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Rheumatoid Arthritis: Prospects for Stopping the Runaway Train by Reintroduction of Tolerance

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Abstract

Rheumatoid arthritis is a common, well studied autoimmune disease characterized by a loss of self-tolerance. Current therapies have significantly advanced the successful treatment of the disease, but have been unsuccessful for a large number of patients. Furthermore, they have failed to induce long term medication free remission because they target a consequence of the disease, not the origins of a dis-regulated immune system. Current research is now focused on finding ways to correct and restore the balance of the immune system rather than just suppress it. The scientific foundations for a number of potential approaches to restoring immune tolerance already have been laid. This paper reviews a number of proposed targets for immunotherapy including vaccinations, shifting from Th1 to Th2 responses, molecules that promote the resolution of inflammation, tolerogenic dendritic cells, mesenchymal stem cells, and T regulatory cells. These strategies will hopefully allow a closer approach to a "cure" for this potentially devastating disease.

Keywords: Rheumatoid arthritis; Immunotherapy; Review; Tolerance; Treg; Tolerogenic dendritic cells; Mesenchymal stem cells

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease affecting between 0.5% and 1% of the population [1]. Twenty five years ago the consequences were devastating, with patients routinely suffering long term damage, loss of function, and increased mortality [2]. Since then the addition of disease modifying rheumatic drugs (DMARDs) and more recently biologic medications such as anti-tumor necrosis factor α (TNFα) to our treatment arsenal has dramatically improved long term outcomes [3,4]. However, these strategies all target downstream consequences of the disease in an attempt to suppress one or more aspects of an over active immune system (Figure 1). None of them focus primarily on the root cause of the disease, which is a loss of self-tolerance and an immune system which is out of balance. This is like trying to stop a runaway train by simply applying the brakes without stopping the malfunctioning engine that started the whole problem to begin with. It might work sometimes, or maybe just slow the train down enough so no one is hurt, but you have to keep the brake on, or the train speeds back up again.

The Holy Grail in the treatment of any disease is not simply improved outcomes, but rather a cure. Even though we have made huge progress in treating rheumatoid arthritis, our current therapies are not always successful, and the patient usually has to continue the medication in order to sustain improvement. However, if we were able to get to the original cause of the problem, and restore tolerance and balance to the immune system back to its pre disease state, we might be able to accomplish much more, with results approaching a cure.

This article aims to review a number of potential such immunotherapeutic options for the treatment of rheumatoid arthritis. These include vaccinations against cytokines, shifting T cell immune response patterns, molecules that promote the resolution of the inflammatory response, tolerogenic dendritic cells (DC), mesenchymal stem cells, and T regulatory cells (Treg).

Vaccination

Vaccines have been proven effective treatments for over 50 years for promoting appropriate responses from the human immune system. This includes vaccination with antigens from pathogenic bacteria and viruses to induce a memory measured response against future infections. It also includes desensitization regimens for various allergens in conditions such as allergic rhinitis. However to date similar approaches to other conditions involving a malfunctioning immune system such as malignancy and autoimmune disease have failed to achieve the same degree of success.

The proof of concept, however, has already been achieved in animal models. For instance in a transgenic mouse model expressing human TNF induced arthritis, vaccination against TNFα has resulted
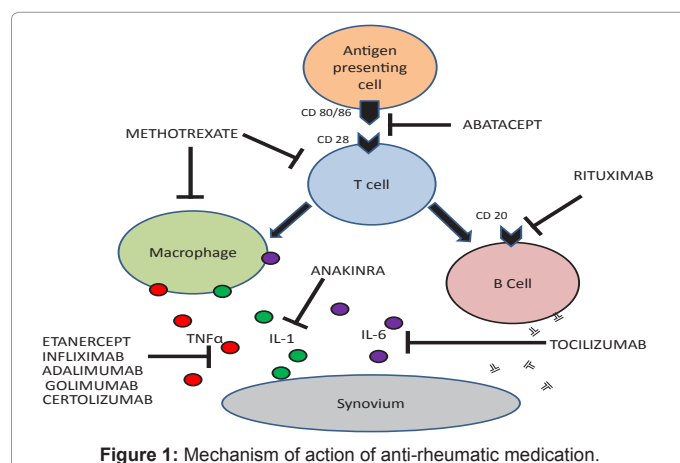

Figure 1: Mechanism of action of anti-rheumatic medication.

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in protection against the spontaneous development of arthritis, as well as improvement in the outcome of established arthritis [4,5]. Similar results have been seen within other animal models with anti-cytokine vaccinations against TNFα, IL-1β, or IL-23 [6-8]. A small phase IIa trial of vaccination against TNFα has already been completed in humans, with successful development of anti-TNFα antibodies. A broader phase IIb/III trial is underway to assess clinical outcomes [9].
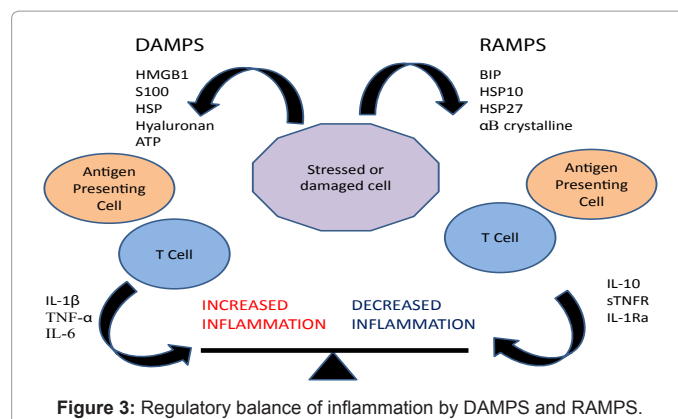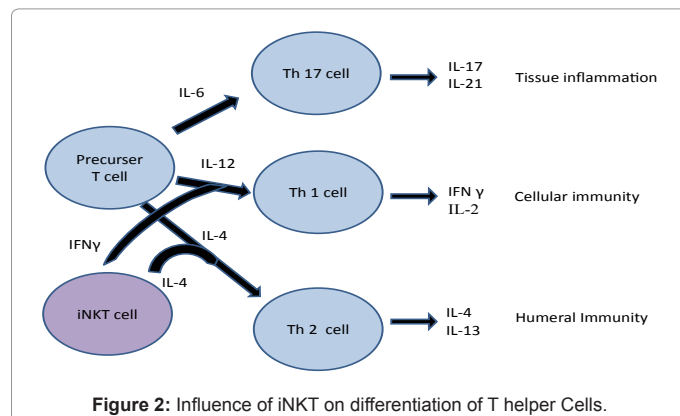
The challenge of this approach is to develop high titers of neutralizing antibodies against the target cytokine, without also invoking a pathogenic T cell response [10]. This problem has already been seen with significant morbidity and mortality in an early vaccine trial in patients with Alzheimer's [11,12]. Additionally, there needs to be a significant concern about immunosuppression caused by anti-cytokine antibodies. For instance, in autoimmune polyendocrinopathy, candidiasis, ecodermal dystrophy (APECED) syndrome, defects in the autoimmune regulator (AIRE) gene lead to a lack of thymic deletion of auto-reactive clones. Among other problems, this leads to high levels of anti–IFN-α, anti–IL-17, and anti–IL-22 autoantibodies, leading to frequent fungal skin infections [13]. Similar problems can be seen in thymoma patients, where high levels of biologically active anti-cytokine antibodies have correlated with infection frequency [14].

The vaccination approach only represents one step forward from our current treatments. While it does provide the added benefit of inducing the patient's native immune system to do the long term work, it still targets downstream cytokines just as our present treatments do, and therefore, may not be able to fully restore balance to the immune system.

Shifting Th-1 to Th-2

Rheumatoid arthritis has long been described as a disease with an imbalance of T helper cells, with too much pro inflammatory cytokine secreting Th-1 cells, and too few anti-inflammatory TH-2 cells [15,16]. Thus shifting the balance back towards Th-2 has seemed a very attractive target for long term remission in RA (Figure 2).

Invariant natural killer T cells (iNKT) are a subset of T cells which have an invariable rearrangement in their α-chain, resulting in a lack of diversity of repertoire compared to other T cells. They recognize glycolipids presented not by MHC but rather the MHC-1 like CD1d [17-19]. They are able to very rapidly release large amounts of cytokines due to existing stores of cytokine mRNA [20]. Interestingly, their response can be either with Th-1 or Th-2 depending on the glycolipid being recognized. One such glycolipid is OCH (sphingosine truncated analogue of α galactosylceramide), which has been demonstrated to stimulate a Th-2 response from iNKT cells. Several studies have shown

Figure 2: Influence of iNKT on differentiation of T helper Cells.

Figure 3: Regulatory balance of inflammation by DAMPS and RAMPS.

immunosuppressive benefits of OCH in animal models of rheumatoid arthritis [21-23].

One recently published study using a citrulline induced arthritis model, treatment with OCH prevented the development of arthritis in the mice, as well as stopping clinical progression in mice after the development of arthritis [21]. Whether this can translate into similar benefits in humans remains to be investigated, but OCH seems to be much less effective in human iNKT cells than in mice [24]. Furthermore evidence suggests specific Th-2 polarization may be more difficult in humans [25].

RAMPs

It is well described that invasion of the body by foreign organisms or trauma to the body can induce a cascade of pro-inflammatory signals started by pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) [26]. These families of molecules serve to ring alarm bells which activate the immune system to react to danger. Another family of molecules known as resolution associated molecular patterns (RAMPs) appear later in the course of healing to promote resolution of the inflammatory response, and a return to normalcy (Figure 3). This includes molecules such as HSP-10, HSP-27, αB-crystalline, and binding immunoglobulin protein (BiP) which can act on macrophages to induce anti-inflammatory signals including IL=10, sTNFR, and IL-1Ra [27].

BiP in particular may be important in rheumatoid arthritis [28]. It is a master regulator of the unfolded protein response when the endoplasmic reticulum is subjected to stress [29]. Cells in and around the rheumatoid joint are clearly under significant physiological stress, so it should come as no surprise that BiP levels are increased in both synovial fluid and tissue [30,31]. Recombinant human BiP administered in animal models of inflammatory arthritis has been shown to improve the outcome of the disease. Thus includes decreases in pro-inflammatory markers IL-6, TNFα, HLA DR expression, and CD86 expression, as well as increases on the anti-inflammatory side with IL-4 and T regulatory cells (Treg) [32-35]. Providing a caution to the contrary, BiP has been recently shown to promote angiogenesis in RA synoviocytes, and could therefore play a pathological role [36]. BiP has been shown previously to be important in cancer cell survival, and could be another downside to its use in autoimmune disease [37].

Tolerogenic Dendritic Cells

Dendritic cells (DC) play a dual function in the immune system, with both the initiation of the immune response with the presentation of antigens via major histocompatibility complexes (MHC) to T cells

Figure 4: Effects of stimuli on differentiation of dendritic cells.
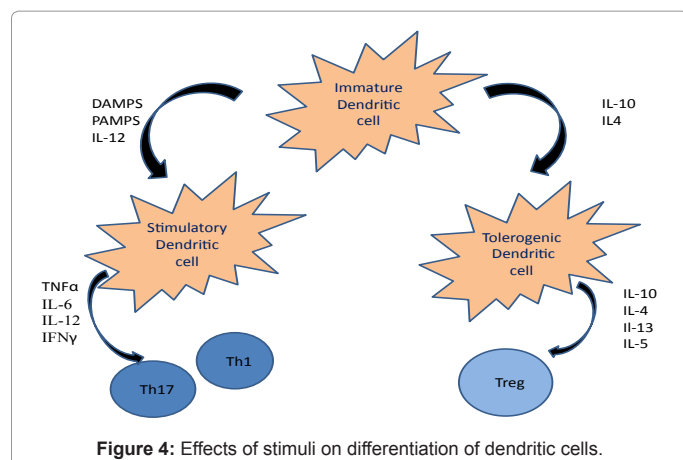
and B cells in secondary lymphoid organs, but also helping establish and maintain tolerance to self-antigens [38]. The plasticity of DC to respond to environmental signals results in their implication as major contributors to autoimmune disease, but also represent a great target to restore tolerance to an immune system out of balance (Figure 4). These tolerogenic DC expresses less co-stimulation molecules, less pro-inflammatory cytokines, and more anti-inflammatory cytokines than their immunogenic kin [39].

In animal models such as collagen induced arthritis (CIA), IL-4 stimulated DC shift T cells to a more Th-2 response with increased IL-4 and decreased (Th-1) IFN-γ as well as (Th-17) IL-17, capable of either preventing CIA or reducing the severity of established disease [40-42]. Tolerogenic DC produced by stimulation with CTLA-4 Igor indolamine 2,3 dioxygenase (IDO) have also been demonstrated to improved CIA disease activity [43].

In patients with rheumatoid arthritis, the intense inflammatory environment can result in maturation of DC, increased antigen presentation, and activation of Th-1 phenotype T cells, despite overall reduced numbers [44]. Conversely, patients whose RA is under control have been shown to have a restoration of normal DC cell levels, and increased Tregs and IL-10 levels [45]. The induction of a non-inflammatory environment by existing treatments may then allow DCs to revert to their previous tolerogenic role, and may be part of the mechanism of action for clinical remissions sometimes seen with these agents. *In vitro*, drugs that inhibit the pro-inflammatory transcription factor nuclear factor κB (NF-κB) can induce tolerogenic DC [46].

One question yet to be fully worked out before human applications is whether Tolerogenic DC need to be "prepped" with the relevant self-antigen prior to administration. Animal models have yielded conflicting results that may be model specific, or stimulation agent specific. Also the potential auto-antigens are less well understood in humans than in mouse models. There is also the danger that the inflammatory environment in RA patients could turn the DC back over to the "dark side" and further drive inflammation.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) have the ability to differentiate into chondrocytes, adipocytes, and osteoblasts. They are immune-privileged cells due to the low expression of class II MHC as well as co stimulatory molecules on their surface [47]. MSC have been demonstrated to have considerable immune-modulating effects, including down regulation of both T cells and dendritic cells [48,49]. Because of these properties,

MSC are intriguing targets for restoring balance to an overactive immune system.

Some studies in the CIA mouse model have shown improvement, [50-54] especially in early disease, while other studies have shown no effect or worsening of disease [55-59]. In CIA, the addition of cord derived stem cells showed no change, but led to worsening in the presence of TNFα. The addition of anti TNFα antibodies along with the stem cells led to improvement in arthritis [60]. In adjuvant-induced arthritis (AIA) and the spontaneous K/BxN arthritis model, pretreatment with bortezomib, a proteasome and nuclear factor kappa B inhibitor with broad cytokine suppressive properties, prior to MSC infusion seemed to restore immunosuppressive properties of MSC. Animals in both models with both bortezomib and MSC had better improvement in arthritis than bortezomib alone, suggesting that the MSC added to its benefits [61].

MSC cells derived from the blood of patients with RA interact with T cells within 24 hours in vitro to promote a Th-17 response [62]. Synovial fluid from patients with RA can also induce an inflammatory differentiation of MSC, including increased IL-6 [63]. One recent study noted a couple of positive results for MSC in human patients with RA, but few details were provided [64].

Collectively these studies suggest that the best target window for MSC therapy in rheumatoid arthritis is either very early in the disease or after clinical improvement is obtained with another treatment, with the hope of not needing to continue that treatment. Use of MSC in patient with very active disease might promote worsened outcomes.

T Regulatory Cells

T regulatory cells (Treg) are T cells characterized by a CD4+, high CD25+, and Fox P3+ phenotype. They are thought to play a strong role in self-tolerance and thus prevention of autoimmune disease, but also preventing tolerance to malignant tumors and chronic viral tolerations. Shifts to one or the other extreme can play a major role in perpetuating disease. Natural Tregs are produced in the thymus, and inducible Tregs can be derived in peripheral tissue [65] (Figure 5).

It has long been recognized that pregnant patients with rheumatoid arthritis can often undergo significant clinical improvement, followed by worsening disease after delivery [66-69]. This observation, in fact, helped lead Hench to the discovery of corticosteroids as the first treatment for RA [70]. In fact, Tregs play a major role in facilitating implantation of the embryo and maintaining the pregnancy despite the presence of "foreign" paternal antigens, effectively inducing tolerance to the developing fetus [71,72]. In fact, it has recently been shown that the enhancer locus conserved noncoding sequence 1 (CNS1)

Figure 5: T regulatory cells differentiation and effects.
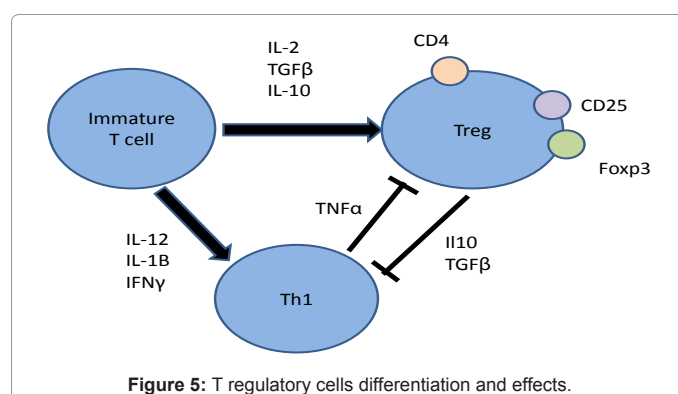
in the Foxp3 gene is present only in placental mammals. This site is rich in SMAD and RXR binding sites, and appears to be necessary for the differentiation of peripheral but not thymus derived Tregs. CNS1 deficient mice show decreased fetal survival associated with lymphocytic infiltration of the placenta [73]. Decreased ratios of Treg to Th-17 phenotypes have also been associated with recurrent fetal loss in human pregnancy [74]. Levels of Tregs during pregnancy have been shown to inversely correlate with RA disease activity, so that the more Tregs, the less active the arthritis [75]. One recent study in the CIA mouse model demonstrated that CD 25$^+$ T cells transferred from pregnant mice which had been previously primed with collagen injections could prevent the development of arthritis in the recipient, but not if the mouse had been primed [68]. This suggests the protection is antigen specific. Being able to replicate this pregnancy induced tolerance could have huge benefits for RA patients, although with some concerns about long term effects on infection and tumor surveillance [76,77].

Further animal data in the CIA model also support Tregs as a potential RA therapy. Depletion of Tregs from the mice before immunization with collagen or afterwards but before the disease has led to both higher arthritis incidence and more severe disease [78,79]. Transfer of Tregs from naïve mice was also able to reduce disease activity [80].

Patients with rheumatoid arthritis, however, do not have a shortage of Tregs in their blood or synovial fluid [78]. Rather, their Tregs appear to be dysfunctional, with a loss of ability to suppress inflammatory cytokines such as TNF-α and interferon γ [81,82]. TNF-α, which is present in abundance in the rheumatoid joint, seems to be the major mediator of this down regulation [82-85]. This may occur through TNF-α inducing the release of PKCθ which blocks CTLA-4 binding [82].

There is a growing amount of evidence that many existing RA therapies work at least in part through increased Treg function. A recent placebo controlled trial showed that patients on an anti TNF-α antibody plus methotrexate had higher Tregs and lower T effector cells after 12 weeks than patients on methotrexate alone [86]. Another study of patients on anti TNF-α therapy showed that their Tregs were able to suppress Th-17 phenotypic expression, but not the Tregs from normal controls or active RA patients not on an anti TNF-α. This affect was exerted through monocyte derived IL-6. Interestingly, they observed this Treg suppression only in patients on the anti TNF-α monoclonal antibody adalimumab, and not with the TNF receptor fusion protein, etanercept [87]. Increased Tregs and decreased Th17 cells have also been reported in RA patients treated with the anti IL-6 antibody tocilizumab [88]. In the mouse model proteoglycan induced arthritis, the efficacy of the B cell depleting antibody rituximab was wiped out by eliminating Tregs prior to treatment, suggesting that increase in Treg function may be a very important part of its mechanism of action [89].

However, increased levels of Tregs can play pathological role in human disease. It is well described in chronic viral infections such as HIV and Hepatitis B that Tregs can lead to worsened outcomes [90,91]. It is also known that Tregs are the "enemy" in certain types of cancer, with a direct role in allowing tumor cells to escape immune surveillance, leading to growth and metastasis [92,93]. In virally mediated cervical cancer, tumor cells can directly express Foxp3 themselves, pretending to be Tregs to avoid detection [94]. Tregs seem ideal goals for achieving a successful restoration of immune tolerance in patients with RA, but achieving balance will be the key to success.

Conclusion

This paper has reviewed a number of promising pathways to achieve a restoration of tolerance to the immune system of patients with rheumatoid arthritis, as well as potential stumbling blocks. They all share the goal of a return to self-regulation, and therefore fit our hope to be able to return our runway RA train to its normal route and function, without needing to keep the brakes on. Thus they could lead to that elusive cure, without needing to continue immunosuppressive therapy. However, we have seen in many instances, improvement in the inflammatory environment may be a necessary first step, suggesting that we need to apply the brakes first. Secondly, we need to insure that we do not turn the train around and head in the wrong direction, leading to increased infection and malignancy. So to achieve all these goals, it seems likely that we will need a combination of approaches to be successful, a balanced treatment to achieve a balanced immune system.

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