patient in the decision as much as possible.

- Surgery
- Radiotherapy
- Chemotherapy
- Hormone therapy
- Immunotherapy
- Gene therapy
- Transplantation

Retinoic Acid in Cancer Therapy

Retinol and vitamin A derivatives influence cell differentiation, proliferation and apoptosis and play an important physiologic role in a wide range of biological processes. Retinol is obtained from foods of animal origin. Retinol derivatives are fundamental for vision, while retinoic acid is essential for skin and bone growth. Intracellular retinoid bioavailability is regulated by the presence of specific cytoplasmic retinol and retinoic acid binding proteins (CRBPs and CRABPs) [5].

Metabolism of Retinol and Its Derivatives

Vitamin A can be acquired from the diet either as preformed vitamin A (primarily as retinyl ester, retinol and in much smaller amount as retinoic acid) or provitamin A carotenoids Dietary retinyl esters are converted to retinol within the lumen of the small intestine or the intestinal mucosa and then re-esterified to form retinyl ester (RE) within the enterocyte Provitamin A carotenoids, absorbed by the mucosal cells, are converted first to retinaldehyde and then to retinol [6].

Intracellular retinoic acid pathway

A cell-surface receptor named retinoic acid 6 (STRA6) mediates vitamin A uptake from RBP. Intracellular retinoid bioavailability is regulated by the presence of specific cytoplasmic retinol and retinoic acid binding proteins, CRBPs and CRABPs. In the cytoplasm vitamin A and derivatives are bound to cytoplasmic proteins: Cellular Retinol Binding Proteins (CRBPs) which comprised four isoforms: CRBP-1, CRBP-2 and CRBP-3 and CRBP-4. CRBP-1 is the most represented isoform in many tissues [7].

Retinoic Acid Induces Tumor Suppressors and Protooncogenes

The wide range of genes which are associated with cancer suggests that RA can have a large number of biological effects. Therefore, it is unsurprising that RA has a role in cancer which can be promotional or suppressive. RA induces expression of documented proto-oncogenes and tumor suppressors (e.g. Mucin 4, MUC4; and retinoic acid receptor beta isoform 2, RARβ2) [8, 12].

RA has beenassociated with tumor genesis as well as tumor inhibition. Retinoic-acid receptor responder protein 1 (RARRES1, formerly TIG1) is another RA-inducible gene which is gaining notice as a tumor suppressor in many cancer types. Typical of tumor suppressors, RARRES1 is also often silenced in cancers by promoter such as hyper methylation [9, 10].

Retinoic Acid Signaling In Tumor Multiplication

There is increasing evidence for a significant role of the tumor stroma in cancer progression and metastasis. Activation of stromal fibroblasts occurs early in tumor development and stromal cells cross-talk with the cancer cells of the tumor, resulting in increased tumor genesis. There is support for aberrant RA signaling via the tumor stroma as well as from cancerous cells. High levels of ALDH1A1 (also known as RALDH1), which generates RA from retinal is often expressed in the stroma of breast cancer patient tumors and has been correlated with better survival in breast cancer. With respect to expression of RA-inducible genes such as RARβ in the tumor stroma, the data is conflicting. Supporting its likely role as a tumor suppressor, RARβ expression is frequently lost in the tissue adjacent to tumors. However, confounding this theory, in an ErbB2-induced mammary tumor genesis model, stromally-expressed RARβ is required for mammary tumor genesis. Not only does this provide evidence of a potential role for RARβ in promoting cancer; but, it also illustrates that RA signaling in the stroma can be tumorigenic [10, 11].

Retinoids in Cancer Prevention And Therapy

Now a days the retinoic acid i.e., Vitamin A is used in the treatment of the following Cancers

1. Acute promyelocytic anemia
2. Breast cancer
3. Ovarian cancer
4. Pancreatic cancer
5. Lung cancer
6. Prostate cancer and Neuroblastoma

Fig 1. Pathogenesis of cancer

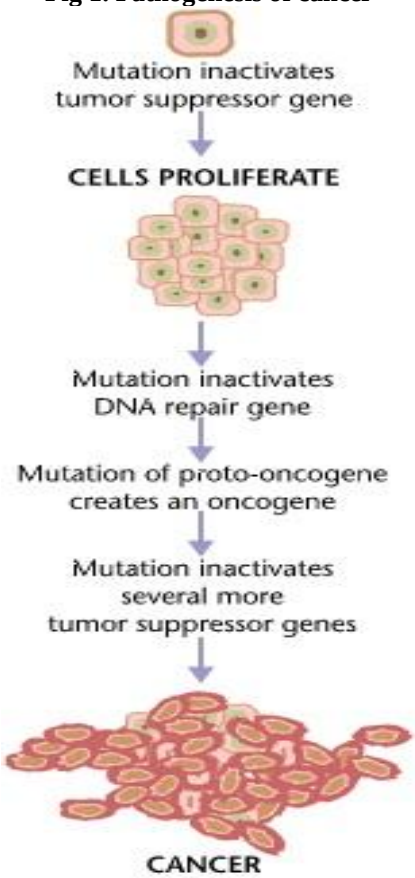


Fig 2. A. Classifications of Brain Tumor, B. Histopathological view of various Brain tissues

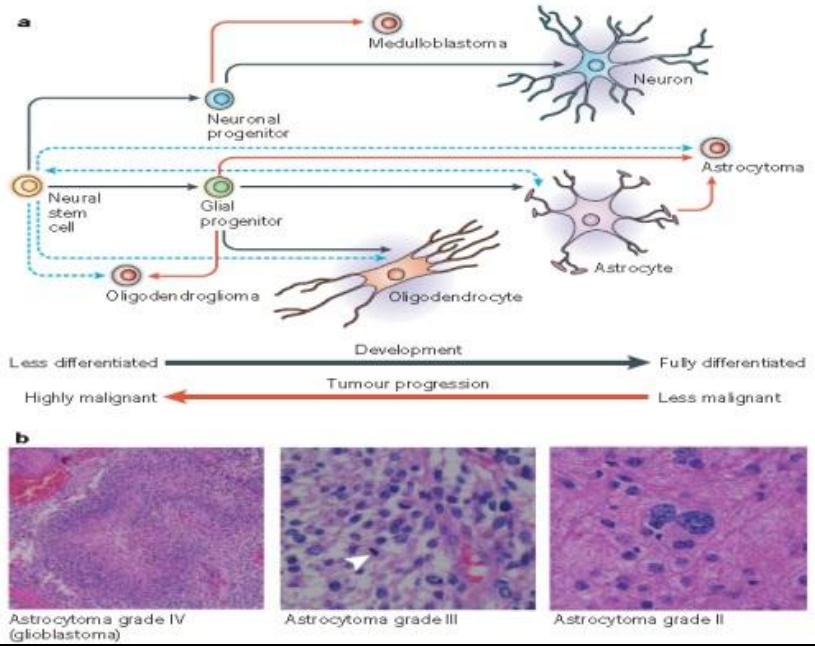


Fig 3. Absorption, transport and distribution of dietary retinoids

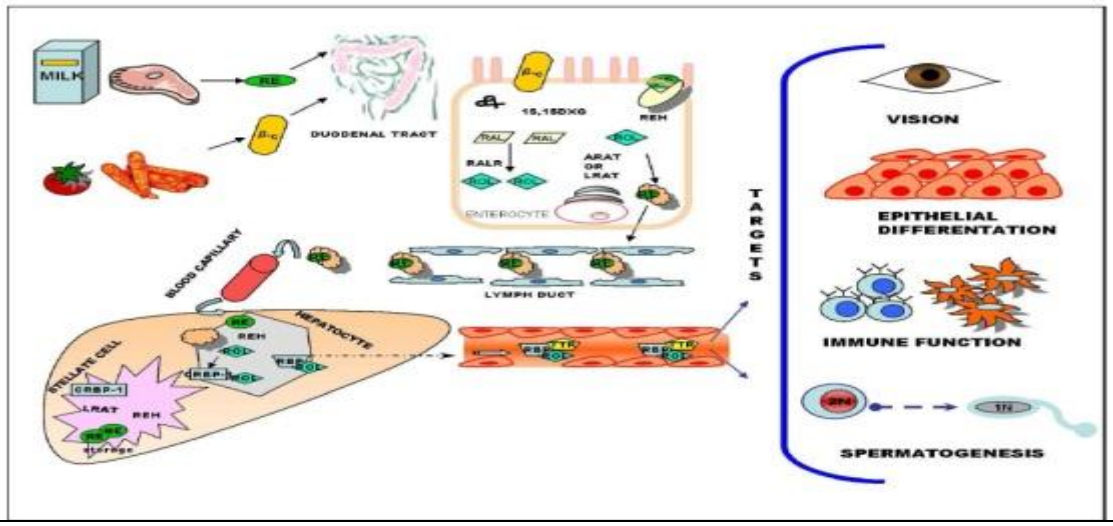
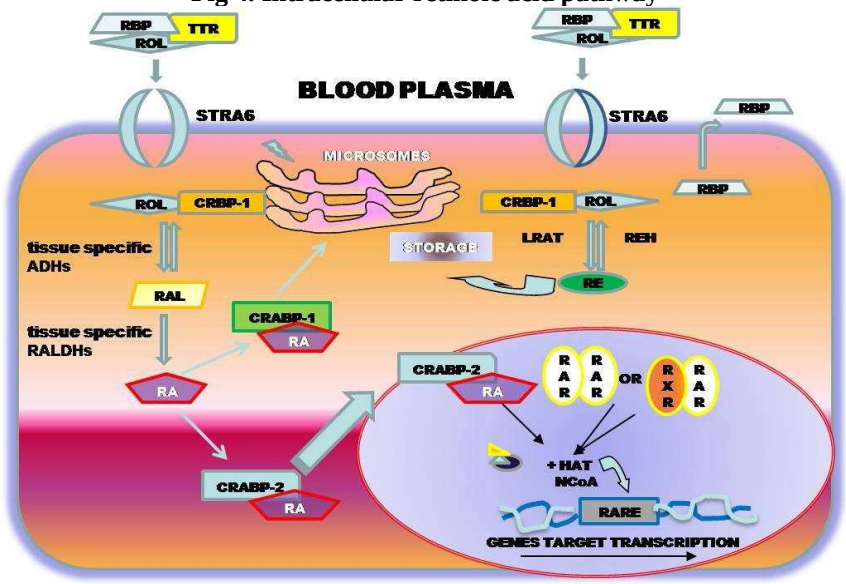


Fig 4. Intracellular retinoic acid pathway



CONCLUSION

Since the retinoic acid is involved in the cell differentiation, proliferation and as it induces the tumor suppressor gene it (Vitamin A) can be used in the treatment of various types of cancer which is not curable with many types of therapy like chemotherapy, Radiation therapy, Gene Therapy Etc.., More studies are required to prove that the retinoic acid can be used in the treatment of cancer.

REFERENCES

1. Anonymous 1. http://www.netofcare.org/content/pdf/6-spec_illness-cancer.pdf
2. Anonymous 2. http://en.wikipedia.org/wiki/Cancer
3. Anonymous 3. http://www.onlinewellness.in/wpcontent/uploads/2014/09/cancercauses.jpg
4. Anonymous 4. http://www.medicinenet.com/cancer_detection/article.html
5. Noy N. The ionization behavior of retinoic acid in lipid bilayers and in membranes. *BiochimBiophysActa*, 1106, 1992, 159-164.
6. Blaner WS, Byrne SM, Wongsiriroj N, Kluwe J, Ambrosio DM, et al. Hepatic stellate cell lipid droplets: a specialized lipid droplet for retinoid storage. *Biochim BiophysActa*, 1791, 2009, 467-473.
7. Kanai M, Raz A, Goodman DS. Retinol-binding protein: the transport protein for vitamin A in human plasma. *J Clin Invest*, 47, 1968, 2025-2044.
8. Kawaguchi R, Yu J, Honda J, Hu J, Whitelegge J, et al. A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. *Science*, 315, 2007, 820-825.
9. Fex G, Johannesson G. Retinol transfer across and between phospholipid bilayer membranes. *BiochimBiophysActa*, 944, 1988, 249-255.
10. Berry DC, Jacobs H, Marwarha G, Gely-Pernot A, O'Byrne SM, et al. The STRA6 receptor is essential for retinol-binding protein-induced insulin resistance but not for maintaining vitamin A homeostasis in tissues other than the eye. *J BiolChem*, 288, 2013, 24528-24539.
11. Posch KC, Boerman MH, Burns RD, Napoli JL. Holocellular retinol binding protein as a substrate for microsomal retinal synthesis. *Biochemistry*, 30, 1998, 6224-6230.
12. Loudig O, Babichuk C, White J, Abu-Abed S, Mueller C, et al. Cytochrome P450RAI(CYP26) promoter: a distinct composite retinoic acid response element underlies the complex regulation of retinoic acid metabolism. *MolEndocrinol*, 14, 2003, 1483-1497.