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Role of Nano Particles and Viruses in Cancer Immunotherapy by Dendritic Cells (Dcs)

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Abstract—**Dendritic cells (DCs) are one of the important cells in our immune system and nobody can forget about their pivotal role for stimulation of Th(Helper T cells) and Tc(cytotoxic T cells) . Recently scientists have understood key role of DCs in stimulating high responses against cancer cells. Immunologists have been loading DCs outside of body, but the researches are shown loading the DCs outside of body is very costly. Thus, the scientists are working hardly to find a way to impulse DCs inside the body. The investigation that were done on viruses and more recently nano particles showed that these are the two important areas which can be considered more and more especially in loading the DCs inside the body. Viruses such as retroviruses, adenoviruses and vaccinia viruses can be used to modify both host cells, such as DCs, and cancer cells. On the other hand, nano particles have the potential to radically change cancer therapy for the better and to dramatically increase the number of highly effective therapeutic agents. However, there are some limitations for using viruses and nano particles, for example, immunogenicity of viruses and toxicity of nano particles. This review discusses different pathways that can be used for better cancer immunotherapy by DCs. Potential of viruses for gene therapy make them an interesting subject for cancer immunotherapy. In contrast, nano particles and their role for drug delivery and gene delivery made them another interesting candidate for cancer immunotherapy by DCs.**

Key words-Immunotherapy, Dendritic cells, Nanoparticles, Viruses

I. INTRODUCTION

Immunotherapy is the "art" of stimulating the immune system to react against something specific [1]. Variety of cells can be used in immunotherapy, for example, NK cells, T cells and even monoclonal antibodies, and the most important ones are dendretic cells (DCs). DCs are important due to their role as APCs (antigen presenting cells). Hence, they can stimulate both humoral and cellular immune system by presenting antigens to T cells and then B cells. The unique ability of DCs to induce and sustain primary immune response, makes them ideal candidates for vaccination protocols in cancer [2, 3, 4].The first clinical trial with (DCs) was started in the early 1990s, though Steinman and Cohn discovered this cell in 1973. Interestingly, DCs were recently reported to be cytotoxic for several tumor cell lines suggesting that this may have important consequences for their ability to stimulate tumor-specific CTL [5, 6]. Table1 is shown the result of dendritic cell based immunotherapy in solid tumors.

A. How DCs can be used as therapeutic

For therapeutic purposes, large numbers of DCs can be generated either from proliferating CD34+ bone-marrow precursor cells, which differentiate under different cytokines like IL-2, IL-6, IL-7, IL-13, IL-15, hepatocyte growth factor (HGF), stem cell factor (SCF), granulocyte macrophage-colony stimulating factor (GM-CSF) or G-CSF, transforming growth factor-b (TGF-β) and tumor necrosis factor-a (TNF--α) or from non-proliferating peripheral CD14+ cells (monocots)[7], yet DCs should be matured because mature DCs are more potent in inducing Th1 and CTL responses *in vitro*. Immature DCs are not stable *in vitro*. Maturation of DCs has been achieved by using different cytokine cocktails [8, 9]. Addition of cytokines like TNF-α or IL-6 or IL-1β or PGE2 and TNF-α [10] or by culturing in monocyte conditioned medium elicits the required maturation signal.

B. Chose the best antigens for antitumor response

Another important aspect in immunotherapy by DCs is to choose the best antigens to give us significant antitumor response. The right choice would be the antigen, which would be efficiently processed and expressed on the cell surface of a DC and elicit the activation of CTLs, which in turn would lead to a significant antitumor response [11]. For pulsing of dendritic cells, scientists use antigens are either tumor-specific or tumor associated antigens (TAA) [12]. For example: DC pulsed with defined peptides, proteins, tumor cell lysates or exosomes; DC pulsed with apoptotic or necrotic tumor cells/bodies; DC genetically modified to express tumor antigens; and DC fused with tumor cells. However, studies in a variety of solid tumors with the above strategies have failed to stimulate curative responses [13, 14].Pulsing of DCs with small peptides is the easiest method of delivering antigen to immune cells. The first clinical study involved injecting monocyte derived DCs pulsed with idiotype protein derived from B cell lymphoma [15].

However one of the methods to overcome the problem of identifying and introducing appropriate TA in DC is the intratumoral injection of *ex vivo* generated DC [16].

C. *Which mechanisms are used by tumor cells to escape from DCs?*

Recent studies on the generation, maturation, longevity, and function of DC in cancers suggest that (I) tumor-induced apoptosis of DC and (II) inhibition of DC capacity to present tumor antigen(s) (TA) are the two principle mechanisms employed by different tumor types to suppress the DC system and, thus, increase the likelihood of evading immune recognition [17, 18].Thus, some steps must be done to prevent this phenomenon, first increased numbers of tumor-infiltrating DC are associated with better outcome in cancer patients with a variety of tumors [19]. Second, the lost expression of chemokine CXCL14 in human SCCHN (squamous cell carcinoma of head and neck) may be associated with decreased migration of DC to the tumor site and, thus, suboptimal induction of antitumor immune responses [20]. On the other hand, overproduction of CCL20 (MIP-3a) by tumor cells causes the local accumulation of DC and activation of tumor specific CTL in four murine tumor models [21]. Third, the clinical benefits from intratumoral administration of DC, including tumor rejection, prolonged survival, and induction of immune memory, have been reported in mice and rats [22, 23].Although induction of DC apoptosis and suppression of DC function are the two main mechanisms mediating suppression of the DC system in the local tumor microenvironment [24, 19], pretreatment of DC with certain cytokines, including TNF-α, CD40L, and IL-12, also protects DC from tumor-induced apoptosis [25, 26]. The data comparing the effect of different factors on DC maturation and function, demonstrate that IL-15, protects DC from tumor-induced inhibition of antigen processing machinery (APM) component expression without affecting the endocytic capacity of DC. IL-15 also preserves the potential of DC to present antigenic peptides to specific autologous T cells after being exposed to tumor derived factors. Importantly, IL-15 not only protects APM in DC but also stimulates recovery of APM in DC from tumor-induced suppression [26]. Thus, IL-15 not only increases survival of DC in the tumor microenvironment, but can also protect or recover tumor induced suppression of DC function; Hence, IL-15 is an important candidate factor for stimulating DC prior to their intratumoral administration. Researchers are shown that human DC cultured with IL-15 are potent antigen-presenting cells (APC) with the ability to induce both primary (mixed leukocyte reaction, MLR) and secondary (recall responses to flu-matrix peptide) immune responses [27, 28]. In addition, IL-15 is required for IL-2 production by DC and DC-derived IL-2 increases DC-mediated NK cell activation and T-cell priming both *in vitro* and *in vivo* [29].Furthermore, IL-15 activated DC result in the up-regulation of co stimulatory molecules, an increase in production of IFN-γ, IFN-α, IFN-β and IL-12, and an enhanced ability of DC to stimulate Ag-specific CD8+ T cells [30, 31]. IL-15 also blocks IL-10 production but augments the release of TNF-α and IL-1ß by DC [32].

D. *Deferent ways for pulsing the DCs*

There are many ways for pulsing and stimulating DCs. Nucleic acids in the form of DNA or RNA have been increasingly used to transfect DCs. DNA vaccination has become an attractive strategy since it induces both cellular and humoral immunity but it has a limited potency to induce immune response [33]. Using adenovirus-MART and alpha-fetoprotein constructs, DCs were tranduced effectively and strong CTL response was reported [34]. Others have investigated the potential of RNA to deliver antigen to DCs [35].

II. VIRUSES

One promising line of investigation is the virus therapy of cancer. This approach entails the use of viruses, such as retroviruses, adenoviruses, and vaccinia virus, to modify tumor cells so that they become more susceptible to being killed by the host immune response, chemotherapeutic agents, or programmed cell death. For decades, virus modified tumor cell membranes, or viral oncolysates, have been known to induce antitumor immunity against non virus-modified tumor cells [36]. On the other hand, viruses can be used for modification of host. This is the point that should be considered precisely. For example to minimize the destruction of the bone marrow precursor cells, the multiple drug resistance gene (MDR1) has been transduced into CD34+ stem cell-enriched populations [37]. The MDR1 gene product, also known as P-glycoprotein, acts by providing resistance to naturally derived lipophilic chemotheraputic agents by pumping these agents out of the cell. Recent studies have shown that human hematopoietic cells can be transduced with the MDR1 gene using an SV40 pseudoviral vector [38]. Also, using retroviral transduced chimeric receptor genes, Hwu et al. [39] altered the specificity of tumor infiltrating lymphocytes (TIL) to recognize ovarian tumor line.

III. NANO PARTICLES

Macro size has notable draw backs when compared to nano size with regard to biological applications, due to size of cellular and subcellular compartments. The main advantages of scaling dawn to nano size in biological applications are, accumulate in the tissue of mononuclear phagocyte system (MPS), leave vasculature through leaky angiogenic and accumulate in tumor interstitial, achieved enhanced permeability and retention effect. [40]. Current trends in reaserch focus on creating multifunctional nanoparticles for *in vivo* use. In this case, nanoparticle gene delivery systems are one of the important issues. Nonviral delivery systems have been increasingly proposed as alternative to viral vectors because of potential advantages since they are amenable to synthetic manipulations, cell/tissue targeting, low immune response and unrestricted plasmid size. Nanviral gene delivery systems are typically composed of plasmid DNA condensed into nanoparticles by cationic polymers. Polyethylenimine (PEI) is the most important polymers that is used for gene delivery, because it has the highest cationic charge density [41].

IV. CONCLUSION

To make the long story short, DCs have critical role in immune system and also in immunotherapy. Research on DCs get to hot ashes nowadays especially stimulating them inside the body not outside. In previous methods DCs must be taken out the body and loaded them and then injected into the body. The scientists and especially immunologists are looking for a way to pulse the DCs into the body. The viruses are one of the important creatures that may have critical role to induce the DCs. On the other hand, nanotechnologists are trying to make nanoparticles and send them to exact places, for example the places that DCs are get together and pulse them or may they carry cytokines at the place of tumor cells and stimulate the immune cells and DCs to come over there and make an immune response against tumor cells. Thus, these two weapons can be applied by scientists for stimulation of DCs. However, nanoparticles should have characters that could escape from immune system. In addition, toxicity of nanopartcles must be considered. Viruses, in contrast, are harmful for some people especially those who have problems with their immune systems. So, it needs more experiments to get highest effect of these tools.

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