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Gene Therapy for Treatment of Melanoma Cancer

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Abstract

Melanoma occurs when the pigment-producing cells (melanocytes) that give colour to the skin become cancerous. Malignant melanoma has become one major problem for its higher rate of occurrence among patients than any other type of cancer throughout the world. Hence, it has become very crucial to treat melanoma skin cancers by early detection and prevention. It is remarkable how an advanced therapy like gene therapy is leading towards a better solution for melanoma skin cancer. Not only can gene therapy cure an individual, it also prevents same set of diseases throughout a blood line. With supported evidences from research and clinical trials, gene therapy also provides clue for a new generation treatment for different diseases including cancer.

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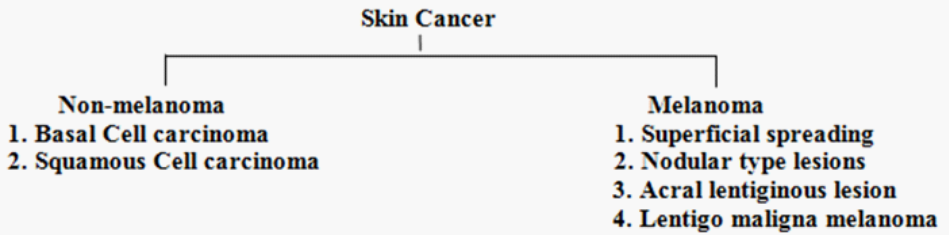
Introduction

Melanocytes are the pigment containing cells in the body that lead to malignant melanoma. Melanomas typically occur in the skin but may also occur in the mouth, intestines, or eye rarely. Survival of patients with malignant melanoma is directly related to early detection. Melanoma that is confined to the epidermis (*in-situ*) carries no risk of death and a thin melanoma lesion carries very little risk of metastatic spread. Again, the disease can be caused up to 25% from moles. It also results from a number of genetic mutations that are hereditary. For example, some rare genes have a relatively high risk of causing melanoma; some more common genes, such as a gene called MC1R that causes red hair, have a relatively lower elevated risk. Hence the need for gene therapy to treat Melanoma is important [1].

Skin cancer can be of several types depending upon their place of occurrence, aetiology and also their visibility. Before moving onto the details of treatment of the disease, its causes and variance should be discussed.

Types of Skin Cancer

Malignancies in the skin are the most diagnosed types of cancer worldwide today. The disease depends on several factors like, the anatomy of the skin, source of the cancer (though it is mostly due to exposure to UV radiation) etc. An individual's skin colour is determined by their genes, and their environment of residence. The pigment that colour our skin is called melanin which occurs in melanocytes and is present in the stratum basale in the epidermis of the skin. Again, our skin changes colour in response to the sun, the phenomenon known as the "tanning response". Skin cancer can be classified into the following types:



Basal cell carcinoma

Tumours develop on regions of the body that is regularly exposed to the sun, such as the face and hands. Due to slow growth rate, basal cell carcinoma spreads rarely and is usually treatable. A common form of basal cell carcinoma is nodular basal cell. Lesions appear as pearly nodules in various colours including brown, black and blue.

Squamous cell carcinoma

Tumours appear on parts of the body that experience increased levels of sun exposure such as the face, lips and back. This cancer spreads more likely compared to basal cell carcinoma. The cancerous lesions have numerous forms. They can be rough, scaly, lumpy or flat. Blood vessels may appear at the edge of a lesion that causes it to bleed easily.

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Melanoma

Melanoma is a cancerous growth of melanocytes and mostly develops in the skin. Melanoma may also develop in other parts of the body that contain melanocytes including the meninges, the digestive tract, the eyes and lymph nodes. The types of Melanoma are based on their appearance to the naked eye or microscope. Previous studies have shown an association between germline mutations in tumour suppressor p16 and development of melanoma in melanoma affected kindred's, and recent studies have noted somatic p16 mutations in sporadic melanoma, as well [2].

The disease might be in various sizes and forms but the symptoms for the all of the types of melanomas or non melanomas are apparently the same.

Symptoms

Studies reveal the ABCDE rule that guides as the usual symptoms of Melanoma. The symptoms are as follows:

A. Asymmetry: When one half of a birthmark, specially a mole does not match the other half.

B. Border: When the edges of the mark are irregular, blurred, ragged or notched.

C. Colour: When the colour does not follow a similar pattern or shade throughout, i.e. includes different shades of brown or black and sometimes with patches of other colours like pink, red, white or blue.

D. Diameter: When the spot is larger than or about 6 millimetres in size.

E. Evolving: When the mole changes it size shape or colour [3].

Other than these certain other factors like a sore that doesn't heal, spread of pigment from the border of a spot into surrounding skin, redness or a new swelling beyond the border of the mole, change in sensation, such as itchiness, tenderness, or pain, change in the surface of a mole – scaliness, oozing, bleeding, or the appearance of a lump or bump are also factors that determine melanoma.

Prevention and treatment

Melanoma skin Cancer is a type of cancer that is likely to spread very easily. Malignant Melanomas become metastatic very easily. Immunotherapy is the first and basic step of prevention of this disease after early detection. Prior to 2011, treatment of melanoma was limited to interferon α2b for adjuvant therapy and high-dose interleukin 2 (IL 2) for metastatic disease [4]. But since 2011, three new agents have been approved for the treatment of patients with melanoma which can be well classified under Bio chemotherapy:

1. Pegylated-interferon α2b in the adjuvant setting.
2. The anti-CTLA4 monoclonal antibody ipilimumab for metastatic disease.
3. An oral BRAF inhibitor drug vemurafenib in patients with metastatic melanoma harbouring BRAFV600 mutations [5].

Since virtually all of the known risks for melanoma are related to susceptibility to, and the magnitude of exposure to the sun, i.e. UV radiation to be specific, protection from the sun's rays plays a critical role in prevention. The most appropriate endpoint for determining the effectiveness of public policies regarding sun protection is the melanoma incidence rate. Sun-screen is the most commonly used method of sun protection in Australia, it is clear that these products have played a major role in this turnabout [6].

Melanoma tumour can be excised by surgery. The success of surgery depends on thickness of the tumour and depth of the surgery [7]. Another surgical method of lymph node biopsy can be also implemented to remove malignant tumour from skin. Stage-1 clinical trials have raised controversies regarding elective lymph node dissection. Results from clinical trials that have been conducted by WHO has conferred no progress in healing by lymph node removal. But Mayo clinical trials have concluded that patients showed better survival after undergoing elative lymph node removal [8].

As upcoming and promising technologies many new non surgical methods have aroused. Chemotherapy has been applied to heal melanoma cancer but the success rate is very low. Only one drug Dacarbazine has been approved by FDA for chemotherapy [9]. Other than chemotherapy immunotherapy has been used to treat melanoma skin cancer. The promising technology has been designed to generate immune response by antibodies against tumour specific antigens. Successful and specific immunotherapy has been effective in some cases of tumour regression [10] (Figure 1).

Moving forward onto the modern treatment methods, the most flourishing technology is based on clinical trials and experimental success in a new field termed as 'Gene therapy'. It has been found very promising to treat cancer. Gene therapy has been applied to few melanoma patients in experimental level [11].

Gene therapy can be also applied with viral vectors and other non-viral approaches. Surgery, chemotherapy, immunotherapy can be very effective but gene therapy is a more advanced technique of solving the problem which might prove to be even more effective in the near future.

Gene Therapy

It is an advanced therapy aimed to cure the disease in patient's body by introducing the correct copy in place of defective genes. If there is one or more mutation in a specific gene, this may give rise to a faulty protein. The faulty protein may results in genetic and complex diseases such as cancer in some cases [12] (Figure 2).

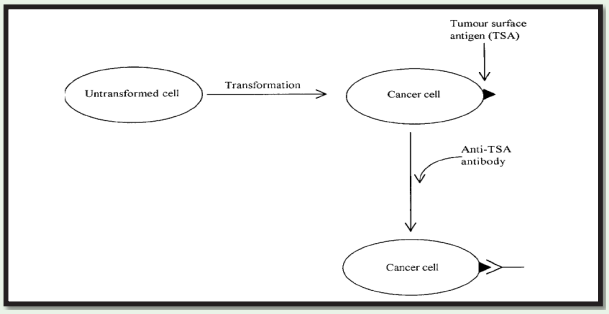

Figure 1: Upon transformation, cancer cells often express unique surface antigens termed 'tumour surface antigens' (TSAs). Antibodies raised against these will selectively bind the tumour cells. The antibody used may be unconjugated or conjugated to a drug, toxin or radioactive tag.

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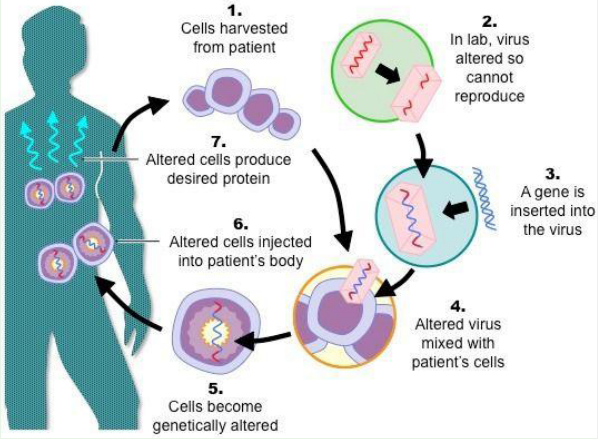

Figure 2: Flow chart of gene therapy.

Gene therapy can be implemented through several approaches in a patient.

A mutated or faulty gene can be replaced by a healthy copy of the gene to prevent certain disease [13]. Spliceosome-mediated RNA trans-splicing with recombinant adeno-associated virus vector or SMaRT vector can be implemented to do this type of gene therapy [14]. A gene that is inserted directly into a cell usually does not usually function. And thus, a carrier called a vector is genetically engineered to deliver the gene. The vector can be injected or given Intravenously (by I.V.) directly into a specific tissue in the body, where it is taken up by an individual cell or cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in laboratory setting. The cells containing the vector are returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein. The term 'trans-splicing' encompasses several technologies that combine two RNA or protein molecules to generate a new, chimeric product. RNA trans-splicing reprograms the sequences of endogenous messenger mRNA or pre-mRNA, converting them to a new, desired gene product. Trans-splicing has broad applications, depending on the nature of the sequences that are inserted or trans-spliced to the defined target. This RNA therapy offers significant advantages over conventional gene therapy like; expression of the trans-spliced sequence is controlled by the endogenous regulation of the target pre-mRNA; elimination of undesirable ectopic expression; the ability to use smaller constructs that trans-splice only a portion of the gene to be replaced successfully and the conversion of dominant-negative mutations to wild-type gene products [15].

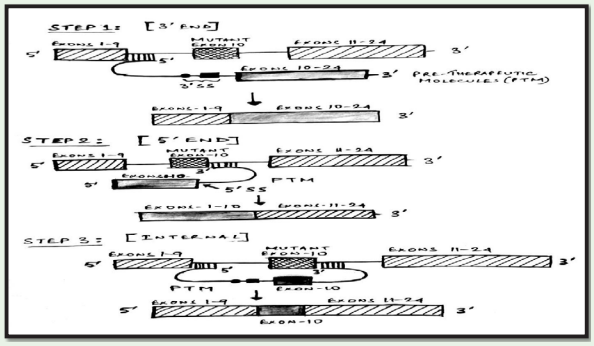

Figure 3: SMaRT vector therapy.

Inactivation or knocking out a certain faulty gene is also an alternative for this purpose. By introducing new genes in the body gene therapy can also be opted. These can be implemented through strategies like antisense or triple helix formation; both of which block translation of faulty RNA and hence faulty protein [16]. Another technology based on RNA enzyme- Ribozyme can also be a potential tool for gene therapy [17]. Throughout different countries until 2012 almost 1800 clinical trials of gene therapy has been performed [18]. As a gene cannot be inserted into the body directly all the time, sometimes small viral vectors are used to carry out gene therapy. Non-viral vectors are also available for gene therapy such as electroporation, injecting naked DNA, gene gun etc [19] (Figure 3).

A retro virus binds to a new host cell by virtue of the interaction of the Env glycoprotein with an appropriate cellular receptor. This interaction triggers a series of events that ultimately lead to fusion of the lipid envelope surrounding the virus with the target cell membrane. Entry of the retroviral core into the cell allows reverse transcriptase enzyme to copy the viral RNA genome into a double-stranded DNA provirus, which is then randomly inserted into a host chromosome through the action of the Integrase protein. Certain sequences in the RNA genome are essential for packaging, reverse transcription, and integration to occur [20] (Figure 4).

Gene therapy and cancer: Molecular mechanism of cancer has been understood with help of research and progress in science. Most of the time, cancer occurs due to activation of onco-genes which creates a malignant tumour or due to the inactivation of cancer suppressing genes. To eliminate both the problems gene therapy can provide a potential solution. To stop the activation of onco-genes, an antisense sequence can be used which blocks the onco-gene translation into defective protein by hybridization and creation of a double stranded complementary RNA sequence [12]. Another therapeutic strategy is called suicide gene therapy; where a set of trans-gene is introduced into a cancerous cell which causes cell apoptosis to prevent cancer [21].

Gene therapy for skin

Skin is an easily accessible organ which covers a large surface area of body. Skin also gets affected by cancer, other skin diseases and accidental wounds and burns. These all give a reason to treat skin with gene therapy [20]. Recombinant adeno associated virus (rAAV) has shown high efficiency in gene transfer in human skin keratinocytes. The results of gene expressions were observed using reporter gene, green fluorescence protein or GFP. The transferred genes and signal GFP were expressed up to 50 days in a human cell line and were able to pass the trans-gene in daughter cells [22]. The adenoviral mediated

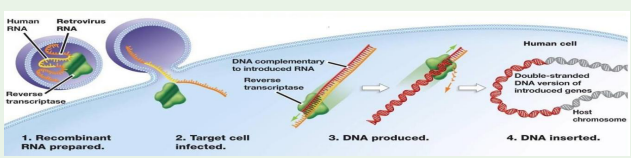

Figure 4: Prevention of translation using antisense technology.

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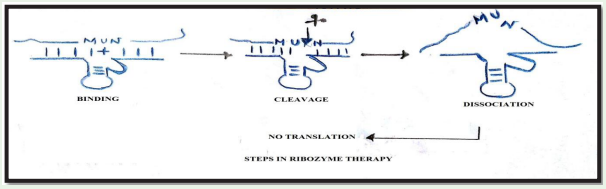

Figure 5: Triple helix DNA therapy.

gene transfer in human epidermal cells has also showed ability to heal burn and wounds [23]. Non viral gene transfer systems have also been effective in gene therapy for the skin wounds. For transferring genes in HaCAT keratinocyte cell line, Lipofectamine 2000 and DOTAP/Chol lipoplex have shown significant enhancement in gene transfer ability. The expression of transfected genes have been observed by bioluminescence and fluorescence [24] (Figure 5).

Gene therapy for skin cancer

Genetically engineered white blood cells carrying foreign gene can be a potential tool for skin cancer treatment. The viral mediated genes used in gene therapy, code for a specific tumour-targeting molecule called a T-cell receptor or TCR. These genes help in shrinking large tumours on the skin. The results have been tested for melanoma cancer but it is expected that after therapy the tumour infiltrating lymphocytes or the anti tumour cells will be able to induce other types of cancers including lung and breast cancer [25]. The host immune cells or the tumour cells are targeted to introduce foreign genes. The objective is to introduce suicide genes and tumour suppressor genes that in turn will inactivate the aberrant onco-genes from being expressed and proliferating. The suicide genes are genes that trigger apoptosis. These genes have a main cellular switch. Activation of a suicide gene induces apoptosis in the p53 proteins and hence the name. p53 gene is present in the body in suppressed forms as anti-onco gene, which may be activated into onco-gene that may induce tumour. Hence, that suicidal effect of these proteins can be considered as the best way to deal with cancer. Other than the mutation of tumour suppressor genes, the constitutive activation of onco-genes such as members of the RAS family and c-myc frequently occur in melanoma and contribute to the malignant phenotype (Figure 6).

Like everything else suicidal gene therapy also has its pros and cons. They might sometimes result in severe side effects on normal cells that proliferate highly. The advancements in cancer biology and genetics have opened new horizons to overcome such problems [26].

While referring to gene therapy for a specific disease it must mean there are certain specific genes associated with the events that are responsible for the disease and can be targeted and treated. Thus,

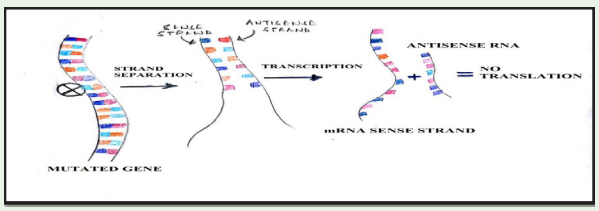

Figure 6: Ribozyme therapy.

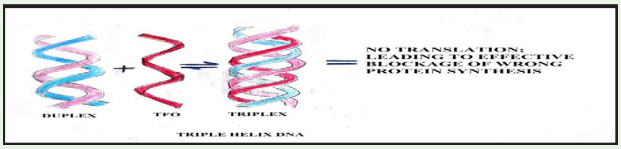

Figure 7: Gene therapy using retroviral vector.

the genes responsible for melanoma must be discovered and studied about before going into the therapy for the same (Figure 7).

Melanoma skin cancer and associated genes

Mostly melanoma skin cancer occurs due to mutation in BRAF genes, which leads to altered BRAF protein causing the cancer. Sometimes melanomas have changes in the C-KIT gene that help them grow. Changes in the CDKN2A (p16) gene causes some melanomas that run in certain families through their bloodline. The cancer can be treated by surgery, immunotherapy and chemotherapy. Targeted drugs for these specific genes can also serve as a solution which will control the changes of these certain genes [27].

There is a certain determined process within the biological system which the genes in accordance with specific enzymes follow to lead to the disease, i.e. for transforming a normal individual into a diseased person affected with Melanoma. This mechanism is likely to be studied for better understanding of the cancer and hence it's better treatment (Figure 8).

Molecular Mechanism of Melanoma

Targeting the enzyme BRAF kinase in melanoma holds a lot of promises. Mitogen Activated Protein (MAP) pathways have been found to provide few targets for melanoma cancer therapy. In this pathway, at first the RAS proteins stimulate the RAF kinases (ARAF, BRAF, and RAF1). This causes the phosphorylation of the

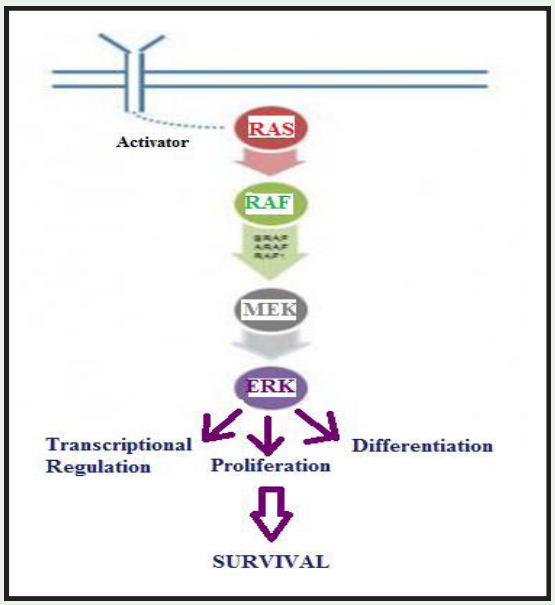

Figure 8: Schematic model exhibiting the molecular mechanism behind melanoma that regulates the cellular processes.

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MEK kinases, which phosphorylates the ERK kinases. Activated ERK regulates cyclin D1, which subsequently regulates multiple cellular processes involved in cell division. It is observed that in 40-60% of melanomas there is a mutation in gene that encodes BRAF which leads to the activation of MAP pathway. In 80-90% cases the mutation of glutamic acid to valine at amino acid 600 of BRAF gene product producing a faulty protein leads to melanoma cancer. So, these mechanisms suggest the need to stop mutation of BRAF gene by drugs or gene therapy [28].

After having a brief idea about melanoma, its types mechanism if not mastering it all, learning about how to treat the ailment could be the only subsequent step.

Drugs to Inhibit the BRAF Mutation of Melanoma Cancer

Vemurafenib and dabrafenib are two BRAF kinase inhibitors drugs approved by FDA available in the United States. Trametinib, a mitogen-activated extracellular signal regulated kinase (MEK) inhibitor is another FDA-approved drug [23,26]. Another drug by Roche Pharmaceuticals called Plexxikon is also a potent inhibitor of BRAF gene mutation at the 600th position of valine [29]. Approaches based on gene therapy can be implemented to inhibit the mutation of BRAF gene to stop faulty protein production causing cancer. Inspite of recent progress in gene therapy and gene delivery systems, clinical trials have been performed to cure melanoma cancer but the field deals with lots of complex issues and uncertain results.

Gene Therapy for Melanoma and Clinical Trials

Phase I and Phase II trials performed on patients suffering from melanoma cancer was done by injecting interleukin-2 (IL-2) mediated by adenovirus as vector. The trials showed tumour regression and T-cell proliferation. The results promised treatment of melanoma cancer but side effects of flu-like symptoms were observed [30].

Another study included treating melanoma patients with genetically modified lymphocytes. The genetical modifications were expressed in the cancer germ line gene MAGE-A3. The modified lymphocytes were able to express self/tumour antigen TRP-2 showing antitumor activity which targets the dendritic cells *in-vivo*. The trials were done on 10 patients and showed hints of clinical benefits to cure melanoma cancer without any adverse side effect [26].

Other than genetically engineered lymphocytes, genetically modified T-cells also serve as a tool for immune therapy and gene therapy. NY-ESO-1 cancer antigen is a target for melanoma cancer patients. T cells transduced with a T-cell receptor (TCR) have been directed against the NY-ESO-1 antigens resulting in tumour regression in clinical trial for melanoma cancer. Clinical responses were seen in 5 out of 11 melanoma patients and 2 of those patients complete regression of cancer for almost 1 year [31].

Another clinical trial of melanoma used T-cell receptors to a different antigen called MART-1 and showed tumour regression in patients [32,33].

Surgically incurable melanoma cancer patients had undergone clinical trials of gene therapy which were performed on 7 patients by injecting doses of vaccinia/ GM-CSF recombinant virus for 6 weeks. Only one patient showed the tumour regression among seven and few showed mixed response [34,35].

Gene transfer in humans with melanoma using Tumour Infiltrating Lymphocytes (TIL) and interleukin-2 modified by retroviral gene transfer has promised successful gene therapy through clinical trials. The modification of the TIL was done by introducing Neomycin resistant gene (NeoR) as a foreign gene. The modified TIL was able to survive for at least several months in the circulating blood and at tumour sites after intravenous injection into patients with cancer. This experiment was an important landmark as it also helped to understand the therapeutic efficacy of TIL cells other than its anti tumour activity in human body [36].

Present scenario

Melanoma cancer can be cured by early detection and treatment. Treatments include surgery, immunotherapy, chemotherapy or targeted drug administration. But for a better solution to treat the disease, gene therapy can play an important role. Advanced treatment like gene therapy can be performed on patients with their informed consent for clinical trial which will have several benefits as followed: Significant progress in gene therapy have been achieved by advanced vector technology, targeted gene expression, gene replacement, and the availability of appropriate animal models for a variety of candidate diseases.

Advantages of gene therapy

It is remarkable how replacement of a set of faulty gene can eliminate a genetic disorder without using any drugs or surgery. In many cases of clinical trials it has been proved that even if the disease is not completely cured, the patient gets an improved life with slow rate of progress of the disease. In long term it may be also possible to eradicate a disease completely with gene therapy. Through germ line gene therapy it is possible to eliminate a disease before it can occur in any further upcoming generation [37]. Gene therapy also provides two options of *in-vivo* therapy and *ex-vivo* therapy. In *in-vivo* therapy the cells are replaced or introduced within the body, the process has been advanced by transferring retroviral and adeno viral vector systems into human cell lines [38]. Gene therapy can be also performed outside the body by *ex-vivo* approach on somatic cell lines of human which can introduce effective gene transfer [39]. It is remarkable how the infectious viral particles such as retrovirus, adenovirus are used for packaging foreign genes to implement gene therapy for prevention against certain diseases accompanied by better gene delivery systems [40].

Advancement in science and technology is not just discovering new methods or inventing new machineries. It is about its usefulness, it application in the practical world, its availability to the commoners and its acceptance among the mass. For gene therapy related to melanoma, problems arise in the fields of selective conversion of non-toxic compounds into cytotoxic drugs inside cancerous cells. As a result, therapeutic index can be increased significantly by introducing high concentrations of cytotoxic molecules to the tumour zone while minimizing impact on normal tissues.

Another problem of this technology is the efficiency of gene transfer, particularly when it is used for the inactivation of onco-genes, the replacement of tumour suppressor genes, or the introduction of suicide genes. With these strategies, it is necessary for the gene to be delivered very well to every cell so that no remaining non-transduced malignant cells will continue to proliferate, leading to disease relapse subsequent to an apparently successful initial response.

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In addition to this is the transfection efficiency with respect to the bystander effect. Mechanisms like cell-cell transfer of toxic substrates, angiogenesis inhibition, and an immune component, have been considered to play a role in this bystander effect. The cellular or molecular mechanism has not been deciphered yet [41]. Further ethical issues and disadvantages are discussed below.

Disadvantages and Ethical Issues

During clinical trials it has been observed proliferation of the faulty genes again after certain time to bring back the disease. It has been one of the crucial down fall of gene therapy. The short lived nature of the vector and the chances in reduction of efficacy of the genes once injected may cause a futile therapy. The immune response of the body against the introduced viral vector may also cause problems. Another disadvantage may be if the inserted gene replaces or causes mutation in another set of genes in the host other than the faulty one that may lead to a complex scenario and will not cure the disease at all. There are also few ethical issues which questions the use of gene therapy.

There are ethical concerns such as if the therapy in future is used to enhance abilities like intelligence, power and other traits as per demand. What will be the reaction if gene therapy is available only for rich people in the future? There are also problems related to religious and social forums as genetic engineering in human may lead to lots of complexities.

As in many trials for gene therapy the path has been chosen almost at the end stage of the diseases (like HIV, cancer) it can be helpful on one hand as it provides an extended life, on the other hand the therapy also raises doubts regarding the efficiency of the treatment of the disease [42,43].

Future Aspects and Conclusion

It is because of the clinical success, safety and feasibility that have been achieved from gene therapy on human malignancy that it has emerged as a potential alternative treatment. It is because of the clinical success, safety and feasibility that have been achieved from gene therapy on human malignancy that it has emerged as a potential alternative treatment. The bystander effect which is the regression of tumour when a fraction of the mass is genetically modified triggered by gene transfer approaches would provide the tools to validate gene therapy as an effective modality of treatment for malignant Melanoma. Gene therapy, in today's world is one of the most novel treatment methods owing to the recent developments in the field of genetics and gene transfer method. But it can be further improved with the invention of better DNA vaccines and further developed vectors. Surgical excision is mainstay of therapy in malignant melanoma. Despite potentially exciting developments in the treatment of malignant melanoma in an advanced platform, prevention and early detection remain the primary goals in the fight against cancer [7,44].

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