RNA Vaccine: novel approach for cancer treatment
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Abstract
Cancer is still an unsolved puzzle and a major cause of mortality and morbidity in the world. Today, about one in every thousand people is dying due to cancer. Not any agent which can cure it in metastatic stage is found very effective so far. Though, attempts in the shape of chemotherapy, immunotherapy and vaccines are employed worldwide to find the remedy through a proper regimen. In continuation of that tumor specific mRNA is introduced as a part of vaccine in recent days. It is mostly used in transfection with Dendritic Cells (DCs) for better affectivity and safety. The DCs are selected for transfection because they are highly potent antigen presenting cells (APCs) with the ability of taking up & processing tumor antigen in peripheral blood & tissues also they can migrate to the draining lymph nodes to present antigen to naïve T lymphocytes & induce the immune response. Though, initially the RNA vaccination was done alone but due to instable & easily degradable nature of it, found quite less effective which leads to be used in combination with some stability enhancers viz RNA packaging in liposome. It increases not only RNA’s stability even worked as active immune stimulator as well. However, it shows the significant promises in cancer treatment but some time immune suppression was noticed after vaccination. To enhance the affectivity it is now days being used in combination with some drugs viz, SUNITINIB which can reduce the suppressive effect of suppressor cells. It might be a good choice for combinational therapy with RNA vaccine.

Key words: RNA Vaccine, Dendritic Cells (DCs), Vaccination through APCs, SUNITINIB, Combinational therapy

Introduction
Cancer, with an account of 7.9 million deaths (around 13% of all) in 2007 is a major cause of mortality and morbidity in the world. It is projected to continue rising with an estimate of 12 million deaths by 2030. The risk of cancer to human beings are elevated by the life style they lead today viz. imbalanced dietary habits, augmented alcohol and tobacco consumption, extensive pollutants’ exposure, exercise less day routine and carelessness about health.

In India alone, approximately 8.2 lakh histopathologically confirmed cases of cancer are reported annually. Among them, cases reported in male and female are about 3.9 lakh and 4.3 lakh respectively. Districts in central, south, and northeast India had the world’s highest incidence of cancers associated with tobacco, chewed as well as smoked in India. Though many therapeutic regimen viz. Radiation therapy & Chemotherapy, Surgery and Immunotherapy are employed for its treatment but none of these methods are employed for its prevention. Though, attempts to reduce its incidence are made worldwide to find the remedy through a proper regimen. In continuation of that tumor specific mRNA is introduced as a part of vaccine in recent days. Though, efforts are made by Dannull et al. in their studies to do the same by recombinant IL-2, they conjugate DASp-IL-2 (ONTAK) which selectively eliminates CD25 positive regulatory T-cells. Even a significant increase of tumor specific CD8 and CD4 T-cells responses was observed for the combinational therapy than to injection with DC vaccines alone.

RNA as a cancer vaccine

It contains the genetic information for proteins.
It is unlike peptide-based vaccinations so is not MHC restricted.
It is considered to be safe vaccines due to easily degradable nature.
They are intended to clear quickly from the organism and like DNA vaccines, they do not integrate into the genome.

Why mRNA as cancer vaccine?

They observed IgG1 antibodies against β-galactosidase after vaccination. In another study by Grunebach et al. the influence of cotransfection of dendritic cells with RNA coding for HER2/neu and 4-hydroperoxynonenal on the induction of antigen-specific CD8+ T-cells responses was also observed for the combinational therapy than to injection with DC vaccines alone.

Overview of RNA-vaccination using with DCs (A) or pure/stabilized RNA (B)

How does it work?

Next, under antigen processing and presentation pathway these expressed proteins are intracellularly degraded into peptides of specific molecular weight. These peptides are then translocated via MHC-I and MHC-II molecules onto the cell surface. In the process some extent by the elevated suppressive effect of Tregs in cancer patients.

Further, efforts are made by Dannull et al. in their studies to do the same by recombinant IL-2, they conjugate DASp-IL-2 (ONTAK) which selectively eliminates CD25 positive regulatory T-cells. Even a significant increase of tumor specific CD8 and CD4 T-cells responses was observed for the combinational therapy than to injection with DC vaccines alone.

T cells attack cancer cell

Vaccination scheme with RNA-transfected DCs

In-vivo studies

In a study by Carrol et al. β-globin UTR-stabilized RNA encoding β-galactosidase was injected intradermally into BALB/c mice. They observed significant CD8+ T cell responses were induced.

In-vitro studies

In another study by Grunebach et al. the influence of cotransfection of two different TAs & electroporated DCs with Her-2/neu & 4-IBBL RNA was found more immune stimulatory. They found that the costimulatory molecules were upregulated & immune response were increased in comparison to single TAA transfection. Both CD4 & CD8 T cell responses were induced.

NA Vaccine with enhancers

Though initially the RNA vaccination was done alone but due to instable & easily degradable nature of it, found quite less effective which leads to be used in combination with some stability enhancers viz RNA packaging in liposome. It increases not only RNA’s stability even worked as active immune stimulator as well. RNA vaccine administration is code to the nucleic acid on gold particles & subsequent “gene gun delivery”. The particles are used as shuttles to carry the RNA molecule through skin. After incorporation with DCs the encoded proteins are expressed & presented to T cells.

Immunity optimization

In healthy humans the CD4+CD25+ regulatory T (Tregs) cause self tolerance & have suppressor effects on immune system. They control immune response & reduce the risk of T cell responses being harmful to the body.

In the number of Tregs are found elevated in tumor patients which further suppress the immune response generated against the tumor antigen.

The vaccination along with agents having deplective effects on Tregs could prolong the life of patients and strengthen the induced immune responses.

The possibility to enhance antitumor immune response and prevents induction of immune effects is the combination of RNA-vaccination with the administration of tyrosine kinase inhibitors (TKIs).

The cellular TKIs, sorafenib and sunitinib inhibits the intracellular signaling pathway leading to proliferation and angiogenesis.

Sunitinib is administered in Renal Cell Carcinoma (RCC) and gastrointestinal tumor (GIST) treatment. Recent experiments on mouse showed that pretreatment with sorafenib reduce the induction of antigen-specific T cells, while sunitinib had no such effect.

n human monocytes derived DCs, sunitinib had no influence on their phenotype and T cell proliferation but sorafenib was found inhibiting the maturation processes of DCs and the stimulation of T-cells.

They have findings that indicate the sunitinib might be a good choice for combinational therapy with RNA vaccinations.

Future Prospective

The combination of RNA vaccination and the further stimulation of the immune system by liposome and TLRs together with the inhibition of cell population death suppress immune responses may enhance the effectiveness of vaccine.

References