TREATMENT OF RHEUMATOID ARTHRITIS BY A "TOLEROGENIC VACCINATION A"USING siRNA MODIFIED DENDRITIC CELLS.

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ABSTRACT:

The immune system is a complex organization of cells and antibodies designed normally to seek and destroy invaders of the body particularly infections. Rheumatoid arthritis is an auto immune disease that mistakenly attacks our own immune system and damage tissues around joints, tendons, ligaments and muscles by means of T-cell differentiation.

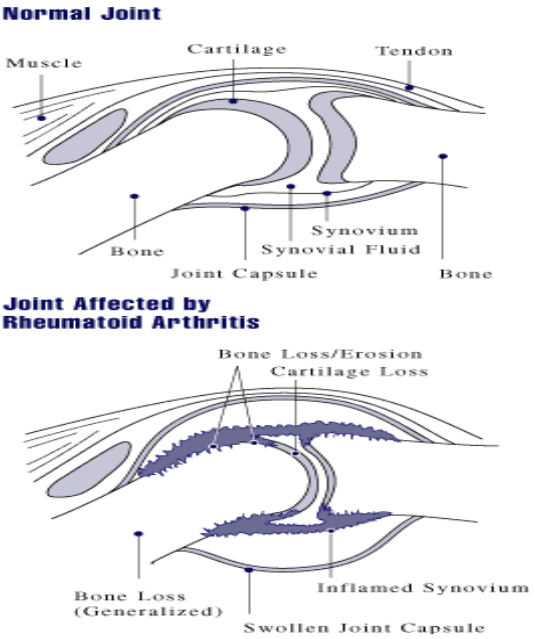
Dendritic cells are main important APC's .These cells on maturation combines with MHC molecules and co-receptors like CD-80, CD-40 activates T-cells and B-cells. This main action is regulated by IL-12gene in dendritic cells. Tolerogenic vaccination signifies exotic tool that is launched in to humans or domestic animals with an intention to enroot immunity and to generate immunological tolerance that is condition marked by stolidity to a specific antigen. Here in this critique we have cited applicability of RNA modified DC in treatment of Rheumatoid arthritis. By using the method of RNA interference using siRNA-IL12 treated DC we can treat RA by decreasing T-cell responses towards our own cells.

KEYWORDS: RA-Rheumatoid arthritis; DC-Dendritic cells; APC's-Antigen presenting cells; MHC-major histocompatibility complex; IL-Interleukin; siRNA-Small interfering RNA; Tolerogenic Vaccination.

INTRODUCTION:

RHEUMATOID ARTHRITIS:

Rheumatoid arthritis derived from the Greek word RHEUMATOS norms flowing OID norms resembling and ARTHRITIS norms joint pain and inflammation. Rheumatoid arthritis is an auto immune disease that mistakenly attacks our own immune system and damages the tissues around joints, ligaments, tendons and muscles by means of T-cell differentiation. Finally this may result in joint deformity and limited range of motion of joints [1-3].



Inflammation of the synovial membrane during RA:

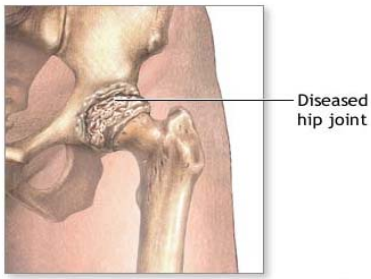
The inflammation of the synovial membrane that lines joints and tendon sheets is said to be Synovitis. Mostly affected parts are hands, feet and cervical spine.

Some other parts that may effect systemically during RA:

Skin:

Rheumatoid nodules: It is often sub cutanious most characteristic feature of RA.

The main cause for this is fibrinoid necrosis formation which contains macrophages and fibroblasts there by formed in to a swelling.



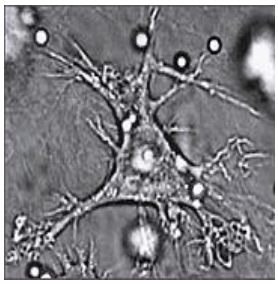
Lungs:

Fibrosis of the lungs is a recognized response to rheumatoid disease. Pleural inflammations are also associated with rheumatoid arthritis.

TOLEROGENIC VACCINATION [4]:

TOLEROGENIC: Capable of producing immunological tolerance.
TOLERANCE: The immunological state marked by unresponsiveness to a specific antigen.
VACCINATION: Any thing that is introduced in to humans or domestic animals for the purpose of inducing development of immunity.
Here we are introducing RNA modified dendritic cell.

DENDRITIC CELLS [5, 6]**:**



These are immune cells that form a part of mammalian immune system. These are one of the important antigen presenting cells which are present in tissues that are mostly exposed to external environment like skin and inner lines of nose, lungs etc. These are derived from hemopoietic bone marrow progenitor cells. They are also found in blood in immature state. The other APC's mainly present in our body are macrophages and B lymphocytes. Macrophages and B cells can only activate memory T-cells where as Dendritic cells can activate both memory & native T-cells. So scientists have been selected these dendritic cells for targeting RA using tolerogenic vaccination by siRNA modification.

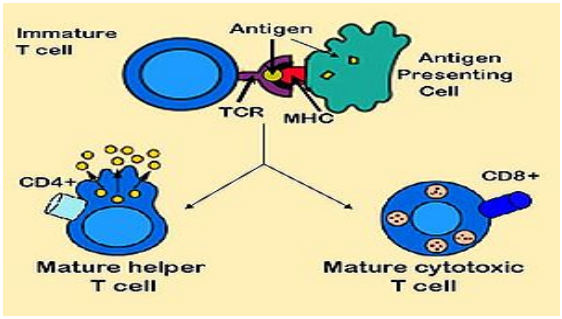
TYPES OF DENDRITIC CELLS:

There are two types of dendritic cells.

1. Myeloid dendritic cells.
2. Plasmacytoid dendritic cells.

The Myeloid dendritic cells (mDC) contain two subsets namely mDC-1which is a stimulator of T-cells and mDC-2 subset which mainly shows its functionality during wound infections. The main secretion of these myeloid dendritic cells is IL-12.
The Plasmacytoid dendritic cells (pDC) are characteristically similar to myeloid dendritic cells and these are interferon producing cells.

FUNCTIONALITY OF DENDRITIC CELLS:



Toll like receptors [TLR's] which are pathogen recognition receptors, when recognize specific chemical signature of pathogen, mature DC's are produced. These DC's present pathogen fragments at cell surface using MHC molecules. MHC is major histo compatibility complex which is a large genome family which plays major role in auto immunity [7]. These MHC's finally up regulates cell surface receptors & co receptors like CD-30, CD-80, and CD86 for T-cell activation. These MHC's encode proteins & cytokines like IL & interferon's which in turn result in differentiation of T-cells. The co receptor cells like CD-30, CD-80, and CD-86 helps in facilitate ligand recognition and as a result an antigen may physically bring towards the action of IL-12A.

Activity of IL-12 gene [8]**:**

It is T-cell stimulatory factor which can stimulate the growth & function of T-cells. It also stimulates tumor necrosis factor and natural killer cells.

But its role is quite exasperating during Rheumatoid Arthritis [RA].During RA the antigens as well as our own cells is targeted mistakenly by this IL-12 and produce T-cell responses towards our own cells [9].

So by using Tolerogenic vaccination we are trying to produce IL-12A gene suppressed dendritic cells.

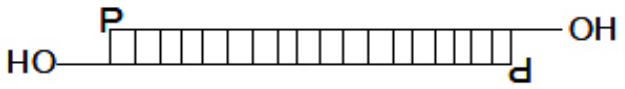
WHY SHOULD WE TARGET IMMATURE DC's?

The immature DC's are characterized by high endocytic activity and low T-cell activation potential. Their main function is that they constantly sample the surrounding environment for pathogens such as virus and

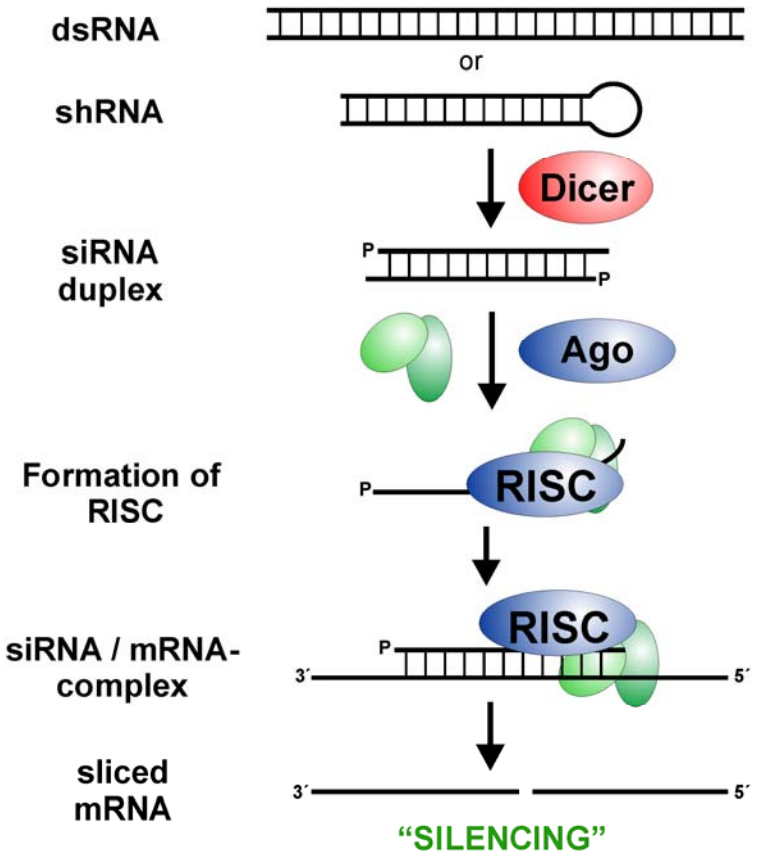
bacteria. They phagocytose pathogen and degrade their proteins. Besides we can easily suppress a particular gene and can modify to the mandatory task in immature DC's.

MODIFICATION OF DC's AS ANTIGEN SPECIFIC TOLEROGENIC VACCINE[10, 11]:

By using siRNA transfection we can produce Tolerogenic Dendritic cells. SiRNA is a class of 20-25 nucleotide long dsRNA molecules which interfere with expression of specific genes. The dsRNA can be modified to siRNA by Dicer processing. The Dicer is an endoribonuclease which helps in the formation of RISC that is RNA induced silencing complex which is a multi protein siRNA complex that cleaves viral double strand RNA and binds short antisense RNA strands which helps in the expression of genes. After the production of siRNA, it is transfected by inducing the modified nucleic acids in to the cells by opening transient pores in the plasma membrane of a cell using calcium phosphate.



Schematic representation of a siRNA molecule: a ~19-21basepair RNA core duplex that is followed by a 2 nucleotide 3' overhang on each strand. OH: 3' hydroxyl; P: 5' phosphate.



CULTURE OF MODIFIED DENDRITIC CELLS:

In order to maintain DC's in immature condition low GM-CSF factor [granulocyte macrophage colony stimulating factor] and by inducing inhibitory cytokines like IL-10 and IL-4.

CONCLUSION:

This review suggests that RNA modified DC is applicable for the treatment of Rheumatoid Arthritis by following the method of RNA interference. This helps in decreasing T-cell responses towards our own cells.

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