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RESEARCH ARTICLE

EXPLORING THE DEVELOPMENT OF DENDRITIC CELL-BASED CANCER VACCINES WITH A FOCUS ON CANCER RESEARCH

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Abstract

The fundamental premise behind clinical approaches for dendritic cell mediated immunization in cancer is that the limiting defect in natural antitumor immunity is at the level of antigen presentation. In contrast to vaccines for the prevention of infections, cancer vaccines are administered in a therapeutic mode, to eradicate antigen-bearing tumor cells already present in the host. Over decades, the identification of antigens that can serve as targets for immune effectors have resulted in a profusion of strategies for activating tumor antigen-specific immune responses. Therapeutic vaccines, unlike prophylactic vaccines for the prevention of infections, all share some basic attributes, the presence of target antigens, and a method for delivering the antigen into the antigen-presentation machinery in conjunction with other molecules required to provide T- and/or B-cell activation.

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Introduction:-

Dendritic cells (DC's) are potent antigen-presenting cells (APC's), [1] roles of APC in the body is to ingest, [2] digest [3] and present antigens to other cells of the immune system [4]. Presentation of antigens to white blood cells is a crucial step in the development of an adaptive immune response; [5] it activates 'naïve'[6] or 'inert' T cells [7] whose T cell receptor is specific for the particular antigen being presented by the APC [8]. The cytotoxic T lymphocyte (Killer T cell) adaptive immune response is the principle way in which tumors can be destroyed by the body [9]. Targeting tumor antigens to dendritic cells, either ex vivo or in vivo, [10] therefore allows an opportunity to bypass these defects in antigen presentation, [8] and takes advantage of the many specialized features of dendritic cell as potent antigen presenting cell [9]. It has long been realized that many tumors are poorly immunogenic [10]. That is, if they are merely disaggregated and reinjected, they frequently grow unabated and do not activate a protective immune response [11]. The modified white blood cell injections can be used as a potential therapeutic vaccine against lethal diseases [12]. If successful, this vaccine will revolutionize the future of cancer treatment [13]. The dendritic cell cancer vaccine exploits the powerful antigen-presenting capacity of the dendritic cell and uses it to develop therapeutic immunity against cancer-associated antigens [14].

Maturation Of Dendritic Cells And Immunotolerance

Dendritic cells are a class of bone-marrow-derived cells arising from lymphoid and myeloid haematopoiesis [15] that form an essential interface between innate sensing of pathogens and the activation of adaptive immunity [16]. Immature dendritic cells are found in peripheral tissues and in circulation [17]. The concentration of chemokine receptors is increased by the dendritic cells on receiving the maturation signals [18]. This in turn increases the

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antigen presentation by MHC molecules and aids in amplification of T cell responses [19]. Further, additional danger signals are required by the dendritic cells to turn them to activated form [20]. The maturation of dendritic cells depends on the various types of signals for maturation [Figure 1] [21]. The resultant mature phenotype affects the T cell interaction and cytokine secretion [22]. Other than activation of immune system, dendritic cells can also produce immune tolerance, which can be used as a strategy to produce successful vaccine [23]. From the previous studies it is known that immature dendritic cells are more likely to exhibit tolerance [24]. Some other studies also suggest that immature or not fully mature dendritic cells will not produce any desired effect in vaccination [25]. With the help of these studies, we can say that dendritic cell maturation is most essential to overcome immune tolerance and its barriers [26]. Research on DCs has recently emerged as a fundamental aspect for the comprehension of the mechanisms underlying the pathogenesis of viral diseases, [27] as well as for the progress on the development of prophylactic and therapeutic vaccines [28]. In addition, the recent advances in dendritic cell biology have opened perspectives in the research on new adjuvants and novel strategies for the in vivo targeting of antigens to DCs, which are instrumental in the development of cancer vaccines [29].

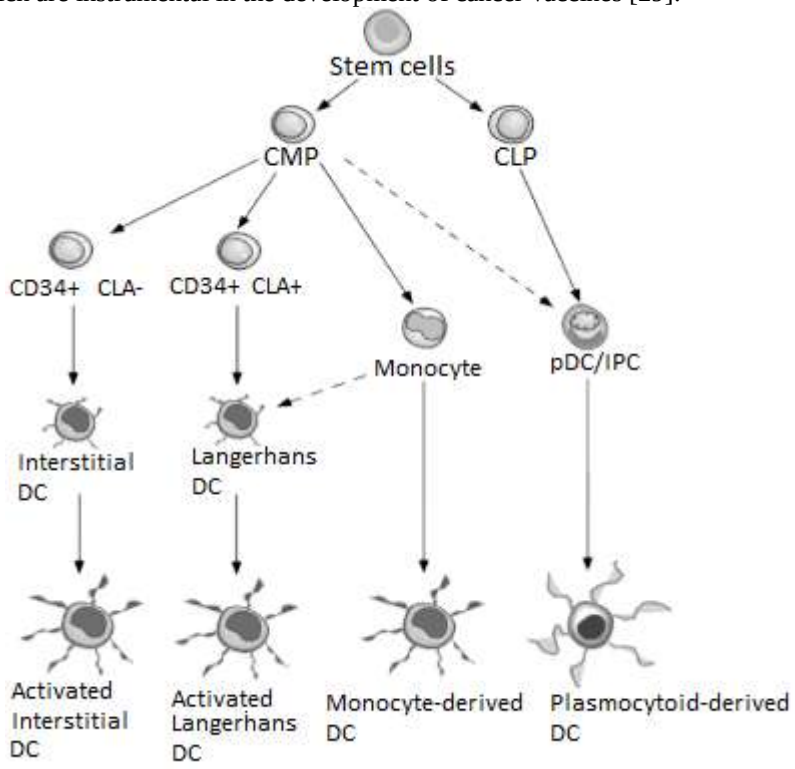

Figure 1:- Origin and development of dendritic cells.

Antigen Presentation By The Dendritic Cells

After a dendritic cell has ingested and processed an antigen, it must communicate its finding to the rest of the immune system [30]. This may be achieved by physically bringing the pieces of the antigen to other immune cells [31]. However, since other cells do not have ready access to the engulfed particle inside the cell, the antigen fragment must be presented on the cell surface [32]. One of the ways this is achieved is through antigen binding to a special 'presenting' molecule, MHC I (Major Histocompatibility Complex – Class I) [33].

This allows the small morsel of antigen to be held in place on the cell surface and gives context to other immune cells, allowing them to respond properly [34]. Usually, proteins that APCs ingest (exogenous proteins) [35] are presented on MHC II, not MHC I; that is, MHC I is reserved for fragments of proteins that cells produce themselves (endogenous proteins) [36]. However, APCs have a special ability to cross-present exogenous antigens on MHC I, [37] which allows APCs to activate cells that can recognize tumor cells expressing tumor specific antigens in the context of MHC I [38].

Developing An Immune Response

After a dendritic cell has successfully presented an antigen bound to an MHC I molecule on its cell surface, it migrates to a lymph node where many other white blood cells are waiting [36]. Here, dendritic cells interact with CD8+ T lymphocytes [Figure 2] [37]. Dendritic cell antigen/ MHC I complexes bind with T cell receptors on CD8+ T lymphocytes [38]. This contact, in conjunction with other co-stimulatory and adhesive processes, causes CD8+ T lymphocytes to multiply and mature into selective cellular perforin, commonly known as killer T cells (or cytotoxic T lymphocytes) [39]. These cells then migrate from the lymph node back into the blood and throughout the body in search of the antigen by which they were stimulated [40]. When they find cells that express the antigen, presented with an MHC I molecule, they destroy them [41]. Since cells normally present parts of their internal proteins on MHC I molecules, cancer cells produce antigens can be recognized and destroyed in this way [42].

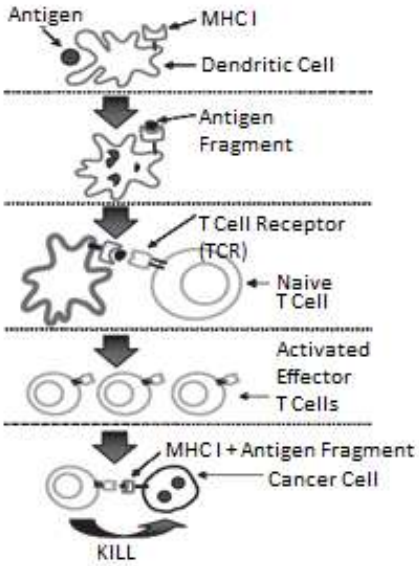

Figure 2:- Response from a dendritic cell to an activated cytotoxic T lymphocyte.

Most dendritic cell-based vaccines [43] are usually composed of the following four basic steps [Figure 3] -

1) collect dendritic cells
2) culture dendritic cells in vitro
3) expose dendritic cells to the cancer antigen(s) of your choice
4) Administer the dendritic cells into a patient as a vaccine

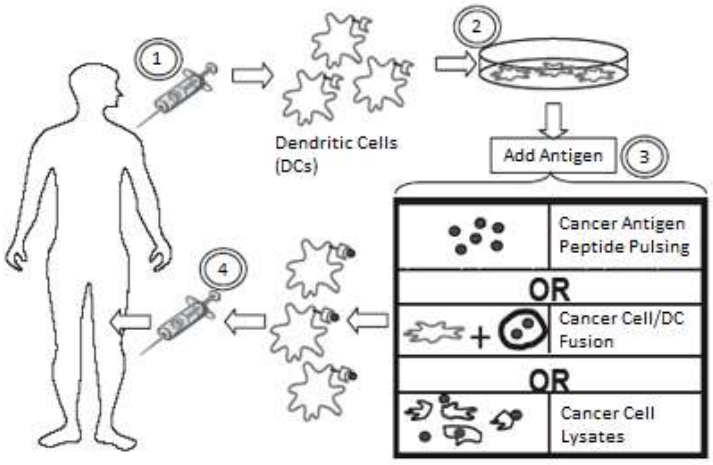

Figure 3:- The four basic steps in a dendritic cell cancer vaccine.

Improving The Vaccine

Currently, mild therapeutic effects of DC vaccines are available [44]. Scientists are now looking for new ways to increase this therapeutic effect. Some of the concepts and techniques that are being used to bring a curative vaccine for cancer closer to fruition are presented below [45].

Gene Transduction

In addition to methods that apply the antigen to the DC directly, it is also possible to transfer the gene encoding the tumor-specific antigen into the DC [Figure 4] [46]. Such an approach can be beneficial because it provides:

1) A continuous production of antigenic fragments
2) An intracellular source of antigen, easily accessible to the MHC I pathway

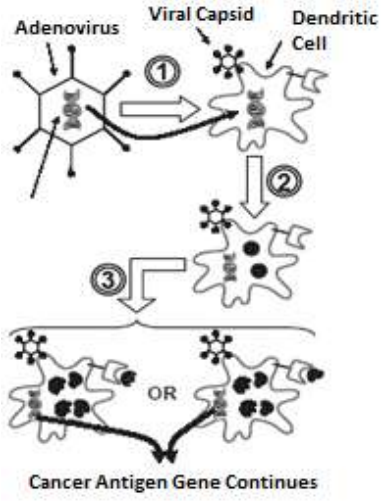

Figure 4:- Using viral gene transduction to introduce antigen genes into a dendritic cell.

Continuous production of antigen allows for prolonged availability for loading into the MHC I pathway [47]. Compared with peptide-pulsing techniques that provide short-term exposure, antigen gene transduction provides long-term exposure [48]. Given that MHC I/antigen complexes are unstable and degrade relatively rapidly with time, it is believed helpful to have constant antigen present for continuous loading onto MHC I. By providing an intracellular antigenic source, gene transduction improves the access of antigen fragments to the MHC I pathway [49]. Exogenous antigen sources, as in peptide pulsing, are normally presented on the MHC II pathway and require cross-presentation by the dendritic cell [50]. However, if the antigen is produced within the cell, it will be naturally loaded onto MHC I without the need for the less-efficient cross-presentation process.

To achieve gene transduction, viruses are normally used, [51] one of the most effective techniques for dendritic cell gene transduction [52] makes use of genetically modified adenoviruses [53]. The adenoviral vector boasts high transfection rates and allows for several vectors to be introduced into the same DC population [54]. In addition, this technique can also be used to transduce genes encoding immunostimulatory cytokines that stimulate the killer T lymphocyte response (cytotoxic T lymphocyte response) [55].

Gene technology can be united with dendritic cell cancer vaccine research, the results has been promising [56]. Dendritic cell vaccine effectiveness could be increased by a combination of both antigen and immunostimulatory cytokine gene transduction [57]. The cytokine IL-12 was chosen for the experiment because of its ability to activate immune cells and strengthen the killer T cell response in Mycobacterium tuberculosis [58]. Using adenoviral vectors, we can simultaneously introduce a breast cancer antigen (ErbB-2/neu) [59,60] and an IL-12 gene into dendritic cells ex vivo before administering the vaccine [Figure 5]. The result was a significant strengthening of the protective and therapeutic immunity of mice against injected breast cancer cells [61].

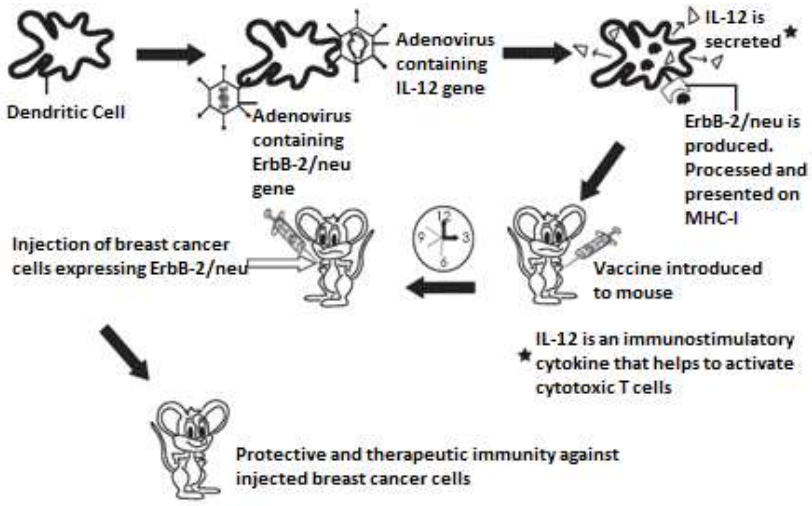

Figure 5:- Successful transduction of breast cancer antigen, ErbB-2/neu, and IL-12 genes into dendritic cells before administering the DCs as a vaccine to induce protective and therapeutic immunity against injected breast cancer cells.

Likewise, new natural [62,63] and synthetic molecules [64,65] capable of restoring and/or enhancing DC activities, often impaired in patients, have recently been identified and can be tested for their possible role in strategies of immunotherapy of cancer [66]. In addition to this, a considerable interest has focused on the use of patients' dendritic cells loaded with cancer antigens [67, 68] as a potentially more effective strategy of therapeutic vaccination in cancer individuals [69]. Of particular note, DCs are important targets of cancer, and attention should be paid to the choice of DCs used in clinical studies [70]. Different types of DCs may exhibit not only a different potential in inducing antiviral immunity but also a different degree of susceptibility to cancer and capability to transfer the virus to the target cell [71]. Thus, both preclinical and clinical studies are needed in order to evaluate the effectiveness of DC-based vaccines in the immunotherapy of cancer [72]. We conclude this review by emphasizing that although the possible future validation of DC-based vaccines for the immunotherapy of cancer [73] will certainly not solve the drastic needs of cancer individuals in the developing countries, [74] the progress of the research in this field will help us to identify novel and practical strategies for the in vivo targeting of the relevant cancer antigens to the right DCs [75]. All this will lead to the definition of new cost-effective immunotherapy for various types of cancer [76].

Conclusion:-

Although it is too early to determine the ultimate role for cancer vaccines, the results do provide an increasingly clear picture of the challenges that require attention. First, it will be necessary to identify from among the many strategies a few vaccines with enough promise to warrant large-scale clinical trials. This will require novel clinical trial designs and intermediate markers of activity such as immunologic assays to determine which induce the most potent antigen-specific immune responses. Recent attempts to reach a consensus on the immune assays to use and how to interpret them should simplify comparison across various studies. Second, the level of immune response detected by these assays is still fairly low. If one were to assume that the magnitude of the T-cell response necessary

to clear viral infections is similar to the magnitude required to destroy tumors, then most cancer vaccines activate T-cell responses two or more orders of magnitude less than is necessary. Third, tumors possess a variety of mechanisms for evading even a high-level T-cell or antibody response. Finally, before a vaccine can be administered to patients, it will require considerable regulatory scrutiny to ensure that it is safe and effective. Although the regulatory requirements for infectious-disease vaccines have been honed over many years, the use of cellular vaccines poses new issues for the Food and Drug Administration and other regulators.

Conflict Of Interests:

The authors declare that there is no conflict of interests exist among them regarding the publication of this paper. Praveen Kumar Vemuri taken responsibility in the construction of the whole or body of the manuscript. Ankitha Kunta and Rishitha Challagulla have contributed substantially to the writing, Elizabeth Anwitha Jose and Vijaya Lakshmi Bodiga in revising of the manuscript.

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