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Review Article

Dendritic cells in the treatment of HIV, cancer and systemic lupus erythematosus

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ABSTRACT

Vaccines have been one of the best weapons against diseases that have affected humanity for years, their development has allowed the eradication of important epidemics such as smallpox in 1980. Previously, complete microorganisms, or parts of them, were used to fight a disease. Nowadays vaccines make use of more sophisticated components such as genetic material and/or viral vectors. However, although technology in vaccine development has increased considerably in recent years, there are still limitations for the treatment of diseases caused by viruses such as HIV and complex diseases that are difficult to address such as systemic lupus erythematosus and cancer. This article briefly describes an overview of such diseases and the current trend of directing the immune response by vaccinating cells, not people. The importance of dendritic cells and the new technologies that have emerged in recent years are highlighted.

Key words: cancer; dendritic cells; immune system diseases; systemic lupus erythematosus; vaccines; HIV.

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RESUMEN

Las vacunas han sido una de las mejores armas en contra de enfermedades que han afectado a la humanidad durante años, su desarrollo ha permitido la erradicación de importantes epidemias como la viruela en 1980. Anteriormente, se hacía uso de microorganismos completos o partes de ellos para combatir una enfermedad. Hoy en día las vacunas usan de componentes más sofisticados como material genético y/o vectores virales. Sin embargo, aunque la tecnología en el desarrollo de vacunas ha aumentado considerablemente en los últimos años, aún existen limitaciones para el tratamiento de enfermedades causadas por virus como el VIH y enfermedades complejas difíciles de abordar como el lupus eritematoso sistémico y el cáncer. Este artículo describe brevemente una visión general de tales enfermedades y la tendencia actual de dirigir la respuesta inmunitaria mediante la vacunación de células, no de personas. Se destaca la importancia de las células dendríticas y las nuevas tecnologías surgidas en los últimos años.

Palabras clave: cáncer; células dendríticas; enfermedades del sistema inmune; lupus eritematoso sistémico; vacunas; VIH.

INTRODUCTION

For many years, humanity has been struggling against different infections that have caused millions of deaths around the world. However, researchers have found the perfect weapon to protect people from them, with the development of vaccines. The impact has been so important that diseases such as smallpox have been eradicated.[1,2] It is estimated that vaccines save between 3.5 and 5 million lives each year[3] however, their progress has been limited in some cases, for example on diseases caused by the HIV virus, and other more complex pathologies such as systemic lupus erythematosus and cancer. These pathologies, although in some cases have a unique and well-defined causal agent, still have no cure. But why is it hard to develop a vaccine to withstand these pathologies? As an example, HIV due to its high capacity to produce a high rate of mutations, generating a great diversity of sequences at the time of its retrotranscription, especially in the coding of its envelope proteins (env), allows the virus to scape from therapeutic targets.[4] This is why HIV has been treated through pharmacological schemes which only minimize symptoms such as Pre-Exposure Prophylaxis (PrEp),[5] Post-Exposure Prophylaxis (PEP)[6] and Antiretroviral Treatment (ART)[7] since they decrease the transmission of the virus and increases the life expectancy of undetectable seropositive patients. Nonetheless, several studies have shown that prolonged use of these drugs can affect different organs such as the liver and kidneys.[8]

Talking about complex pathologies like cancer, the approach is even more challenging and difficult since it involves different non-isolated etiological agents that represent an important hurdle on the development of vaccines. In these cases, why is it hard to produce a vaccine? The answer is quite complicated since it depends on tumor variability; one tumor can have different origins for example, one organ has multiple cell types and depending on the localization of the cell, the tumor behaves differently.[9] We must also consider mutations which makes cancer be subcategorized into different subgroups and finally a genetic variation could affect the same signaling pathway for example in colorectal cancer; the MAP kinase pathway can be altered by mutations in the EGFR gene but also by mutations in KRAS or BRAF.[10] Therefore, addressing all the variables that promote cancer makes it difficult to eliminate the problem with a single vaccine.

Finally, in Systemic Lupus Erythematosus (SLE) how can we address this pathology with a vaccine? There is a way to do it which will be discussed in more detail later. The management of the disease focuses on achieving remission or, at least, on decreasing symptoms[11] because its manifestation is different for most patients, becoming refractory in many cases. The treatment of patients with SLE is based on the use of immunomodulatory drugs such as hydroxychloroquine (HCQ) and glucocorticoids (GC) and others like prednisone, nonsteroidal anti-inflammatory drugs (NSAIDs), which cause gastrointestinal problems,[12] and antimalarials; as well as the use of monoclonal antibodies such as belimumab and rituximab.[11]

VACCINE DEVELOPMENT OVERVIEW

Historically, vaccines were developed due to the need to protect the population against deadly disease-causing pathogens The first attempts to develop a vaccine involved the inoculation of dried pustules, mixed with specific plants, from smallpox patients to healthy people[13] and it was not until the 18th century in Europe that Edward Jenner inocu-

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lated a preparation of infected tissues to an 8-year-old boy against rabies, becoming the first person to be vaccinated.[14] As mentioned above, it was enough to take fragments of infected tissue, make a preparation and inoculate it to say that it was already protected against the disease; However, over the time, the way of making vaccines began to change. Between the 19th and 20th centuries, Robert Koch's postulates promoted the development of vaccines beginning with the first microorganisms that could be isolated. Time after, Louis Pasteur developed a vaccine against fowl cholera and rabies, which consisted of a 13-dose schedule with a gradually increasing concentration of live virus.[15] Later it was no longer necessary to include the entire microorganism but only parts of them (protein or conjugated subunits and polysaccharides) capable of generating immunity and incapable of causing disease (see Figure 1). Examples include the pneumococcal polysaccharide vaccine that protects against pneumonia or the bivalent vaccine against HPV. Progress allowed for a deeper understanding the pathogen genome through sequencing and editing techniques, which would later be great tools for the Research and Development of therapeutic targets. That is the case of mRNA vaccines against SARS-CoV-2. In spite of the technology presented by the development of these vaccines, there is still a long way to go in order to understand the complexity of this issue.[16]

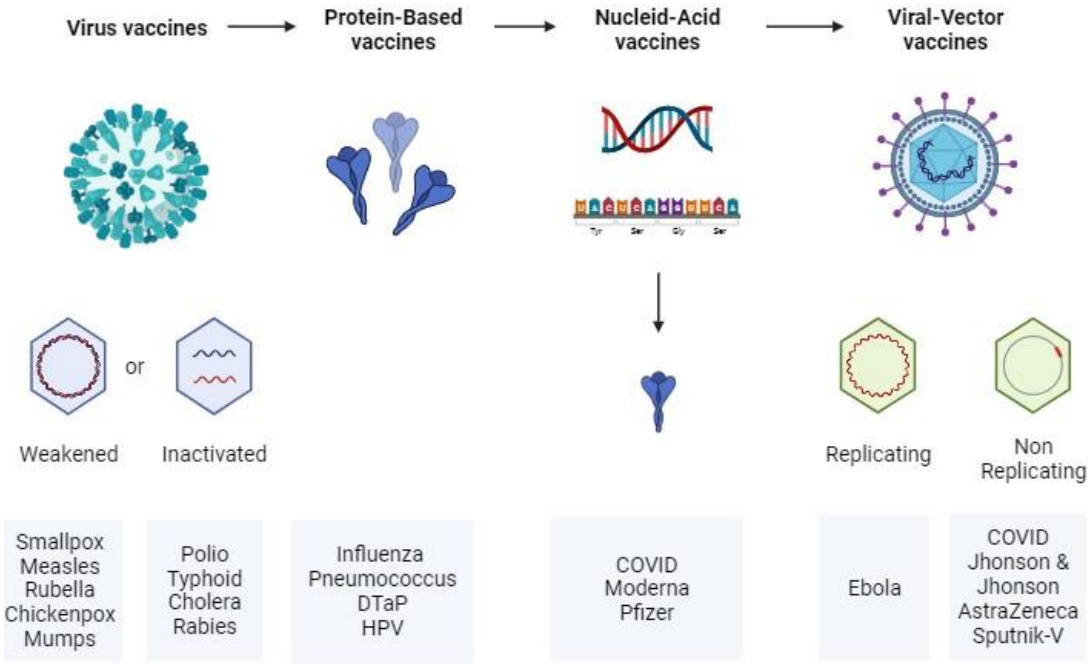

Figure 1. Evolution of vaccine development. More representative examples of the different types of vaccines that exist, some use complete viruses (live or attenuated), specific proteins or genetic material, as well as viral vectors (replicating and non-replicating).

THE APPROACH TO COMPLEX PATHOLOGIES NOWADAYS

So great has been the impact of vaccines that they are now being used to combat diseases such as HIV, cancer and SLE by different methods, for example, the most recent studies on HIV vaccines includes the RV144 vaccine or "Thai trial" which has achieved 31.2% of protection. This study is currently in phase III, but its results were made public in 2009 with a participation of more than 16,000 patients and were based on a "sensitization-booster" regimen consisting of the use of a recombinant vaccine using a canarypox vector that sensitizes and induces T lymphocyte-mediated responses,[17] and a second vaccine that boosts B lymphocyte-mediated activity based on the presentation of recombinant surface proteins.[18] There are also other vaccines still

being studied, such as RV305 and RV306 in Thailand[19] and HVTN 097 and HVTN 100 in South Africa.

In the case of cancer, there are only 2 vaccines approved by the Food and Drug Administration (FDA) which are HPV and hepatitis B.[20] Nonetheless, a type of therapeutic vaccines called immunotherapy has been developed that includes the use of monoclonal antibodies and checkpoint inhibitors like atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, pembrolizumab, among others. Also used are nonspecific immunotherapies such as cytokines, interferons, interleukins and bacillus Calmette-Guérin (BCG) and therapies with oncolytic viruses like Talimogen laherparepvec (Imligic) or T-VEC.[21] Other types of techniques include nanodevices and nanoparticles of silver, gold, zinc or titanium oxides, carbon nanotubes and nanoclays used in melanoma, breast cancer, non-small cell lung cancer, etc.[22,23] Some other vaccines include target antigens that have not been effective in activating strong T-lymphocyte responses. Examples include PANVACTM-VF against pancreatic cancer, Allovectin-7 against recurrent melanoma, abagovomab against epithelial ovarian cancer, tecemotide against non-small cell lung cancer and vitespen against resectable glioblastoma.[24]

In SLE it seems like there is no vaccine approach for the management of this disease by vaccines, however, there are several practical guidelines to treat it that have not been very effective since they are not adapted to all individuals and their effects are heterogeneous and only control symptoms in specific cases such as pregnancy or other specific situations. It should be noted that even within different ethnic groups the behavior of SLE varies with respect to documented clinical manifestations such as neuropathies and myelitis in Latin American population and glomerulonephritis in crossbreed people.[25] Another point to consider is the treatment prescribed to patients, which depends on the degree of organic or multiorgan involvement. It is considered severe when patients report thrombocytopenia, retinal vasculitis, optic neuritis, hemolytic anemia, severe myositis among other life-threatening conditions, and mild when it affects a minor organ such as mucous membranes, joints and/or serous membranes.[26,27]

That is why medication seems to be the only alternative like methylprednisolone succinate and prednisone with vitamin D and calcium supplementation as GC, hydroxychloroquine and/or chloroquine as antimalarials, Rituximab, cyclosporine, methotrexate, azathioprine, cyclophosphamide and/or mycophenolic acid as immunosuppressants have been used.[28] Additionally, most of the studies are focused on analyzing the risk of applying one or several vaccines in patients with this autoimmunity, their implications, safety and efficacy.[29,30,31]

IMPORTANCE OF DENDRITIC CELLS IN VACCINATION

During vaccination, one of the primary mechanisms is the induction of inflammation due to tissue damage and proinflammatory cytokines triggered by adjuvants.[32] Inflammation activates several mechanisms that induce a cascade of events including activation of polymorphonuclear cells, complement activation and chemotaxis of antigen presenting cells (APC) including dendritic cells (DC) to the site of damage to process the pathogen. These lasts cells are considered the bridge between innate and adaptive immunity, and it has been shown that, depending on the type of microorganism and the interaction of APC with naive T lymphocytes, the latter will be able to differentiate into helper T lymphocytes (Th) producing mainly IL-21, IL-22 and IL-17. In addition, these events also induce the differentiation of follicular effector T lymphocytes (Tf) indispensable for the differentiation of B lymphocytes into antibody-producing cells.[33]

DC are also capable of producing varieties of cytokines essential for such differentiation and carry out various effector functions in the inflammatory process, which has led them to be targets of study in the development of vaccines. The interesting thing is that there are different types and the rationale behind the use of these cells in vaccines depends on the type of DC used. The classification depends on their nature and mechanism of action. For example, there are conventional dendritic cells (cDC) type 1 (cDC1) and type 2 (cDC2) or plasmacytoid dendritic cells (pDC) producing IFN type 1. In humans, cDC1 can induce cytotoxic T cell responses and are able to stimulate naive CD4+ lymphocytes, they are also thought to be potent inducers of regulatory T cells, although their mechanism is uncertain. cDC2 carry out mechanisms similar to cDC1, but in smaller numbers. Regarding pDC in mice located in the spleen are divided into 2 types based on CD4 expression, they are characterized as essential machines in viral infections due to an increase in MHC-II and stimulatory molecules such as CD80, 86 and 40 in addition to producing high amounts of type 1 and 3 IFN. pDC are also divided into 2 and promote the production of cytokines in response to viruses and promote a strong activation of T lymphocytes and antiviral immunity.[34] In the inflammatory process, DC are crucial due to the chemotaxis they carry out through CRR7-dependent lymphoid and non-lymphoid tissues, epigenetic reprogramming such

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as DNA methylation, histone modification and non-coding RNAs they produce, which play an important role in the development of innate immune cells. They assist in metabolic remodeling involving enzymes, sensors or intermediates that involve cell migration. Also, it has been studied that CCR7 promotes migration from peripheral tissues to lymphoid tissues through four signaling pathways, the first pathway is PI3K/AKT, PI3K exerts function in immune cell modulation and chemotaxis, CRR7 induces the activation of PI3K and subsequently AKT kinase through FAS which induces the production of CXC and CC chemokines by DC through the ERK pathway. The second pathway involved is MAPK/NF-KB which is critical for TLR-induced DC maturation through IL-1, IL-6 and TNF which are crucial in inflammatory processes. The third pathway is HIF-1α which is key in the migration and inflammation of DC for their cytoskeletal rearrangement and finally the last pathway is IRF which has been showed that in mice a deficiency of IRF shows reduced expression of CCR7 and therefore defective migration.[35] All these processes and signaling pathways ensure DC as an alternative in the treatment of complex diseases.

DENDRITIC CELLS AND HIV

Speaking of cell-based vaccines, it is important to consider that some studies have focused on the characterization of CD4+ and CD8+ T lymphocyte epitopes, as well as the quantification of interleukins (IL) produced upon vaccine delivery with ex vivo-trained DC loaded with IFNα together with LIPO-5 peptides containing Gag, Nef and Pol sequences in HIV patients treated with ART. According to the authors, vaccination induced the expansion of IFNγ-secreting CD4+, IL-2 and IL-13 and generated proliferation of IFNγ-producing CD8+, perforin and granzyme A and B, signifying a control in viral replication, as stated by Surenaud M, *et al*.[36] (see Figure 2). Another publication supporting the above work starts from the same principle, which seeks, on the one hand, to develop strategies based on the optimization of CD8+ T lymphocytes that have been implicated with protective effects in clinical trials and, on the other hand, argue that T lymphocyte responses are also enhanced in preclinical trials.[37]

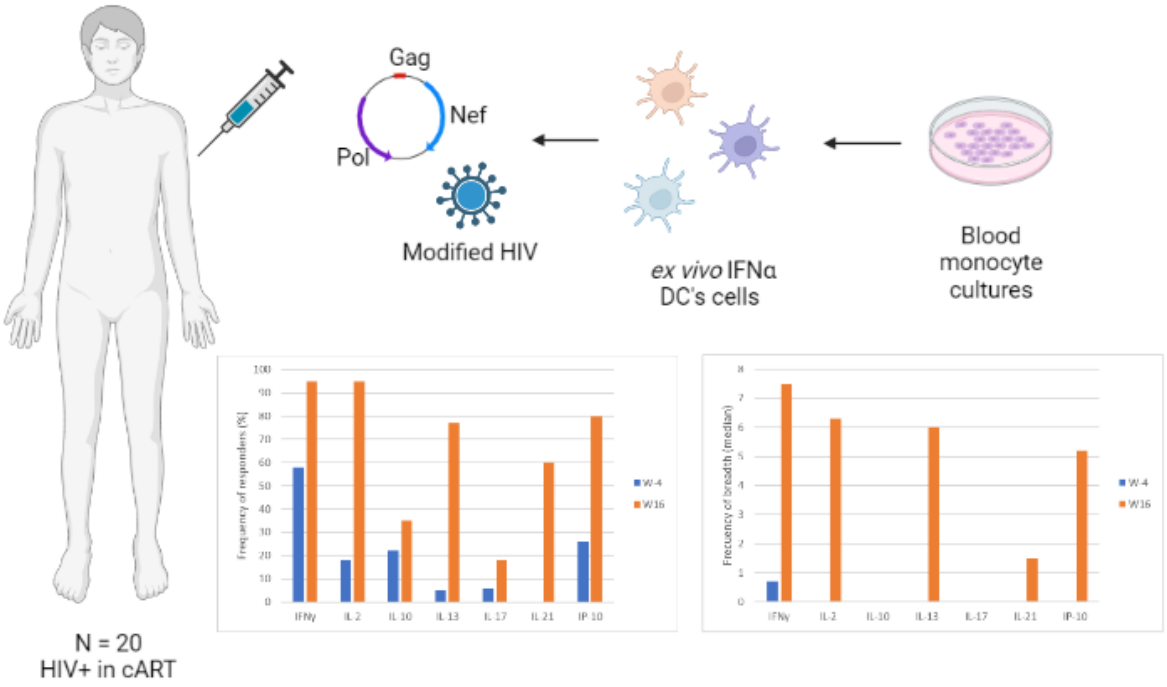

Figure 2. Design of a dendritic cell vaccine for the treatment of HIV-1. A cell culture of differentiated monocytes is performed on dendritic cells loaded with IFNα and exposed to a modified HIV virus for the immunization of seropositive patients treated with antiretroviral therapy (ART). Modified from: PLoS Pathog. 2019; 15(9):E1008011.47.

DENDRITIC CELLS AND CANCER

In cancer this is one of the most interesting fields. Cells have been used, for example, in carcinoma a vaccine composed of autologous Th17-inducible monocyte-derived DC (moDC) pulsed with folate receptor alpha (FRα) epitopes has been developed which promotes increased ovarian cancer remission period. Nagai *et al*.[38] used an adherent population of peripheral blood polymorphonuclear cells stimulated with Wilms tumor gene 1 peptide and mucin 1. In melanoma a monocyte-derived vaccine with tumor lysate has been developed that has worked, but also affects the positive regulation of PDL-1 expression, likewise another electroporated moDC vaccine with mRNA encoding CD40 ligand, CD70 and a CATLR4 (TriMiXDC-MEL) has been developed as monotherapy and in conjunction with Ipilimumab. However, autologous natural myeloid DC loaded with HLA-A*0201-restricted melanoma-associated peptides (gp100 and tyrosinase) have also been used. In glioma, a vaccine called DCVACS®-L has been developed with a cDC loaded with glioblastoma lysates. Another based on α1-type DC pulsed with 5 synthetic peptides and cytokines, and finally Wan *et al*.[39] showed a positive effect on patients using DC. In sarcoma, vaccines with moDC containing tumor antigens have been shown to be safe. However, certain combinations of anticancer drugs are counterproductive, such as temozolomide + irinotecan and a combination (pazopanib + topotecan + cyclophosphamide) negatively affected DC maturation. Similarly, the use of DC loaded with tumor lysate with imiquimod and gentamicin has been studied. Finally, in lymphoma, moDC in the presence of IFNα and GM-CSF (IFN-DC) has shown promising results.[40]

It is important to note that there are still great challenges in the development of this type of vaccine. Interestingly, although DC vaccines have been shown to be effective, there is a study which argues that DC vaccines have not shown efficacy other than provenge, or also called APC 8015 and sipuleucel-T, approved in 2010 by the FDA for the treatment of metastatic prostate cancer. But why have they failed? Although the answer is complicated, there are several alternatives that could improve this type of vaccines, for example it has been seen that most vaccines tend to use only moDC, but it has also been noted that cDC1 could be promising due to the cross presentation of tumor antigens and the use of the vaccine combined with other immunotherapies and not only as monotherapy.[41] Another alternative is the use of hematopoietic stem cells to generate cDC1 and/or induced pluripotent stem cells. In vivo DC-targeted vaccines consisting of administering tumor antigens to host-specific DC subsets using Abs against specific DC receptors some examples include anti-CTLA with DC vaccines using a human monoclonal anti-DEC-205 Abs fused to NY-ESO-1 led to a much higher rate of complete partial response than the 15% observed for anti-CTLA-4 in monotherapy. Another strategy is the use of pDC and finally using DC-derived exosomes (exosDC) as they have been found to be more resistant to tumor-mediated immunosuppression.[41]

It has also been observed that the use of DC has positive anticancer effects, specifically in different types of cancer-causing solid tumors. Two main approaches have been proposed (See Figure 3), the first method consists of isolating cancer cells that are lysed and exposed to DC that will recognize tumor antigens or implement neoantigens, which consists of developing new antigens using omics sciences as stated by Harari A, *et al*.[42] The other method is based on in situ vaccination of DC in the tumor proposed by Castiello L, *et al*.[43] This promotes a faster and more direct arrival of APCs to the tumor and, therefore, the CD8+ mediated cytotoxic effect is activated more rapidly.

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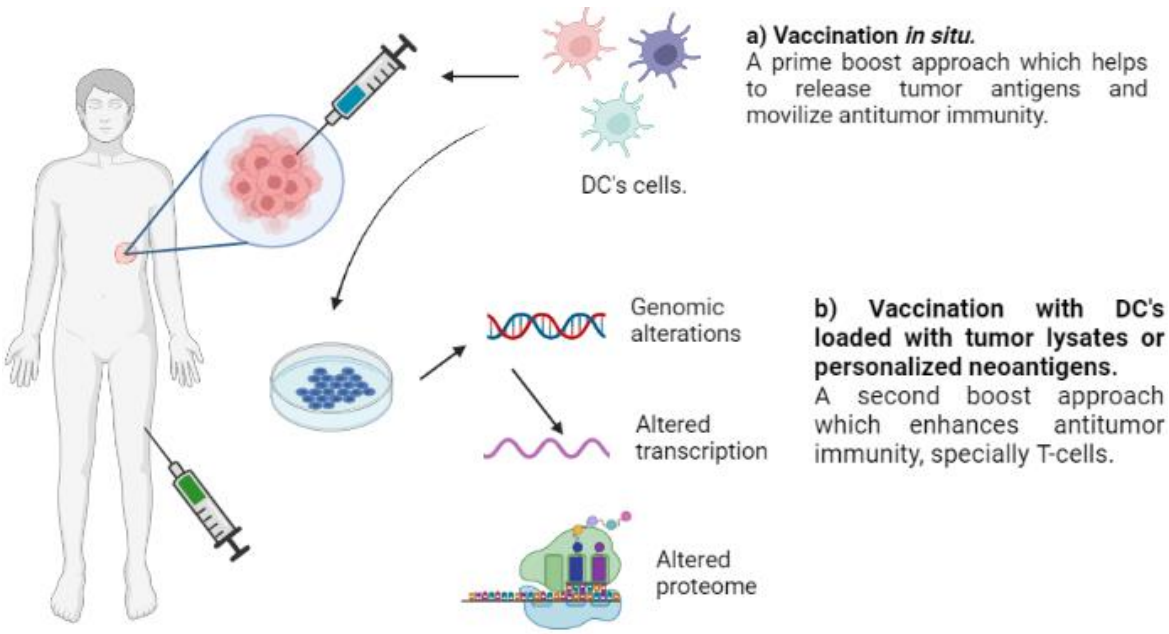

Figure 3. Dendritic cell vaccine approaches for cancer treatment. The first is based on the in situ vaccination of dendritic cells that activate the immune response to various non-metastatic tumor masses and a second approach that is based on the principles of omics sciences and the prediction of new tumor antigens.

DENDRITIC CELLS IN SLE

This field has observed an important relationship between DC cells and autoreactive T and B cells. Preclinical and clinical studies have shown that it is possible to induce tolerogenic DC cells that have a positive impact on tolerance mechanisms; these mechanisms have already been described and this implies their use in vaccines.[44,45] This largely depends on the subtype and the location of the CDs. Regarding conventional DC (cDC), inadequate processing and presentation are believed to lead to the activation of autoreactive CD4+ and CD8+, while in plasmacytoid DC (pDC) the high levels of IFNI and TLR9 expression of the cells B promote the development of autoantibodies. Finally, the role of follicular DC (fDC) in SLE is poorly known. It is believed that fDC are relevant in the protection of B cells; However, poor elimination of these promotes the development of autoantigens and, therefore, the incitement of this disease, as described by Seitz HM, *et al*.[46] Therefore, approaches for the treatment of this disease are aimed at process of peripheral tolerance of T and B cells through tolerogenic DC; that is, those that express low levels of costimulatory molecules (MHC II, CD83, etc.) and high levels of immunomodulators that suppress the activity of T lymphocytes (IL-10, PDL-1, TGF-β, etc.). Tolerogenic CD can be induced by various molecules such as vitamin D3, dexamethasone, neuropeptides such as vasoactive intestinal peptide and rapamycin, radiation, among other processes. The induction mechanisms have already been described by Švajger U, *et al*.[47] (see Figure 4).

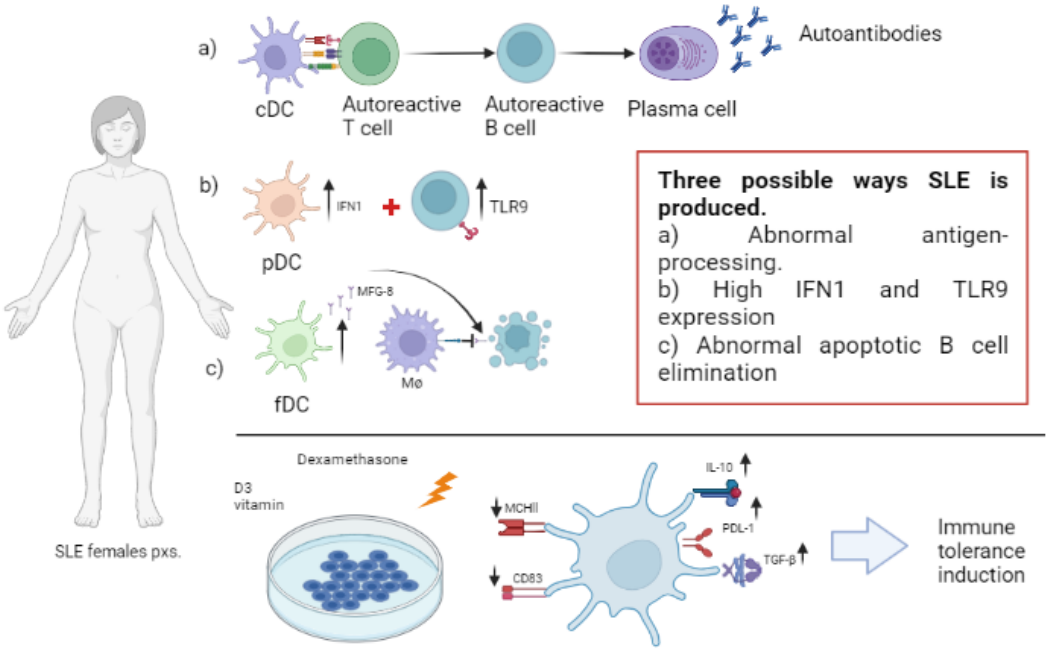

Figure 4. An approach to inducing peripheral dendritic cell tolerance for the treatment of systemic lupus erythematosus. Highlights at the top are the 3 possible ways in which SLE occurs depending on the type of CD, as well as the induction at the bottom of tolerogenic CD by various molecules and its therapeutic implications.

DISCUSSION

According to the World Health Organization (WHO), vaccines represent a form of protection against a disease, without suffering from it. This is a very effective and reliable alternative for acquiring immunity and generating response memory. However, the number of studies in the literature with this new approach is usually quite large and diverse.

Global HIV mortality rates range from 53% in women and girls to approximately 41% in men and boys since 2010.[48] In Mexico, the number of deaths by age is more concentrated in people aged 30-40 years, with 1718 deaths compared to men and 337 women. On the other hand, HIV cases by year of diagnosis have decreased dramatically due to the use of antiretrovirals, having a total of 6560 in 2021.[49] Although reported cases have been decreasing considerably over time, it is important to note the emergence of viral resistance to current drugs.[50]

Regarding cancer, figures date a population-dependent mortality rate of about 7.2% in Latin America and the Caribbean, 7% in North America, 19.6% in Europe, 58.3% in Asia, 7.1% in Africa and finally 0.7% in Oceania.[51] In Mexico, mortality rates for malignant tumors are estimated by decennial group and sex, 51% in women and 49% in men. Alarmingly, cancer deaths are increasing over the previous month and years, having a January to August rate of 4.65 in 2019 and 4.73 in 2020 per 10,000 population. The leading cause of death from malignant tumors in men and women aged 0-29 years is leukemia. In men aged 30 to 59 years, the most common malignant tumors are colon, rectum and anus. From 60 years of age onwards, the most common tumor is the prostate. While in women aged 30 to 60 years and older it is given by breast cancer.[52] However, it is important to decide and evaluate in which cases it is feasible, since in many cases it is counterproductive to puncture a tumor due to the release of cancer cells to other parts of the body. As we have seen above, there are more alternatives that have maximized the effectiveness of cancer vaccines.

Finally, in the case of SLE, it is difficult to find statistics both in Mexico and in other parts of the world. Interestingly, even in the United States there are no exact figures for this disease. However, in Mexico, Dr. Rocío Catana Hernández estimates that for every 10 people who suffer from SLE, 9 are women whose highest prevalence has been between 20 and 40 years per 100,000 from 2014 to 2017.[53]

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Now, why are these diseases relevant? In the first instance, they are diseases that have no cure. Secondly, their high incidence worldwide makes them a clear example that requires more research and more therapeutic alternatives. Finally, because the treatments currently used generate overwhelming side effects for patients leading to great detachment from them. In cancer it is important to mention that there are still great challenges when developing vaccines due to the various methods that cancer cells have to suppress and evade the immune system; and finally in SLE a vaccine would cause a lot of confusion and controversy, since the main objective of vaccination is to enhance and reinforce the immune system, which would be counterproductive. However, tolerance is a topic that has been studied and that may be a therapeutic target for the development of a candidate vaccine that can modulate this response,[54] since it has been observed that there are cells capable of performing this function, such as dendritic cells. In this sense, knowing the benefits of cell vaccines is of utmost importance since the amount of information found in the literature, as mentioned above, turns out to be very wide and varied. Therefore, it is important to publicize the new approach to the modern era.

This is the reason why the new trend in vaccinology implements the use of cells within its preparations, specifically DC, and this is partly since these diseases, being more complex, are more difficult to study. Therefore, this type of "vaccines" would help avoid a more heterogeneous response and address the problem in a more targeted way. However, classical mechanisms are still used to develop new vaccines which creates a challenge for researchers and pharmaceutical industries related to cell-vaccine development. In this sense, also in autoimmune diseases this idea allows us to address the problem in a more efficient way, since being multifactorial it can be derived from one, several or a combination of variables. This allows us to rescue the "danger model" described by Matzinger P. where in this theory the immune system is not only capable of distinguishing between its own and that of others but is more focused on activate on what causes "harm".[50] This new way of manufacturing vaccines focuses more on regulating the damage generated and reducing the effects of the disease. Finally, this work demonstrates that the study of vaccinology is constantly evolving. However, it is essential to think about pharmacovigilance aspects that include cost-benefit, best route of administration, dose, stability, possible events attributable to vaccination and immunization (ESAVIS), storage among other details that may affect the course of development of this type vaccines in the future.

CONCLUSION

The new trend in vaccinology makes use of cells as possible targeted therapies in diseases that still have no cure. The new approaches involve vaccinating cells, not people. In this regard, the importance of implementing DC in vaccines is desirable, since they are capable of modulating the immune response to damage.

CONFLICTS OF INTEREST

The authors declared that they had no conflicts of interest.

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