A.Anusha et al /J. Pharm. Sci. & Res. Vol. 9(5), 2017, 662-666

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Cancer Immunotherapy

A.Anusha, Sanni Kumar, Sanket Kaushik, Anupam Jyoti*

Amity Institute of Biotechnology,
Amity University Rajasthan, Jaipur, 302006, India

Abstract

Cancer is a broad classification used for the set of diseases characterized by the unusual way in which they grow and divide, thereby destroying the healthy cells in the body. Cells of malignant tumours are abnormal in nature and proliferate in an uncontrolled manner. Immunotherapy enhances the immune system of body in such a way that it can self attack cancer and protects the person from succumbing to it. Immunotherapy includes checkpoint inhibitors, therapeutic vaccines and monoclonal antibodies with various approaches to boost or restore the ability of immune cells to combat cancer. The unremarkable effects of vaccines for cancer observed in early years are not surprising given that vaccines had their greatest impact in medicine in the deterrence or forestalling of infectious disease, not in the treatment of active disease, as most vaccine-based treatments of cancer have been tested. Propitious areas of research and transpiring immunologic treatments also include tumor specific T-cell directed therapies, immune checkpoint targets and small molecule immune-modulatory drugs.

Keywords: Cancer, Immunotherapy, Vaccine based treatments, Immuno-editing.

CANCER

Cancer is a broad classification used for the set of diseases characterized by the unusual way in which they grow and divide, thereby destroying the healthy cells of the body. People can be exposed to the cancer-causing agents during consuming food, drinking water and breathing. In cancer cells the normal control systems that deter cell overgrowth and the invasion of other tissues are stalled. These docotred cells divide and grow in the response of signals that normally constrain cell growth; thereby no longer requiring special signals to induce cell growth and division **[1]**. Tumours can be grouped into benign or malignant. Benign tumours are expunged and, mostly, they do not reappear in the body. Cells of benign origin do not expand to other parts of the body and are seldom life-threatening. However, cells in malignant tumours are bizzare and proliferate in an unchecked way. Cancer cells invade and crush the tissue surrounding them and can also break away from a malignant tumour and insuniate into the circulation including blood and lymph. Cancer is the second leading cause of mortality worldwide. Out of a total of 58 million deaths worldwide in 2005, cancer accounted for 7.6 million or 13%. The main genres of cancer are: lung (1.3 million deaths/year), stomach (almost 1 million deaths/year), liver (660 000 deaths/year), colon (655 000 deaths/year) and breast (500 000 deaths/year) **[2]**.

Properties which separate cancerous cells from healthy cells/ tissues:

- They are resistant to apoptosis (the main form of programmed cell death).
- They have an unconstrained ability to divide, often at an increased rate.
- They are self-sufficient in growth signals.
- They display raid differentiation.
- They are not susceptible to anti-growth factors and contact inhibition.
- They can infringe adjacent cells or tissues (usually by secreting metallo-proteinases, enzymes which digest extra-cellular matrices from other cells).
- They secrete molecules, including growth factors which stimulate the growth of blood vessels.

Carcinogenesis is thought to be provoked by mutations of genetic elements that influence homeostasis-balance of proliferation and cell death. The result is uncontrolled cell division leading to tumour formation. An uncontrolled and swift division of cells can at first form benign tumours which can later develop into malignant tumours. Cancer is also regulated by neutrophil extracellular traps (NETs), a novel mechanism of pathogen elimination. Firstly reported by Brinkmann et al in 2004, NETs are consists of chromatin fibres decorated with antimicrobial proteins/ enzymes that capture and kill pathogens **[3]**. Neutrophil elastase (NE) released by NETs are taken up by cancer cells, where NE upregulates PI3K expression hence promote tumor growth **[4]**. In another study conducted by concluded that tumor associated neutrophils release NETs in Ewing sarcoma (ES) **[5]**.

Viruses and cancer:

Many viruses infect humans but rather only a few viruses are known to promote cancer in human beings. These include both DNA viruses and retroviruses (a type of RNA virus).

Viruses associated with cancer include:

- Human papillomavirus (HPV): cervical cancer i.e. genital carcinoma.
- Hepatitis B and C virus (HBV and HCV): hepatocellular carcinoma.
- Epstein-Barr virus (EBV): Burkitt lymphoma, Hodgkin´s lymphoma, nasopharyngeal carcinoma
- Human herpesvirus-8 and human immunodeficiency virus (HHV-8 and HIV): Kaposi´s sarcoma
- Human T-cell leukaemia virus (HTLV-1): adult T-cell leukaemia.

Oncogenes:

A sequence of DNA which has been mutated from its original form, the proto-oncogene. The proto-oncogene is involved in the normal growth and and proliferation of

normal cells. Different types of proto-oncogenes are implicated in various steps of cell growth, and a change in the proto-oncogene's sequence or in the amount of protein it produces can interfere with its normal role in cellular regulation **[6, 7**]. Uncontrolled cell growth ultimately results in the formation of a cancerous tumor. In humans, proto-oncogenes can be mutated into oncogenes resulting in a loss of accuracy in cell regulation **[8]**. A point mutation, that occurs spontaneously or as a result of environmental factors including chemical carcinogens or ultraviolet radiation.

Immune response towards cancer:

Since cancer cells originate in our body, the way immune system reacts and responds is different. When the body is unable to differentiate tumour cells from normal cells, the tumour cells hide themselves well. In some cases, however, the DNA changes (mutations) that cause the cancer may be different enough to stimulate an immune response, similar to how immune cells notice virally infected cells. Cells of the immune system communicate with each other through cytokines produced by the body, tumour cells also have the ability to create cytokines **[9]**. Hence, cancer cells also communicate with and confuse immune cells, allowing the cancer to take control of certain parts of the process that the body uses to regulate the immune response **[10]**. To provide a blood supply for all the cells in the tumour, it must form new blood vessels to supply the cells in the centre with nutrients and oxygen, a process called angiogenesis. Tumors cells secrete angiogenic factors, helps in the formation of new capillary vessels. Without the additional blood supplied by angiogenesis, tumors can grow no larger than about half a millimetre **[11, 12, 13]**.

Immunotherapy

Immunotherapy is basically a genre of treatment which enhances immune system of the body in such a way that it itself can attack cancer and protect the person. Based on the studies of the past 10 years we can say that even though a tumour may grow in a functional immune system, but the way the tumour develops and grows is influenced by the immune response **[14, 15]** and this is the basis of immunotherapy **[16, 17]**. During immunotherapy adoptive transfer of immune-modulators including cytokines, tumor-specific antibodies, or immune cells takes place **[18, 19, 20]**. These molecules, or cells, are then administered to the patient to initiate an antitumor action. In general, these therapies do not generate immunologic memory and, therefore, require chronic infusion-based treatment **[21, 22, 23]**.

Immunotherapy strategies:

This includes immunotherapy alone or in combination with other treatments. Details are as follows.

Monoclonal Antibodies - Monoclonal antibodies (mAbs) are manmade antibodies engineered to target specific tumor antigens. Monoclonal antibody therapy is also referred to as "passive immunotherapy," meaning it does not directly stimulate a patient's immune system to respond to a disease. Instead, a monoclonal antibody reproduces a natural antibody processed by the body. In this therapy, a monoclonal antibody binds a specific target present on the surface of a cancer cell. Hence, also known as "targeted therapy" as it is directed to a single target on the cancer cell **[24]**. They work in a few different ways:

i. Marking cancer cells for destruction – This targeted therapy adheres as flag targeting cancer cells for destruction by other immune cells.
ii. Blocking growth signals and receptors – Monoclonal antibodies are engineered to block the access to the blood vessels necessary for growth and proliferation of cancer cells.
iii. Delivering other therapeutic agents directly to the cancer cells – The monoclobal antibodies can be engineered to carry cancer drugs, radiation particles or manmade cytokines (chemical messengers) directly to cancer cells present **[25]**.

Technically tumor immunotherapy can be divided into two broad categories named nonspecific and antigen-specific therapies. In nonspecific immunotherapy it stimulates the immune system by enhancing the immune cell function regardless of their antigen specificity **[26, 27, 28]**.

Non-specific immunotherapy strategies:

Non-specific immune stimulation involves boosting the immune system in order to produce increased and longer-lasting immune responses.

Bacille Calmette-Guerin (BCG) therapy - Like other nonspecific immunotherapeutic agents, it is unknown about the exact mechanism by which BCG generates anticancer immune responses in certain patients. However, BCG approved to treat bladder cancer, is tuberculosis bacteria modified to ensure they will not spread disease. Treatment causes inflammation in the bladder which stimulates an immune response and guides immune cells towards the bladder **[29]**.

Cytokine immunotherapy – Cytokines are the small molecules, helps in communication among immune cells and thereby activates the immune system. Cytokine immunotherapy treatments include introducing large amounts of man-made cytokines to the immune system to promote specific immune responses **[30]**.

1. Interleukins are cytokines which help in regulating the activation of immune cells. The drug IL-2 (Proleukin) is currently used in the treatment of multiple cancers, and several molecules analogous to IL-2 are being developed **[31]**.
2. Interferons are an example of cytokines which enhances the ability of immune cells to attack cancer cells, and uptil now have been developed into the drug interferon alfa **[32]**.
3. GM-CSF (granulocyte-macrophage colony stimulating factor) is a cytokine which stimulates the bone marrow, promoting immune and blood cell growth and dendritic cell development **[33]**.

Stem cell Therapy - Stem cell therapy involves transplantation of stem cells for regenerative purposes, also known as regenerative medicine. Conventional cancer

therapies are inefficient, in contrast to, cancer stem cells (CSC) therapy because the conventional cancer therapy often are unable to kill CSCs, results in multiple malignancies, and can also damage to the healthy tissues present in the body **[34]**. Hence, CSCs therapy is becoming a precious and challenging area of cancer research aiming at complete elimination of malignancies.

Adoptive T cell transfer – This therapy focuses on embellishing the body's own T cells to battle cancer. This therapy can be classified into two types. In first type, T cells are isolated from patient's tumor, expanding them to large numbers, and then executing them to patients. In the second strategy, collection of T cells is done from the patient and engineered with new receptors (chimeric antigen receptor T cells, or CAR-T) to recognize specific antigens on the surface of cancer cells, and then administered back into the patient. In both the above mentioned cases the T cells multiply, scout for and destroy the cancer cells on which those specific antigens are carried. The hindrance in this very therapy is that the transferred killer or cytotoxic T cells (CTLs) is short-lived after infusion into patients than contemplated. This is owing to the fact that the patient's body can't provide all the accessory immune molecules the killer T cells call for to be maintained well and to finish the job. If the original immune response to the tumor cells had been effective, immune cells responsible for producing these ancillary molecules would have been called into action and this problem would not have prevailed **[18]**.

Specific immunotherapy: Vaccination

Vaccination Cancer vaccines is a type of therapy created from either recast viruses or tumor cells, engineered to direct immune cells to the cancer cells.

There are two categories of cancer vaccines: Prophylactic vaccines- used to limit the viruses that cause cancers Therapeutic vaccines- used to doctor existing cancers.

Tumour based /cell vaccines

These are affected from tumor cells that are suitable to a patient's cancer type. This has upper edge over other types as this does not involve isolation of specific antigen. Main disadvantage is that it is difficult to span specific immune responses without knowing the stimulating antigen within the crude mixture **[35]**.

Vector based vaccines

These are made from docotred viruses or bacteria which are imbued into the body to create an immune response, both specific and overall. Tumor specific vectors are genetically refitted to train the immune system to recognize, target and destroy cancer cells. These vaccines are known to use special delivery systems to make them more effective as compared to others. First of all, they can be used to deliver more than one cancer antigen at a time, which is probably going to make the body's immune system more likely to mount a response. Secondly, vectors such as viruses and bacteria might prompt their own immune responses from the body, which could help make the overall immune response even stronger. Finally we can conclude that, these vaccines might be easier and less expensive to make as compared to other vaccines **[36]**.

Viral vector-based vaccines need estimation of safety and efficacy, involving immunogenicity, genetic stability, replication deficiency or attenuation, and genotoxicity. One vector-based vaccine being studied at present to treat leukemia is a modified HIV virus which targets B cells, the cells primarily affected by leukemia **[37, 38]**.

Antigen based vaccines

They are a type of subunit vaccines. These particular type of vaccines trigger the immune system by utilizing only one antigen. The antigens are generally proteins or pieces of proteins called peptides. Antigen vaccines are specific for each type of cancer. They are known to be typically made from one to five of the antigens that are either unique to (or over-expressed by) the tumor cells. They may be specific to a certain genre of cancer but are not exactly patient-specific **[37]**.

Dendritic cell vaccines

These vaccines are contrived from the person in whom they will be used. Immune cells from the patient's blood are removed and then exposed to the cancer antigens that turn the immune cells into dendritic cells and further help them grow. The dendritic cells are then injected back into the patient, where they would incite an immune response to the cancer cells present in the body. These vaccines have presented the highest success rate so far in treating cancer. Sipuleucel-T (Provenge), which is sanctioned for the treatment of advanced prostate cancer, is one such example of a dendritic cell vaccine **[39]**. Dendritic cells are immune cells present that help the immune system to identify cancer cells. They degrade cancer cells and present them to T cells for further immune reactions **[40]**.

Genetic strategies for cancer immunotherapy

Many approaches for the genetic immunization of solid tumors have been investigated.

Naked DNA Immunization

Naked DNA is a eukaryotic expression plasmid, i.e., neither complexed with chemical formulations nor contains viral components. It has been ascertained for a long time that such a plasmid can't be taken up by the cells efficiently. Plasmid-based DNA immunization is a effectual method of immunization against microbial and viral antigens, competent enough of generating both antibody and cellular responses, especially in mice. Plasmid immunization into skin via gene gun was known to be minimally immunogenic. Uptake of processed antigens and presented by antigen presenting cells is thought to be the main mechanism of production of T cell immunity, although direct gene transfer to local APCs has earlier demonstrated similar T cell immunity **[41]**.

Viral Vectors

Viral vectors can be very efficient gene transfer vehicles and many setes have been tested in clinical trials, often with the goal of achieving long-term replacement of faulty genes **[42]**. These viruses differ in important aspects of transgene size, capability, host genomic integration, encoded viral genes, and virus immunogenicity. Various types of viral vectors are:

Retroviruses

These well-studied, small, integrating viruses were the first delved into replacement gene therapy. They transduce only dividing cells and can undergo silencing of the transgene. They are not very immunogenic, and have been known to form at clinical grade for many years.

Lentiviruses

These retroviruses also integrate, but they transduce non-dividing cells, including APCs, more efficiently, and are less immunogenic than adenoviruses.

Adenovirus

This virus is a highly immunogenic vector that can carry 2 to 3 transgenes and has a long safety record. It does not integrate. Direct injection of antigen encoding adenovirus is limited by potent induction of neutralizing antibodies. These are easily produced at clinical grade.

Adeno-associated virus

This low-immunogenicity vector is small and has a low efficiency of APC transduction.

Vaccinia

The Vaccinia virus is the most researched of the poxvirus family. These are the largest known DNA viruses which replicate within the cytoplasm of infected cells. Vaccinia virus can accept 25 kb of foreign DNA and can integrate foreign genes stably **[43]**. These are large, complex, immunogenic viruses and are often lytic to transduced cells. Different subtypes exist, which allows for serial vaccination without cross-reactive neutralizing antibodies. They have been produced at clinical grade for many years. Both viral vectors and plasmid DNA have been used to transduce/ transfect immunogenic molecules into cells for genetic immunotherapy vaccines **[44]**.

FUTURE PROSPECTS

The description of a wide assortment of human cancer antigens that are articulated on multiple cancer types, involving many common epithelial cancers, presents novel opportunities for the development of cancer immune-therapies. Although cancer vaccines that activate the humoral immune response remain a vital strategy in the tool-kit of cancer immune-therapists, the present method of choice for practitioners involves the activation of the cellular immune response. Some of the strategies that researchers are using to attain this effect include vaccines based on genetically engineered bacteria and DNA. Scientists have acknowledged for a while that bacteria such as Salmonella are very good at tainting professional antigen presenting cells. The bacteria can be genetically altered so that they are capable of carrying tumor antigens directly to the sites of alinment and an immune response can be affirmed. Promising areas of research and transpiring immunologic treatments also involve tumor specific T-cell directed therapies, immune checkpoint targets and small molecule immune-modulatory drugs. Future utilization and clinical trials should take into consideration that immune-therapies may elicit a better immune system response if used while the patient is still immunocompetent. In addition, immunotherapy can endeavor the potential for durable clinical effects and synergy with subsequent therapies.

REFERENCES

1. Gupta, A., Chaphalkar, S. R., *Micro Medicine*. 2015, *3*, 36-44.
2. Siegel, R. L., Miller, K. D., Jemal, A., *CA: a cancer journal for clinicians*. 2015, *65*, 5-29.
3. Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D. S., Weinrauch, Y., Zychlinsky, A., S*cience*. 2004, *303*, 1532-1535.
4. Houghton, A. M., Rzymkiewicz, D. M., Ji, H., Gregory, A. D., Egea, E. E., Metz, H. E., Stolz, D. B., Land, S. R., Marconcini, L. A., Kliment, C. R., Jenkins, K. M., Beaulieu, K. A., Mouded, M., Frank, S. J., Wong, K. K., Shapiro, S. D., *Nature medicine*. 2010, *16*, 219-223.
5. Berger-Achituv, S., Brinkmann, V., Abu-Abed, U., Kühn, L. I., Ben-Ezra, J., Elhasid, R., Zychlinsky, A., *Frontiers in immunology*. 2013, *4*, 48.
6. Chen, J., Zhao, J., Chen, L., Dong, N., Ying, Z., Cai, Z., Ji, D., Zhang, Y., Dong, L., Li, Y., Jiang, L., Holtzman, MJ., Chen, C., *Journal of translational medicine*. 2015, *13*, 293.
7. Kiberstis, P., Marx, J., *Science*. 2002, *297*, 543-543.
8. Mahajan, K., *Oncogene*. 2016, *35*, 2279-2286.
9. Old, L. J., Clarke, D. A., Benacerraf, B., *Nature*. 1959, *184*, 291-292.
10. Pardoll, D., *Nature*. 2001 *411*, 1010-1012.
11. Nishida, S., Sugiyama, H., *The Wilms' Tumor (WT1) Gene: Methods and Protocols*. 2016, 221-232.
12. Haggar, F. A., Boushey, R. P.,. *Clinics in colon and rectal surgery*. 2009 *22*, 191-197.
13. Nakashima, H., Husain, S. R., Puri, R. K., *Immunotherapy*. 2012, *4*, 443-451.
14. Swartz, M. A., Hirosue, S., Hubbell, J. A., *Science translational medicine*. 2012, *4*, 148rv9-148rv9.
15. Baxevanis, C. N., Perez, S. A., Papamichail, M., *Critical reviews in clinical laboratory sciences*. 2009, *46*, 167-189.
16. Restifo, N. P., Dudley, M. E., Rosenberg, S. A., *Nature Reviews Immunology*. 2012, *12*, 269-281.
17. Pollack, S. M., Jones, R. L., Farrar, E. A., Lai, I. P., Lee, S. M., Cao, J., Pillarisetty, V. G., Hoch, B. L., Gullett, A., Bleakley, M., Conrad, E. U., Eary, J. F., Shibuya, K. C., Warren, E. H., Carstens, J. N., Heimfeld, S., Riddell, S. R., Yee, C., *Journal for immunotherapy of cancer*. 2014, *2*, 36.
18. Lamers, C. H., Sleijfer, S., Van Steenbergen, S., Van Elzakker, P., Van Krimpen, B., Groot, C., Vulto, A., den Bakker, M., Oosterwijk, E., Debets, R., Gratama, J. W., *Molecular Therapy*. 2013, *21*, 904-912.
19. Son, C. H., Shin, D. Y., Kim, S. D., Park, H. S., Jung, M. H., Bae, J. H., Kang, C. D., Yang, K., Park, Y. S., *Journal of Immunotherapy*. 2012, *35*, 607-614.
20. Atrash, S., Makhoul, I., Mizell, J. S., Hutchins, L., Mahmoud, F., *Journal of Oncology Pharmacy Practice*. 2016, 1078155215627503.
21. Coley, W. B., *Annals of surgery*. 1928, *88*, 641.
22. Gelao, L., Criscitiello, C., Esposito, A., Goldhirsch, A., Curigliano, G., *Toxins*. 2014, *6*, 914-933.
23. Sarid, R., Gao, S. J., *Cancer letters*. 2011, *305*, 218-227.
24. Milani, A., Sangiolo, D., Montemurro, F., Aglietta, M., Valabrega, G., *Annals of oncology*. 2013, *24*, 1740-1748.
25. Chen, D. S., Mellman, I., *Immunity*. 2013, *39*, 1-10.
26. Olweus, J., *Molecular oncology*. 2015, *9*, 1891-1893.
27. Silva, J. M., Videira, M., Gaspar, R., Préat, V., Florindo, H. F., *Journal of Controlled Release*. 2013, *168*, 179-199.
28. Pulendran, B., *Proceedings of the National Academy of Sciences*. 2014, *111*, 12300-12306.
29. Brandau, S., Böhle, A., *Mod Asp Immunobiol*. 2001, *2*, 37-41.
30. Chiang, C. L. L., Balint, K., Coukos, G., Kandalaft, L. E., *Expert opinion on biological therapy*. 2015, *15*, 569-582.
31. Choi, I. K., Yun, C. O., *Cancer gene therapy*. 2013, *20*, 70-76.
32. De Maeyer, E., De Maeyer-Guignard, J., *Comprehensive virology*. 1979, (pp. 205-284). Springer US.
33. Zaza Dit Yafawi, J., Soubani, A. O., *Clinical Pulmonary Medicine*. 2015, *22*, 230-238.
34. Winquist, R. J., Boucher, D. M., Wood, M., Furey, B. F., *Biochemical pharmacology*. 2009, *78*, 326-334.
35. Lehmann, F. M., Maurberger, A., Feicht, S., Helm, F., Ladinig, C., Kieback, E., Uckert, W, Kammertöns T, Kremmer E, Mautner J, Gerbitz A, Bornkamm GW.,. *International journal of cancer*. 2014,

135, 1153-1164.
36. Yewdell, J. W., Tscharke, D. C., *Nature*. 2002, *418*, 923-924.
37. Chatterjee, S., Johnson, P. R., Wong Jr, K. K., *Science*. 1992, *258*, 1485-1489.
38. Larocca, C., Schlom, J., *Cancer journal (Sudbury, Mass.)*, 2011, *17*, 359.
39. Kantoff, P. W., Higano, C. S., Shore, N. D., Berger, E. R., Small, E. J., Penson, D. F., Redfern, C. H., Ferrari, A. C., Dreicer, R., Sims, R. B., Xu, Y., Frohlich, M. W., Schellhammer, P. F., *New England Journal of Medicine*. 2010, *363*, 411-422.
40. Banchereau, J., Schuler-Thurner, B., Palucka, A. K., Schuler, G., *Cell*. 2001, *106*, 271-274.
41. Lin, C., Li, Y., *Cancer cell international*. 2013, *13*, 13.
42. Walsh, S. R., Dolin, R., *Expert review of vaccines*. 2011, *10*, 1221-1240.
43. Buller, R. M., Chakrabarti, S., Cooper, J. A., Twardzik, D. R., Moss, B., *Journal of virology*. 1988, *62*, 866-874.
44. Al Ali, S., Baldanta, S., Fernández-Escobar, M., Guerra, S., *Viruses*. 2016, *8*, 134.