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Therapeutic Techniques for Cancerous Tumor Cells and Future Aspects of Molecular Cancer Therapy

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ABSTRACT

Cancer the most widely affecting problem in today's day has much research going on all over the world for the treatment of this ailment. There are precise techniques used for generalized treatment and personalized therapies that are separate for individual patients to ensure the termination of this uncontrolled cell division from the patient's body. Cancer is majorly caused by either genetic mutations that result in genetic alteration of the DNA and activation of oncogenes, or by the suppression of certain oncogene regulatory proteins including growth factors, growth factor receptors, PI 3-kinase, and Akt [1]. The treatment of cancer depends on its stage of development, fatality, location, and physiology. Here in this paper, we will be talking about some of the known cancer treatment methods and some uncommon and under research therapeutic techniques that are under development and in the phase of clinical trial and will try to formulate why are the molecular approaches better than the external chemical and radiological treatments.

Keywords: Theraupuctics; p53 Protein; PVSRIPO; Chemotherapy; Radiotherapy; Immunotherapy; Glioma; Nanoparticles

Introduction

Cancer is the uncontrolled and unequal growth of cells which results in the formation of an abnormal mass of cells that disturbs the normal functioning of our body. Cancers are also defined as uncontrolled tumor cells that tend to transport to other parts of the body, this is called a malignant tumor or cancer. Cancers can be caused due to certain genetic alterations or cell cycle disturbances that stop apoptosis (programmed cell death) and induce a faster rate of cell division due to enhanced expression of certain proteins or enzyme molecules [2]. The cancer cell mass can be fatal as it disturbs the normal functioning of the cells around it by blocking the cell signaling pathways and disrupting the blood flow in that area, it also advances further and causes neural damage by damaging the nerve cells and causing lag in the neuron signalings. The cancerous cells are parasitic and feed on the excess nutrients produced by the other cells that are essential for normal body functioning and produce toxins by regulating the different biochemical pathways and altering them according to their beneficial terms. There are currently different methods available for the treatment of different forms of cancers in the human body. These formulated treatment procedures are either target specific for example the use of nanoparticles for the delivery of cancer-specific drugs in conjugation with a biosensor [3] to effectively treat cancer cells or are localized to a certain part of the body only for example the focal therapy for the management of localized prostate cancer [4].

However when it comes to cancers that are very difficult to operate or for the treatment to reach e.g. Glioblastoma we require very specific treatment techniques to effectively treat these kinds of cancers and check for their permanent termination from the body. Glioma also sometimes referred to as glioblastoma is a form of brain tumor that might develop further to form a cancerous tissue inside the cerebrum of the CNS (central nervous system) and is not treatable due to the complex structure of a human brain. The glioma cells transform into glioblastoma when they reach the stage-4 of their development. There are four grades of glioma and each has a different strategy for treatment. The stages of glioma depend on the aggressiveness and the growth potential of the tumor [5].

Treatment of Cancer Cells through Radiotherapy

The most effective and most prominent ways of cancer treatment is the surgical removal of the tumorous cell mass and ensuring that there are no cells left as only one cell is enough for the regrowth of the cancerous tumor [6]. Radiotherapy ensures the elimination of any leftover cancer cells post-surgery by damaging the cell DNA and resulting in the denaturation of the cell cycle. Majorly X-rays are used for these purposes as they are highly penetrative and capable of damaging the genetic makeup of the cancerous cells. The ionized radiation directly affects the DNA makeup by inducing cleavages at certain points causing the breakage of the DNA and destabilizing the amino acid chains so that they couldn't conjugate together again [7]. Radiation therapy uses a high dose of radiation to kill cancer cells and shrink the tumor. The DNA is damaged beyond repair and therefore cannot be repaired by the reversing of damages of the pyrimidine chains and thereby the cell cannot perform the normal metastasis and dies. Radiation therapy doesn't kill the cell instantly but it takes days or weeks of continuous scheduled sessions for the radiation to fully and efficiently show its effects on the cancerous cells. It is a slow process and might sometimes cause collateral damage by damaging the healthy cells surrounding the area. The radiation therapy is very effective and localized to a certain area and therefore the damages caused are centralized to a particular place only.

However, it is not preferable in the treatment of cancers related to brain and gastric cancers as it might damage the neuron cells by damaging the DNA of those cells which might result in a series of ill effects ranging from motor functional loss, memory loss [8,9], endocrine malfunctioning [10], nervous system collapse [11], etc. Though it is a very effective method of killing or eliminating the leftover/ remaining cancerous cells it can play a vital role in initiating another cancerous development as the incomplete damage of the DNA of a normal cell might result in the activation of oncogene and the inactivation of oncogene regulating proteins, this will indirectly initiate the growth of another tumor cell mass [12]. The chances of relapse of a cancer patient undergoing radiation therapy are much higher than that of a normally treated person from chemo or molecular techniques.

Treatment of Cancer Cells by Chemotherapy

The word chemotherapy can be explained as the treatment of cancer cells by cytotoxic substances that are administered into the body by the intravenous method. The cytotoxins are the chemical substances that are toxic to the cancer cells. Cytotoxic substances target the uncontrolled growth in the cells and neutralize it by killing the infected cells. Chemotherapy can be used to either cure the cancer completely or to lessen the chances of its return, it is also used in some cases for reducing the size of the tumor as it stops or slows down the growth of new cells in that area. Chemotherapy works on almost all forms of cancer. Chemotherapy is used in accordance and association with other treatment methods and the main purpose served is to prevent the relapse of cancer development in the patient. Chemotherapy targets glycosphingolipids as a site of detection of cancer cells as the over-expression of specific GSLs and associated enzymes is associated with the initiation of the tumor and its transformation into a malignant tumor or cancer [13]. Chemotherapy majorly depends upon the type of cancer being treated as various medications are used as supplements during the chemotherapy associated with the form of cancer under treatment. Chemotherapy is a foreign introduction of a chemical cytotoxin into the human body that might sometimes prove to be fatal as the response of the immune system against these cytotoxins might result in allergic reactions [14]. Chemotherapy also is not a good choice as a treatment as it not only affects the cancer cells but also kills or slows down the growth of healthy cells [14].

The cost of this treatment is also not affordable to all as it might cost ~50,000 INR for one session. Chemotherapy is a prolonged treatment and might in some cases have to be done after regular intervals of time which makes it quite unaffordable for a common person to afford it. The patient prescribed chemotherapy is also given additional drugs to suppress the immune response of the body which makes the patient prone to a lot of severe infections. Chemotherapy though a very good alternative can't stand in a full statement of cure as it doesn't provide the effect it promises to, and a large number of setbacks or effects state it very clearly.

Using of Recombinant Polio Rhinovirus for Treatment of Cancer by Immunotherapy

The technique undermined these days for the treatment of glioblastoma a malignant primary brain tumor that represents approximately 57% of all gliomas and central nervous system tumours is the use of recombinant polio virus as a vector for the development of immunity against the cancer cells. Stage-4 glioblastoma has been cured by using this technique and the result from May 2012 to May 2017 was a total of 61 patients that were cured using this technique [15]. For this technique, the use of recombinant non-pathogenic polio-rhinovirus chimera (PVSRIPO) was administered in a very small quantity into the brain of the patient just close to the tumor development. The overall survival of the patients was more than 50% for the first few tests and then administered high dosage resulted in the formulation of the TCID50 by the researchers which gave it a drop to 21% at 24 months which was sustained for 36 months. The administered PVSRIPO is a recombinant strain of the very deadly and world widely eradicated polio virus which has been genetically engineered to lose its pathogenic abilities, the ssRNA of the polio virus provides an artificially triggered immunogenic response to the normal brain cells, and the T and B cells which once initiated tags the cancer cells and start attacking them. As the blood-brain barrier is very small therefore the polio virus stays localized to one place and kills all the tumor cells thereby removing the cancerous cells. This treatment is followed by a series of very mild chemotherapy to ensure the termination of cancerous cells throughout the body.

This method applies as an immunotherapy-based treatment of cancerous cells that would be natural and therefore will have very few chances of external contamination. The localized travel of the polio virus also restricts the movement of the pathogen throughout the brain. The administered PVSRIPO is non-pathogenic and therefore can have minimal side effects. There are certain ill effects to this technique, firstly polio is one of the nervous system attacking pathogens, and making it compatible to be administered into the CNS requires a lot of manipulation and external treatments which cost a lot of money and is not very economically feasible. The dose might only be administered once but a little daviation in the administered dosage might cause the activation of the pathogenicity of the ssRNA of the polio virus which can be fatal (Figure 1).

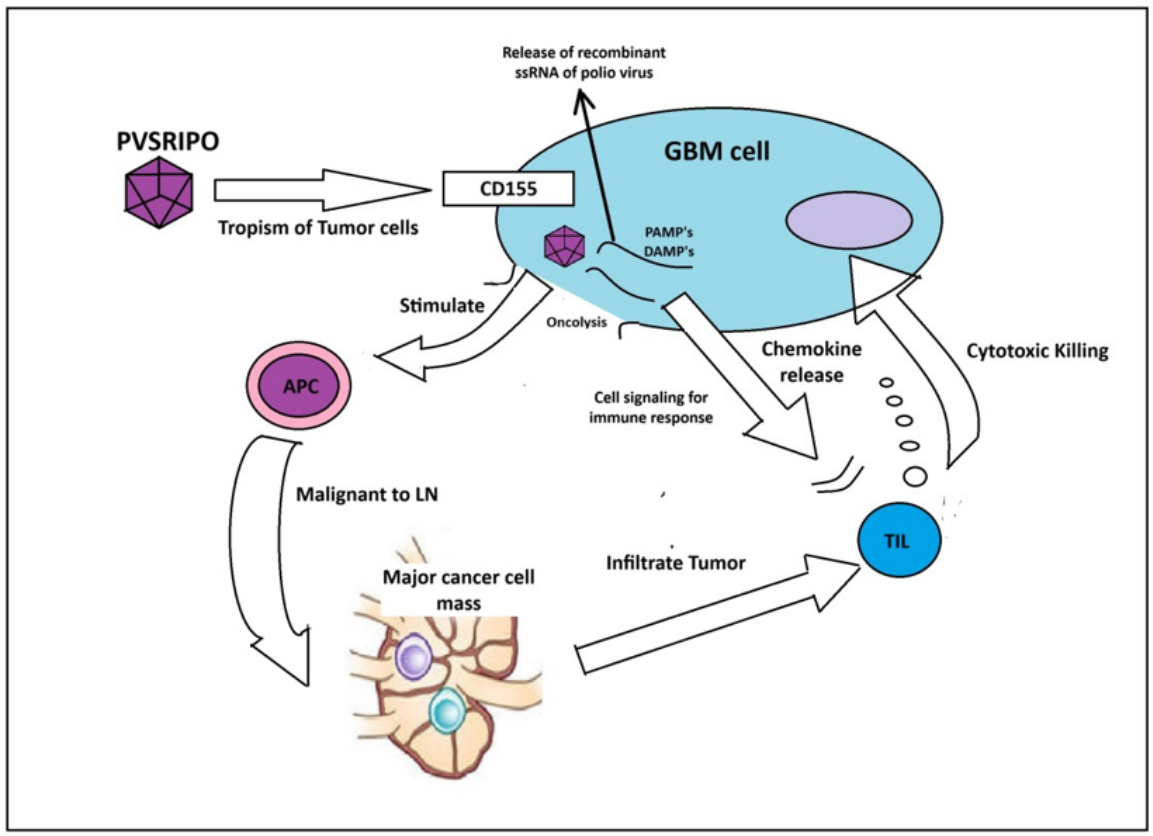

Figure 1: The following diagram represents the cycle of activation of immuno-response against the pathogen i.e., polio-virus.

Nanoparticles Induced Transfer of Conjugated Recombinant p53 Protein to Initiate Apoptosis in Cancer-Affected Cells

Nanoparticles have given us the power of target drug delivery and made it easier for us to monitor drug release at a particular rate. They are trusted particles for the drug delivery of many therapeutic and anti-cytotoxic drugs [16]. The use of Alkylcyanoacrylates polymers ranging from a size of 20-3000 nm is already emphasized in chemotherapeutics for their small size and less molecular mass and therefore they can cross the blood-brain barrier easily and more effectively than other drug molecules [17]. The p53 is the most widely studied protein for the treatment of cancer with more than fifty thousand publications generated till 2010 [18]. p53 is a protein, abnormality which can result in the initiation of cancer development in our body cells as it is the regulatory protein for programmed cell death and DNA repair [19]. The cancerous cells have a silencing mechanism for the p53 protein and therefore have an uncontrolled cell growth and division. The externally provided dormant form of p53 can be a pioneer in targeted drug delivery and natural drug therapy for the tumor. The basis for the technique is the nanoparticles-embedded transfer of dormant p53 protein with conjugation of initiation protein and a biosensor which is present for the specificity of drug transfer. P53 protein is the product formed by the transcription of the TP53[20] gene that is responsible for initiating the process of apoptosis in a normal cell, this protein is the cell suicidal protein that is present in the cell in an inactive form and activated only when the excess of a regulatory protein MDM2 which in stressful conditions activated the p53 protein.

The p53 protein is the protein that can initiate DNA repair, cell division, and apoptosis under the conditions of stress. The p53 protein conjugated with nanoparticles [21,22] can be easily transported into the tumor cell mast, along with the MDM2 dissociative protein that will initiate the dissociation of MDM2 and activation of the dormant p53 molecule [23]. The p53 molecule is induced in its dormant and not active state as it will be targeted to the specific tumor cells and if in case the receptor sites of cancer and the normal cells show similarity the MDM2 present will not be denatured, thereby preventing the apoptosis of a normal cell [24]. The recombinant p53 will have stretches of conjugation sites [25] that will bind with the Bax and Apaf1[26] to initiate the cell death mechanism. For cancerous cell identification, we can also use specific biosensors [27] adsorbed into the nanoparticles to make them target-specific. This technique can be used specifically for treating cell mass cancer and not blood cancer as the efficiency of the nanoparticles is more prominent when it comes to a stagnant mass of cell targeting therapy. This technique can also be used for the treatment of brain cancer as these conjugated particles will be of size <350kDA and so can pass through the blood-brain barrier (Figure 2).

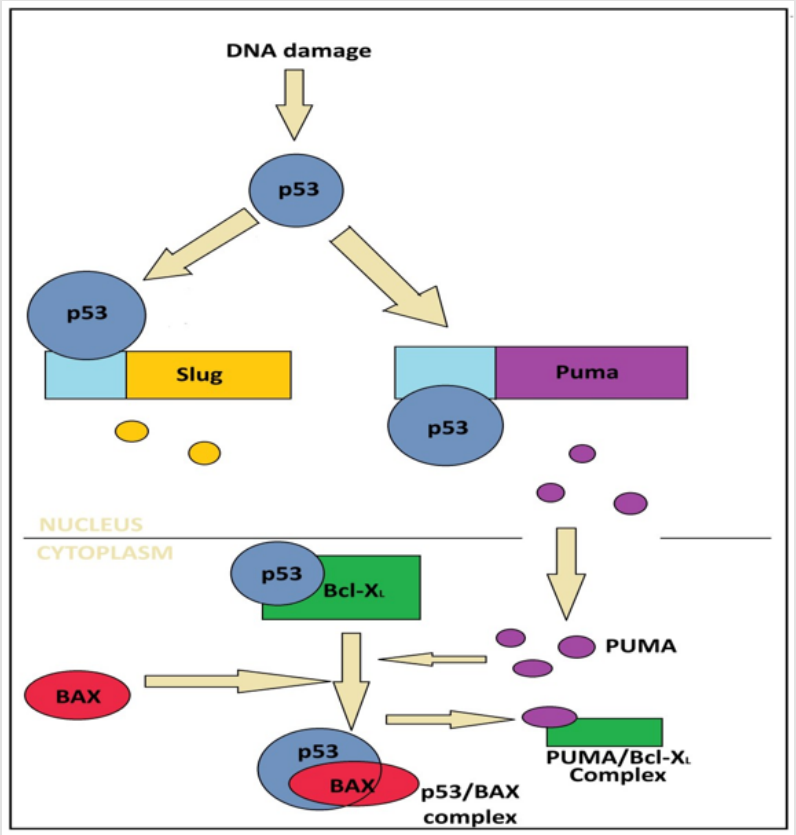

Figure 2: The following figure is the pathway for activation of p53-induced apoptosis. In this figure, the end product i.e., p53/BAX complex is the primary initiative molecule for the activation of programmed cell death.

Discussion

The techniques available for the treatment of cancer are still under development and as cancer is never the same for all we need to understand that different treatments would have different effects on individual patients. The most prominent and in-use treatment methods are chemotherapy and radiotherapy accompanied by the different forms of surgical and immunotherapies. All the available techniques lack in some or the other aspect of the treatment and might have certain drawbacks, but in the case of molecular techniques such as the use of recombinant poliovirus for generating the immune response or the use of conjugated recombinant p53 molecule for initiating apoptosis in cancer affected cell, we can observe that there is no foreign invasion the molecular stability of the biochemical pathways is maintained and the integrity of the body system is not harmed. The polio virus therapy might not prove to be very effective for days to come but will be a breakthrough in the future after all the criteria are met. Similarly, there has been continuous research in the process for the transfer of recombinant p53 protein molecule into the targeted cancer cells and to prevent it from entering into normal functioning cells. The research and clinical trials for new individual techniques or

personalized cancer treatments are undermined and will be in effect very soon but the immunotherapeutic techniques are the natural responses and therefore are more beneficial to our human body.

Conclusion

Cancer might be an uncurable growth of cells but the prospects lie in the natural biomolecular and genetically engineered techniques [28]. The use of biomolecules doesn't interfere with the natural processes of the body and neither cause harm to our body. Immunotherapeutic techniques are under development but have a very low chance of toxicity and ill effects that can be caused by administering foreign chemical substances in our bodies. The recombinant poliovirus technique is under study and has been giving promising outputs [29-31] which shows us that the future lies in the recombinant molecular techniques for the generation of an immunogenic response as it has close to no generative toxicity and therefore is a replacement to the current radiological and chemotherapeutic treatments. The use and prospect of research on the p53 molecule provide us with the hope of a new form of cancer therapeutics that won't involve any form of chemo and radiotherapy and would have a complete, toxic-free treatment of the malignant tumor cells without any incision made on the body. The p53 can also be stated as a drug molecule that will have full effect once its effectiveness and target efficiency have been increased towards the biomarkers on the cancer cells.

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