DENDRITIC CELLS IN RHEUMATOID ARTHRITIS

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1. ABSTRACT

Dendritic cells are the most potent subset of antigen presenting cells. They are derived from bone marrow stem cells and reside in peripheral tissues or blood. Upon exposure to antigens and cytokines the peripheral DC's, express high amounts of peptide-MHC, and upregulate their costimulatory molecules, migrate to draining lymph nodes, and interact with T cells to stimulate or tolerize them.

Dendritic cells have been found in synovium and joint fluid in rheumatoid arthritis, often at the center of a cluster of T cells. These DC's express MHC II, the costimulatory molecules CD40, CD80, CD86, adhesion molecules such as DC-SIGN and chemokine receptors such as CCR7. DC's can polarize T cells into Th1 or Th2 phenotypes depending on the cytokine environment. Th1 responses are initiated in context of IL-12 and IL-23.The cytokine milieu of the RA synovium promotes DC differentiation and function that could lead to autoantigen presentation to T cells. Dendritic cells may be central to the pathogenesis of RA and could also be logical targets for treatment. DC's themselves could be used to deliver therapeutic gene products in autoimmune disease. DC's genetically modified to express IL-4 have been used to treat or prevent collagen arthritis in mice.

2. INTRODUCTION

The functional potency of dendritic cells (DC) in initiating immune responses gives these cells central roles in host defense and in immune mediated disease, even when their numbers are relatively few compared to other leukocyte subsets. In rheumatoid arthritis (RA), DC are, in contrast, quite numerous in synovial tissue and fluid, and likely are of great importance in the pathogenesis of this disease.

This chapter will briefly review general properties of DC, and then consider what is known about their distribution and function in RA. Finally, therapeutic strategies that might act by modifying DC function, and future approaches that could even use altered DC as a novel form of treatment, will be discussed.

3. PROPERTIES OF DENDRITIC CELLS

Dendritic cells (DC) are the most potent population of professional antigen presenting cells. They are produced from hematopoietic stem cell precursors and are distributed in lymphoid and non-lymphoid tissues (1). DC's collect and process antigens from the periphery, transport them to draining lymph nodes, and activate or tolerize T cells. Upon exposure to antigen immature DC's mature and express high amounts of peptide - major histocompatibility complexes and costimulatory molecules, which facilitates primary T cell mediated responses. Peripheral resident DC's are efficient at antigen uptake and presentation. Upon exposure to cytokines such as TNF-alpha, IL-1 β, or IL-13, or activation signals such as CD 40L, or LPS, these resident DC's differentiate into mature activated DC's. At this stage the DC's are upregulating surface MHC expression and costimulatory molecules, down regulating their antigen uptake capacity, and increasing their T cell stimulatory capacity (2-5).While several aspects of DC biology remain controversial, the following sections summarize concepts that are currently accepted.

3.1. Ontogeny

In humans, DC's are produced from CD34+ hematopoietic stem cells under the influence of FLT-3 ligand and GMCSF (6). They differentiate into common myeloid progenitor cells (CMP) and common lymphoid progenitor cells (CLP). CMP's then differentiate into a CD11c+ CD1a+ Langerhans cell precursor and a CD11c+CD1a- interstitial DC precursor, both of which are immature peripheral tissue DC (7-8).

Two phenotypically and functionally different DC precursors are found in peripheral blood, pDC1 and
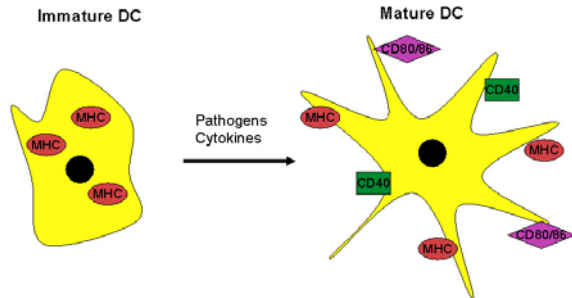
Figure 1. Upon exposure to antigens, immature DC's mature into antigen presenting cells expressing MHC peptide and co-stimulatory receptors on their surface.
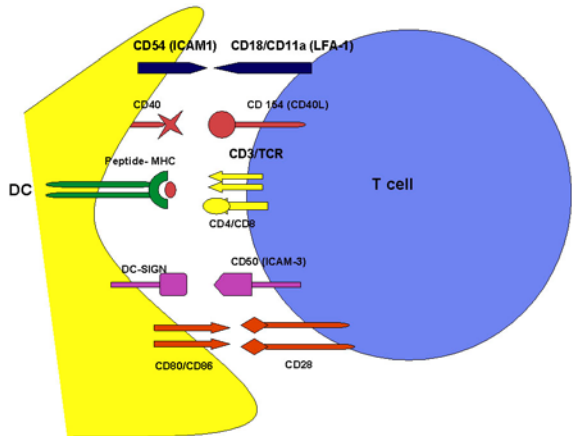

Figure 2. Interaction of mature DC with T cell via peptide-MHC complex, co-stimulatory molecules (CD40, CD54, and CD80/86) and adhesion molecule DC-SIGN.

pDC2, also differentiated from CMP and CLP respectively (8-11). pDC1 are positive for myeloid lineage markers CD11c and CD33, while pDC2 express pre-TCRalpha–chain and CD123 (IL-3 receptor) but lack other lineage markers (6,12).

In mice there are two populations of DC, also produced from bone marrow – CD8a+CD11b- and CD8a-CD11b+ (13). Cells of the CD8a+ subset produce large amounts of IL-12, induce Th1 responses and cross prime CD8 T cells. The CD8- subset of DC can induce Th2 responses and has not yet been shown to prime CD8 T cells, but nonetheless produces IL-12 when stimulated with murine cytomegalovirus or TLR agonists (3,14-16)

3.2. Mature and immature DC
DC's are defined as mature or immature depending on their ability to stimulate T cells. Immature DC include epidermal Langerhans cells, splenic marginal zone DC's and interstitial DC's within non-lymphoid tissues (1). The primary function of immature DC's in the blood and periphery is to capture antigens. Upon pathogenic antigen exposure DC's undergo maturation and express antigenic peptides on their surface in the context of MHC molecules (figure 1). These mature DC's also express high levels of costimulatory receptor CD80 and CD86. Turley *et al* (17) showed that MHC-peptide

complexes and CD86 are present as clusters on DC surface. It is hypothesized that on contact with T cells the peptide MHC complex and CD86 form an immunological synapse with TCR and CD28 on T cells which then stimulates the T cell. Mature DC's also express LFA-3 (CD58) and ICAM-1 (CD54) which enhance adhesion to T cells (1) (figure 2).

Stimuli distinct from antigen exposure can also lead to DC maturation. These include the cytokines TNF-alpha, GM-CSF and IL-1, microbial molecules such as lipopolysaccharide (18-19) and CD40L on activated T cells, platelets and mast cells. These stimuli are receptor mediated and lead to NF-kappaB activation via the TNF receptor-associated factor TRAF 6 pathway (1).

3.3. Antigen capture and migration of DC
DC's differ from other APC'S in that they express higher levels of MHC and accessory molecules, make large amounts of IL-12 and internalize antigens via phagocytosis, pinocytosis, Fc receptors and lectin receptors. In contrast, B cells employ antigen specific immunoglobulin receptors and Fc gamma receptors (1,18,20-22). Other specialized receptors on DC enhance DC function in specific ways. For example, DC-SIGN (DC-specific ICAM-3 grabbing non-integrin) is a C-type lectin receptor on dendritic cells responsible for binding to ICAM-3 on T cells, thus stabilizing the DC-T cell contact (23). DC-SIGN also binds to HIV-1 and carries it to T cells without internalizing the virus (24).

All subsets of DC are adept at antigen uptake, processing and presentation in context of both MHC I and MHC II, but distinct subsets may stimulate naïve T cells to differentiate into a Th1 or Th2 phenotype. DC can also stimulate T cells to become regulatory T cells. In addition to microbial products DC's also capture antigen against which immunity is avoided or strictly regulated. These may be environmental proteins or self antigens (25).

Upon exposure to protein antigens DC's mature and express CCR7, a chemokine receptor which is responsible for migration of the DC to T cell rich areas in lymph nodes. Recent studies have shown that even immature DC's migrate from periphery to lymph nodes (26-28).

Our current view of immature DC's capturing antigens from periphery, maturing en route to lymph node, and then presenting antigen to T cells in lymph nodes might be overly simplistic. Migrating DC's may not always be the cells that actually present antigens to T cells. Instead resident DC's might present antigens brought in by mature peripheral DC (29-30). Not all DC's in the lymph node are mature, and many DC's in lymph node may be immature DC's which can form peptide-MHC complexes and initiate tolerance.

3.4. Immune activation and tolerance
DC's are much more potent in stimulating T cells than are B cells or macrophages. In mixed leukocyte reactions DC's stimulate T cells, resulting in easily identifiable discrete cell aggregates. The activated T cells

then interact with other APC's, produce cytokines and lyse specific targets (31). DC's express 10-100 times higher numbers of peptide and MHC complexes than do B cells and one DC can activate 100-3000 T cells (32). DC's can prime T cells to mismatched MHC, superantigens, microbial proteins that bind to MHC without prior processing (33), and microbial and tumor proteins that require processing before binding to MHC (20-21,34-35).

DC's can stimulate both CD8 and CD4 T cells. DC's which express MHC I cause vigorous proliferation of CD8 cells (36-37). MHC II expressing mature DC's, in the presence of IL-12, differentiate CD4 T cells into IFN-gamma producing Th1 cells. The same DC's, in the presence of IL-4, induce IL-4 and IL-5 secreting Th2 phenotype (1, 38-39).

DC's respond to the DC-T cell interaction as well. Ligation of CD40 on DC with CD40 L on T cells results in upregulation of CD80, CD86 and release of chemokines IL-8, MIP-1alpha and beta (38-40). Interaction of RANK receptor on DC's with RANK ligand on T cells leads to increased DC survival (41-42). DC's are also important in the innate immune response – they produce IL-12 and type I and II interferon, and activate NK and NKT cells which kill targets (25).

Human DC's can upregulate BLyS (B lymphocyte stimulating protein) and APRIL (a proliferation inducing ligand) upon exposure to IFN-alpha, IFN-gamma, LPS and CD40L. BLyS and APRIL then directly act on B cells to induce immunoglobulin gene class switching and differentiation of B cells into plasma cells (37), independent of cognate CD40/CD40 ligand interactions between B cells and T cells.

DC's are also important for central and peripheral tolerance of T cells. DC's present self antigens in the context of MHC to thymocytes in the thymic medulla. Thymocytes with high affinity T cell receptors are deleted (negative selection) (44). There is an increased incidence of autoimmunity if the MHC molecules are presented to the T cells by thymic cortical epithelium and not by DC's in the thymic medulla (45). It is thought that either different DC subsets are involved in activation and tolerance or that the same DC type may be responsible for both outcomes depending on the cytokine context in which DC's are stimulated to mature. It may be possible that DC's induce and activate T regulatory cells – immature DC's trigger IL-10 dependent differentiation and function of Tr1 regulatory T cells (46-47). Antigen bearing DC's are also able to induce development of CD4+CD25+ regulatory T cells (48).

4. IDENTIFICATION AND CHARACTERIZATION OF DENDRITIC CELLS IN RHEUMATOID ARTHRITIS

Cells with a dendritic morphology were described among dissociated RA synovial cells as early as 1979 (49), but these studies could not distinguish between leukocyte DC and synovial fibroblasts that assumed a dendritic morphology in culture – the "dendritic cells" described in this report were shown to produce collagenase, and were, most likely, fibroblasts. Two years later synovial cells with dendritic morphology as well as cells with a typical fibroblastic appearance, were described to each strongly express Class II MHC antigens (50). Shortly thereafter Poulter and colleagues used a panel of antibodies in immunohistochemical studies to distinguish synovial DC from other antigen-presenting cells (51). Although subsequent work would clearly establish distinctions between synovial fibroblasts and DC by analysis of the surface structures and functional profiles of each cell type, a surprising degree of functional overlap continues to be described. Thus, RA synovial fibroblasts interact with lymphocytes in functionally significant ways (52-54), and have even been proposed to possess properties of follicular dendritic cells in interactions with germinal center B lymphocytes (54). Even after multiple passages, RA synovial fibroblasts can be induced to convert to a dendritic morphology (55).

It was the definition of potent immune functions mediated by synovial DC that expressed high levels of Class II MHC molecules that established the importance of DC in RA. Klareskog and colleagues proposed, in 1982, that RA synovitis resembled a cutaneous delayed type hypersensitivity reaction, with T cell activation mediated by synovial dendritic cells that exhibited similarities to Langerhans cells of the skin (56). These cells, which were enriched using a gradient centrifugation procedure, were potent stimulators of allogeneic mixed lymphocyte reactions and of antigen responses to peptide antigens, including Type II collagen (56).

Subsequent work by two independent groups, led by Jacob Natvig and Nathan Zvaifler, confirmed and extended these observations (57-65). These studies showed that 1) DC could be readily identified and isolated from synovial fluid as well as tissue, and accounted for 5-7% of RA synovial fluid mononuclear cells; 2) T cells formed clusters around individual synovial DC; 3) synovial DC stimulated T cell responses more potently than did monocytes, in both allogeneic and autologous mixed lymphocyte reactions; 4) functions of synovial DC depended on Class II MHC and included induction of T cell responses to a variety of nominal antigens; 5) adhesion of T cells to DC depended, in part, on interaction of CD2 on the T cell with CD2 ligands on DC; and 6) DC could be found in synovial fluids of patients with inflammatory arthritides other than RA.

Subsequent studies used immunohistochemical techniques to examine the distribution of DC in RA synovium. DC are associated both with small clusters of lymphocytes adjacent to flat-walled synovial venules, and also with dense lymphoid infiltrates around high endothelial venules, that resemble tissue within lymphoid organs (66). Many of these synovial DC are fully differentiated and highly activated, as indicated by the presence of nuclear RelB, a transcription factor that is a member of the NFkappa-B family. Nuclear RelB is absent from circulating DC in normal or RA peripheral blood, and

is only found in a small percentage of RA synovial fluid DC (67). However, synovial fluid DC in RA are phenotypically and functional more mature than normal or RA peripheral blood DC: they express high levels of Class II MHC molecules, potently stimulate a variety of T cell responses, and express various ligands for co-stimulatory receptors on T cells, including CD58, CD54, CD40 and likely modest amounts of CD80/B7 (68). Synovial tissues from patients with spondyloarthropathies also contain numerous DC associated with lymphoid aggregates, although perhaps not as many as in RA, while far fewer DC are found in osteoarthritis synovia (69). Mature DC in RA synovial lymphoid infiltrates, identified by expression of CD83 and DC-LAMP, also express the chemokine receptor CCR7, which may be responsible for localizing these DC in response to the chemokines CCL19 and CCL21 that are produced in the same areas of synovium by other cells (70). Immature DC that express CD1a (also found on Langerhans cells in the skin), are also present in RA synovium, mainly in the lining layer. These cells express CCR6, while CCL20, a ligand of CCR6, is produced by synovial cells in the lining layer (70).

In addition, CXCL12 (SDF-1alpha) binds to CXCR4, which is expressed on circulating DC, and CXCL12, which is produced locally, has been proposed to play a key role in attracting DC into synovial tissue. (71). Studies involving engraftment of human rheumatoid synovium into SCID mice have shown that CXCL-12/SDF-1a and CXCR 4 are highly expressed in the rheumatoid synovium in the lining, sublining layers and perivascular aggregates. This study further showed that CXCL-12 is a very potent chemoattractant of monocytes/DC into the rheumatoid synovium (72). These findings support the concept that localization of DC subsets in synovium is controlled by specific chemokines and their receptors.

Weyand and Goronzy (73) have proposed that three different patterns of inflammation can occur in RA synovium, diffuse infiltrates, lymphoid aggregates and true germinal centers. Follicular dendritic cells (FDC) are present only in the germinal centers and are likely essential to their formation and to the affinity maturation of autoantibody production e.g. rheumatoid factors in these structures (73-74). Interdigitating DC can be present in both lypmhoid aggregates and germinal centers (30), and are rare in normal synovium (75). Little is known about the presence and function of DC in extra-articular lesions of RA, but they are reported to be present in rheumatoid nodules (76).

What pathways result in the presence of differentiated DC in RA synovial tissue? Two reasonable possibilities are: 1) DC, both immature and mature, migrate into RA synovium from venous blood and assume their positions within the synovial tissue and fluid according to the actions of chemokines and adhesion molecules; and 2) DC differentiation occurs in the synovium from monocyte precursors, with the help of cytokines such as GM-CSF (77). These two possibilities are not mutually exclusive. Implicit in this discussion is the assumption that most synovial DC are derived from CD14+ , CD1a+ precursors.

Recent work has shown that undifferentiated precursors of myeloid DC can be isolated from RA synovial fluid, and readily differentiated in the presence of appropriate cytokines to highly functional mature myeloid DC. Moreover, cell free RA but not osteoarthritis synovial fluid stimulates DC maturation from myeloid progenitors (78). Furthermore, venous blood from patients with active RA or Sjögren's Syndrome contains increased numbers of progenitor cells that can differentiate into DC (79).

Functionally significant molecules on the surface membrane of RA synovial DC include MHC determinants, co-stimulatory structures, adhesion molecules, receptors that facilitate antigen uptake, cytokine receptors, and membrane-bound cytokines (80-86). Since CD28 is the prototypic T cell costimulatory receptor, CD28 ligands on synovial DC have potential importance. CD80 has been reported as absent (87-88) or, more likely, only weakly present on synovial fluid and tissue DC (68,81-82,84). CD86 is expressed a bit more strongly, is readily upregulated *in vitro*, and is functionally important in stimulation of T cells by these DC (81-82). Information about expression of novel, additional CD28 ligands on these cells is currently lacking. The expression of CD40 by synovial DC is significant, since synovial T cells can induce IL-12 production by DC by means of CD40 ligand (83).

DC-specific ICAM-3-grabbing non-integrin (DC-SIGN), a cell surface C-type lectin that binds ICAM-3, is usually viewed as a DC specific molecule. Both of these molecules are widely expressed in RA but not normal synovium, but in this tissue DC-SIGN is actually not DC specific, and is instead primarily found on CD68+ synovial macrophages (85).

The heat shock proteins (hsp) that are produced in response to cellular stress can chaperone a variety of antigens onto the surface of DC. Inducible hsp70 was found at high levels on myeloid DC from RA synovial fluid, but not on control DC. Receptors for inducible hsp70 were also found on these DC and inducible hsp70 was detected in RA synovial fluid (86), suggesting an important role for this chaperone molecule in the function of RA synovial DC.

Interactions between DC and lymphocytes are mediated by cell-cell contact through multiple types of receptor-ligand pairs, and also by secretion of cytokines and chemokines. Th1 immune responses are initiated in the context of IL-12 and IL-23 production by DC. The ability of IL-23 to enhance T cell production of IL-17 (89) may be important in RA, since IL-17 can directly activate synovial fibroblasts and augment their response to other signals from T cells (53). RA synovial DC do not make IL-1 (90), but circulating DC in RA do make this cytokine (91). The significance of this difference is not currently clear. Fractalkine, a chemokine that is abundant in RA and that has both angiogenic and chemotactic properties, is expressed by synovial DC (and other types of synovial cells), as is the fractalkine receptor (92-93). Undoubtedly, future studies will document the production of many other

cytokines by synovial DC that could have important pathogenic roles.

DC's from patients with rheumatoid arthritis have increased expression of FcγRII and also produce high levels of IL-1, IL-6, IL-10, IFN-γ, IL-12 and TNF-alpha compared to normal DC's. Ligation of the FcγR on these DC's with immune complexes resulted in decrease in the production of IL-1, IL-12 and IFN-γ in both healthy and rheumatoid arthritis populations. However there was a decrease in IL-6 and TNF-alpha synthesis by rheumatoid arthritis DC as compared to control DC. This study raises the possibility that Fc-gamma-R may regulate DC function (94).

5. IS ANTIGEN PRESENTATION TO T CELLS BY DENDRITIC CELLS AN EVENT THAT INITIATES RHEUMATOID ARTHRITIS?

In the DBA/1 mouse strain that is susceptible to collagen-induced arthritis, DC pulsed with type II collagen and injected into the footpad induced inflammatory arthritis in adjacent joints (95). Joints in other limbs were not clinically affected, but arthritis could be induced in those joints by local injection of additional DC that were not loaded with antigen or by local injection of TNF. In a different series of experiments, human DC (and also macrophages) from HLA-DR4 (shared epitope) positive individuals were able to present arthritogenic peptides from type II collagen and gp39 to clonal, antigen-specific T cell hybridomas derived from HLA-DR4 transgenic mice (96). However, the initial location of antigen presentation (synovial versus extra-articular) as well as the nature of the arthritogenic antigens in human RA remain open questions. It is possible that foreign antigen rather than autoantigen has a primary role, and RA synovial DC have been found to contain antigenic material derived from intestinal bacterial flora (97).

Rheumatoid synovial tissue and fluid is enriched with DC in comparison to peripheral blood and normal synovium. It is thought that the abundance of cytokines including IL-1, IL-6, TNF-alpha, GM-CSF, IL-8 and IL-10 in the rheumatoid synovium is involved in the migration and activation of DC's (98). These DC's can stimulate T cells in an autologous but not allogeneic MLR. Exposure of normal or RA blood DC to TNF-alpha and GM-CSF can differentiate them such that they stimulate autologous T cells (99). GM-CSF and TNF-alpha may have effects on presentation and processing of antigens in addition to differentiation of DC's. Analysis of peptides eluted from human HLA-DR molecules expressed by human EBV transformed B cell line demonstrated a striking number of peptides derived from class I and class II MHC molecules (100). It is speculated that in addition to increasing the synthesis of MHC molecules GM-CSF and TNF-alpha might be also increasing the amount of improperly folded and degraded MHC molecules, thus loading intact MHC class II with MHC derived peptides. These peptides may be serving as an antigenic stimulus for the T cells in the rheumatoid synovium (98,101).

The presentation of arthritogenic antigen to T cells and the promotion of B cell activation and immunoglobulin class switching in the rheumatoid synovial tissue by DC may be sufficient to drive memory T cells and B cell mediated responses in RA. These events then can influence macrophage and synoviocyte responses (102). It is thought that the inflammatory cytokine milieu found in the rheumatoid synovium may result in abnormal life span of DC that would be contributing to the chronic nature of the disease (103-104).

6. DENDRITIC CELLS IN THE TREATMENT OF RA

If DC are indeed important in the pathogenesis of RA, they ought to be a logical target for treatment. It is possible that currently used methods to treat RA work by affecting DC function. Removal of articular cartilage from the joints of human RA patients, which is generally effective in suppressing synovitis, is associated with depletion of DC from the synovial membrane (104). Aspirin inhibits maturation of DC although it does promote differentiation of immature DC from precursor cells (105). Aspirin-treated DC captured antigen well, but expressed lower levels of Class II MHC and co-stimulatory molecules and were weak T cell stimulators. They had intact migratory capacity but could not induce contact hypersensitivity. Although IL-12 expression was inhibited in these cells, IL-10 expression was also impaired (106). Dexamethasone was also found to inhibit DC maturation, but this effect was not seen if DC were first exposed to LPS (107). Several agents not currently used to treat RA have effects on DC that could provide a rationale for their use. The anti-estrogens toremifine and tamoxifen were reported to inhibit differentiation of DC from RA synovial macrophages, as well as function of such DC (108). Glucosamine was found to inhibit *in vitro* activation of DC by LPS (109). A stinging nettle leaf extract with anti-inflammatory properties blocked DC maturation *in vitro* (110).

Given the association between synovial TNF expression and infiltration of various mononuclear leukocytes including DC (111), it is possible that a mechanism by which TNF blockade works in RA is by interfering with DC maturation. TNF has direct activating effects on DC, but other cytokines that can participate in DC differentiation (IL-13 and IL-6) are also down-regulated in RA patients treated with the TNF blocker etanercept (112). Since IL-4 is generally absent from the joint in RA the role of IL-13 as an IL-4 substitute may be especially important in local differentiation of DC (112). It is interesting that etanercept did not seem to suppress M-CSF, a cytokine that is a growth factor for monocytes but not DC (112).

IL-10 has immunoregulatory properties that make it a potential candidate cytokine for therapeutic use in RA. However, RA synovial fluid DC, unlike DC from RA blood, were shown to be resistant to IL-10 due to failure to express IL-10 receptors (113). Transforming growth factor-beta is another cytokine with immunoregulatory

properties, and it, like IL-10, is present in RA joints. TGF beta may account for some functional deficiencies that have been noted in RA synovial fluid DC (114).

In view of the immunoregulatory capabilities of DC, one might be able to manipulate these cells to treat RA or other immune-mediated diseases. While clinical use of DC in humans has thus far focused on augmentation of anti-tumor responses in experimental approaches to the treatment of cancer (115), the possibility of using DC to treat autoimmunity is being considered (116-117). Antigen-pulsed DC in which activation of NFkappaB is inhibited induce T cell tolerance or apoptosis (118). In RA, however, the evidence for a single dominant antigen driving the disease is not compelling. Therefore strategies have been developed, in the collagen arthritis RA model, to prevent or treat arthritis using non-antigen-pulsed DC that have been genetically modified to express IL-4, a cytokine that DC do not normally secrete (119-120).

Studies done by Morita *et al* showed that a single injection of DC transfected with IL-4 could suppress the development of collagen induced arthritis and pathogenic antibody to Type II collagen in mice. This effect was not due simply to the overproduction of IL-4 since T cells or fibroblasts transfected with IL-4 did not produce the same effect. The ability of splenic T cells to produce IL-4 in response to anti-CD3 was enhanced after administration of IL-4 transduced DC's, suggesting that an altered Th1/Th2 balance is responsible for the amelioration of arthritis (119).

Robbins *et al* have shown that DC's transfected with IL-4 using an adenoviral vector ameliorated established murine CIA. This anti-arthritogenic effect was far greater than the effect of IV injection of the IL-4 vector. The therapeutic effect of DC modified with IL-4 was accompanied by reduced levels of IgG2a and IgG2b anti-collagen antibodies and a lower IFN-γ response to type II collagen (120).

While such strategies work well in the mouse model, and alter *in vivo* pathogenic immune responses, many questions remain to be answered before this approach should be used in human RA. These questions include how the IL-4 DC actually affect autoimmunity and arthritis, and which human DC subset would be optimal for this therapeutic approach. Eventually, however, DC, which are important in the development of RA, could also become valuable for its treatment.

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