Dendritic Cell Based Vaccine for Human Tuberculosis

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Citation: IBRAHIM M S A W SHNAWA (2017). Dendritic Cell Based Vaccine for Human Tuberculosis. Int J Vac & Im Sys. 2:1 1-6

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Received January 17 2017 Accepted January 18 2017; Published February 10 2017

Abstract:
Immune cells may serve for vaccine technology and for gene therapy. They are basically of lymphocyte and dendritic cell types. These cells can be of adoptive and educated forms. Dendritic cell based vaccine technology can be established through; in-vitro, ex-vivo and/or in-vivo procedures. Subunit target antigen loading onto DCs or through insertion of gene construct cloned into a specific viral or plasmid vectors. Dendritic cell based vaccine designs are found of use for infectious and cancer diseases. Experimental dendritic cell based vaccine specific for viral, bacterial, fungal and protozoal infectious diseases are being ongoing in current research. Tuberculosis in man and animals is problematic at worldwide scale including our country. The approved BCG vaccine is being of questionable efficacy in infants, immune-compromised and pulmonary tuberculosis patients. The SO2 attenuated live tuberculosis vaccine is in its way for clinical trials. Experimental dendritic cell based vaccine designs specific for tuberculosis are being of educated DCs loaded with the target protein, peptide or trans-fected with gene construct codes for these proteins. Laboratory animal immune evaluations have found to be the inserted gene DC is superior to antigen loaded DC based vaccines in sense of immune protectivity. The current layout of tuberculosis vaccine is; BCG questioned, SO2 is being in its way for clinical trials and DC-based vaccine still experimental. Approved DC based tuberculosis preventive and therapeutic forms are still the near future goal of vaccinologists all over the world.

1. INTRODUCTION
Dendritic cell serves as critical vaccine adjuvant or vaccine design for prevention and/or treatment of microbial infections, allograft rejection treatment of cancer and autoimmune diseases[1]. The objective of the present mini-review is to sum-up the current attitude about the DCs based vaccine for the rather common disease all in this area or over the world, the tuberculosis [2,3,4,5,6].

2-Phylogeny:
As a phagocyte and phagocytosis in turn, they definitely appeared as functional professional phagocytes in earth worm with coelum passing through the evolutionary animal group ranks up to vertebrates[7]. Boney fish devoted from bone marrow with an evident extra-medullary haemopoiesis[8]. From amphibian up to mammals, bone marrow haemopoiesis were evident[6]. In boney fish, however, mononuclear cell system appeared as Melanomacrophage centres in spleen and in liver [9,10,11].

3-Ontogeny:
Tracing the ontogeny of the mononuclear cell system, it is rooted back to embryonic yolk sac, then fetal liver and fetal bone marrow during the embryonic life of the fetus. They arose as pluri-potent stem cells [12,13].

4-Stem Cells:
The embryonic stem cells are; self-renewable, multi-potent, and non-differentiate cells with a set of characteristic surface markers. These surface markers can be changed on differentiation to definite cell entity. Such cells have the ability to be differentiated to any
cell type in accordance with the surrounding micro-environment
tissue mellue .Among these cell entities are the mononuclear cell
system [14]

5-Macrophages:

Macrophage is a general term denoted to all cells of the mononuclear cell
system that have phagocytic activity. Mononuclear cell
system(MCS) is a group of human and mammalian leukocytes
harboring peripheral blood and the reticulo-endothelial organs
, with rather different surface markers, Table 1. They performed
an array of immunobiologic functions[6]. Mature mononuclear
cell forms and functions varies in accordance with their own
surrounding tissue microenvironment Their nomenclature will be;
glia, alveolar ,kupffer ,dendritic ,Langerhans, monocyte and
osteoclasts harboring ;brain, lung , liver, lymph node and bone
marrow , skin, blood and bone respectively [15,16,17]. The MCS
displayed the functions of; uptake, process, present and immune
recognize the antigens as a preliminary step in the immune
response events .In ,Pyres patches ,MCS have the antigen delivered
by M cells, they take up and present it to helper T cells then
triggering B or T cell responses. At the lymph node interdigitating
dendritic cell delivered antigens directly presenting them to B
lymphocytes to initiate immune response events. Langerhans cells
are skin defenders. Kupffer cells in liver on antigenic stimulation
undergoes shape changes and increase in numbers within the liver
parenchyma and contribute to the local liver immunity against
the invading pathogens[18]. Resting alveolar macrophage in
lung tissue mellue are small ovoid in active, on stimulation they
appeared larger in size and becomes rather ameboid in shape[18].
Glia cells in brain and CNS tissues during infectious invasion
undergoes cell form changes to satellite appearance, increase in
numbers and produce cytokines as well as contribute in tissue
regeneration[19]. Osteoclast contribute in bone tissue catabolism.
Monocytes are phagocytic ,antigen presenting, cytokine producer
and might be differentiated into immature dendritic cells then
to mature dendritic by local cytokine action[13]. MCS, form the
model systems for testing; phagocytosis, macrophage inhibitory
factor, ex-vivo cytokine production and antibody production by B
lymphocytes[20,21,22].

6-Dendritic Cells:

DC is satellite in shape with irregular nucleus in mature form and
bean shaped nucleus and ameboid shaped in the immature form.
DCs are professional phagocytes and acting as antigen presenting
cells(APC). They process antigens through MHC1, MHCII and CD1
pathways. DCs circulating within the host capture and deliver
microbial and/or cancer cell subunit antigens. Their circulation
starts from lymphoid tissue to peripheral blood and back to
lymphoid tissue. DCs differentiation path starts with lympho-
myeloid progenitor cells to pro-monocyte immature monocyte
then to mature monocyte. From monocyte by the effect of cytokine
to immature DCs then to mature DCs. The surface marker for
both mature and immature is basically the same but with marked
quantitative differences, Table 2. DCs are hetero-genus group
of cells that displayed difference in various anatomic sites ,cell
surface phenotypes and functions. Thus ,its sub-grouped into three
subsets, Table 3 . DCs expressed a sort of cell plasticity[23,24,25].

7-Dendritic Cell Technology:

Immune cells can be use for vaccine or gene therapy
technologies. The most tempted immune cell types were
lymphocytes and dendritic cells[26,27,28 ]. These cells are either
in adopted or educated forms. Hence several technologic trends
are currently useable for educating DCs to be valid as a base for
vaccine technology both for preventive and therapeutic vaccine
types .Details of the DCs based vaccine technology are being
stated in the followings;

i-Blood samples with anti-coagulants collected from patients
dendritic cells are separated, purified and incubated with the
subunit antigen of the causal and re-injected back to the
patients[29].

ii- Ex-vivo approach involves the separation purification and
culturing of DCs in cell culture system. Then the target gene
construct is added through an appropriate vector to facilitate its
journey to the appropriate target cells[29].

iii- Blood samples with an anti-coagulant collected from the
patients, dendritic cells are separated, purified and cultured in
cell culture system in presence of antigen source, loading agent
,maturation agent[23].

iv- In-vivo within the host, antigen targeted to dendritic cell
through binding to ICAM3 DCs sign or to CD209 establishing
promising in-vivo loading of antigens to DCs[30].

8-Dendritic Cell Based Vaccines

For an effective DC-based vaccine designs development against
polio, measles, and hepatitis B. These vaccines composed of
microbial antigens are often made with adjuvant ,Table 4 ,
that activate DCs . There are urgent need for both preventive and
therapeutic vaccine for tuberculosis replacing the currently blamed
as ineffective the BCG [ 31]. Since till now no approved dendritic
cell based tuberculosis vaccine are developed, evaluated and
licensed. However several experimental DCs based tuberculosis
carried vacine tested iv-vitro, ex-vivo and in-vivo to the rank of
labotory animal evaluations are being documented all over the
world[23,30,31,32].

9-DCs based vaccine induced Immune Conversion;

The M tuberculosis is obliged intracellular pathogen on invasion of
the host it will stimulate Th1 or Th1 and TH2 responses[33] at the
week 4 up to the week 12, the immune conversion sought as cytokine
rise in concentration and/or specific antibody concentration
or titres together with immune protection percentages. Here we
abstructing two experimental vaccination protocols in laboratory
animal models to give a clue to the nature of post vaccination
immune conversions.

i- Three groups of mice were the test laboratory animals; first wa
vaccinated with DC loaded with Ag85 , the second with DC loaded
CD4/Cd8 T cell peptide and the third vaccinated with adeno-virus
cloned with Ag85 gene transfected to DCs. The of IL12 and was more immunogenic than group one and two. Comparing the first group to the second and third. The third elicited a remarkably higher levels of ex-vivo INFg at the weeks 2,6 and 12 post-immunization which was paralleled with high frequency of Antigen specific T cells[34].

ii- Two groups of mice were the test laboratory animal. The first immunized with calf Mtbag-calf serum –DCs vaccine and the second immunized with Mtb ag-mouse serum-DCs vaccine in a three doses protocol, animal was watched in first, second and third dose in both groups for bacillary load after challenge, INFg level, survival and immune protection percentages. The second group have shown reduced bacillary load in lungs and spleen, increase of survival times, and as well as increase of INfg producing cells in lung and lymphoid tissue. DC based vaccine group two pays critical role in induction of protective immunity against M tuberculosis challenge[35].

**Table 1 : The Cell Surface Markers of the Macrophages[6,37].**

| Cell marker | Langerhans cell | Interdittating Cell | Follicular DCs | GCDC | Macrophagic |
|-------------|-----------------|---------------------|----------------|------|-------------|
| MHCII       | +               | +                   | -              | +    | +/-         |
| CD32        | +               | -                   | +              | +    | +           |
| CD64        | +/-             | -                   | -              | -    | +           |
| CR1         | +               | -                   | +              | +    | +           |
| CD21        | -               | -                   | high           | Low  | +           |
| CD1a        | +               | -                   | -              | -    | -           |
| CD40        | ?               | High                | +              | Low  | +           |

DC = Dendritic cells  
GCDC= Germinal Centre Dendritic Cells.

**Table 2: Cell surface and intracellular markers of mature and immature DCs.[24]**

| DC stage/ Surface markers | MHCII Molecule | CD54,CD58, CD88,CD86 IL12 | CD40CD25, IL12 | CD83,P55 | Granule antigen | M3242A1 MIO38 |
|--------------------------|----------------|----------------------------|----------------|----------|----------------|---------------|
| Immature                 | High Intracell | Low                        | Low            | Low      | Low            | Normal        |
| Mature                   | High Surface   | High                       | High           | High     | High           | Low           |

**Table 3 : Dendritic Cell subset characteristics[24].**

| pDCs subset | One | CD303,CD1C,CD14, C type lectin, Surface and intracellular TLR, Intracellular Helicases |
| mDC subset  | Two | Reciprocal CD1C,CD14,MHC1, X-CL1, C type lectin, Surface and intacellular TLR, Intracellular helicases |
**Table 4:** DCs based vaccines for infectious diseases [1,31,38].

| Microbial Agent          | DC based construct Inserted Vaccine | DC based antigen loaded Vaccine        |
|--------------------------|-------------------------------------|----------------------------------------|
| Virus                    | HIV, LCMV, EHV-1                    | Poliovirus, Measlesvirus, HepatitisB virus |
| Bacteria                 | Chlamydia Sp. M, tuberculosis       | M. tuberculosis                        |
|                          | Borrelia burgdorferi                | P. aruginosa                           |
| Protozoa                 | Toxoplasma gondi                    |                                        |
|                          | L. donovani                          |                                        |
| Fungi, Opportunistic     | Candida sp. [38]                    |                                        |

**Table 5:** Evaluation of DC-based Vaccine for human tuberculosis

| NIH criteria 1998 [29] | BCG vaccine [40] | SO2 vaccine [39] | DCs gene Construct vaccine [34] | DC antigen loaded Vaccine [34] |
|------------------------|------------------|------------------|-------------------------------|-------------------------------|
| Understanding Disease  | +                | +                | +                             | +                             |
| Understanding Disease agent | +            | +                | +                             | +                             |
| Developing Vaccine candidate: |            |                  |                               |                               |
| Safety                 | +                | +                | +                             | +                             |
| Identity               | +                | +                | +                             | +                             |
| Antigenicity           | +                | +                | +                             | +                             |
| Immunogenicity         | +                | +                | +                             | +                             |
| Testing Vaccine in Volunteers |            |                  |                               |                               |
| Phase I                | +                | To be tested     | Still                         | Still                         |
| Phase II               | +                |                  |                               |                               |
| Phase III              | +                |                  |                               |                               |
or candidate vaccines in this paragraph we apply this set of criteria onto tuberculosis DC based vaccine and the evaluation layout is depicted in the table 5.

**11-Dendritic Cell Based Vaccine In Brief:**

The developed and laboratory animal evaluated experimental DC based vaccine for tuberculosis own several immune features depicted in the following points:

i-Gene construct inserted DC based tuberculosis vaccine are more immunogenic and more protective than antigen loaded DC vaccines.

ii-Mouse serum is better adjuvant than calf serum DCs based tuberculosis vaccine in mouse model for immune conversion parameters.

iii-The laboratory animal evaluation parameters include INFg, IL12, reduction in bacillary load, survival time, and immune protection percent.

iv-Subcutaneous route is rather better than ,intramuscular , and intravenous routes for DC based vaccine for tuberculosis.

v-The general vaccine NIH 1998 evaluation parameters are being partly applicable on DC based vaccine for tuberculosis.

vi-The current tuberculosis vaccine layout is being as; BCG questioned, SO2 in its way for clinical evaluation and DC-based vaccine is still experimental.

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