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Immunotherapies and Rheumatoid Arthritis-Introduction

Charles J. Malemud

Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, School of Medicine, Cleveland, Ohio, USA

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Rheumatoid arthritis (RA) is a systemic autoimmune disturbance of unknown etiology. RA is characterized at the cellular level by alterations in the innate and adaptive immune system which produces a chronic synovial joint inflammatory response that may affect other peripheral organs [1]. Studies of the natural history of RA have provided evidence that RA is a progressive immune cell-mediated disease which is initiated and promoted by aberrant activation of T-cells with associated B-cell hyperactivity. The deregulation of immune cell activity gives rise to chronic synovial joint inflammation that is characterized mainly by T-cell mediated activation of synovial fibroblasts [2]. This drives the progressive destruction of articular cartilage and subchondral bone resulting in joint failure [3].

The cells in the RA synovium undergo a continuous activation surge from the effects of elevated levels of vasoactive amines, arachidonic acid metabolites, neuropeptides and a host of pro-inflammatory cytokines which are increased in the peripheral circulation. The cytokines implicated in this response, include, mainly, interleukin-1 (IL-1), IL-6, the IL-6-type cytokines, namely, leukemia inhibitory factor, oncostatin M and adiponectin, IL-7, IL-12/IL-23, IL-15, IL-17, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [4]. Anabolic growth factors, such as growth hormone, fibroblast growth factor-2, vascular endothelial growth factor, transforming growth factor-β, insulin-like growth factor-I and platelet-derived growth factor also appear to play a critical role in the pathophysiology of RA [4-8].

In normal individuals, the levels of pro-inflammatory cytokines and anti-inflammatory cytokines in the peripheral circulation are in relative balance. However, in the active RA patient, serum pro-inflammatory cytokines levels greatly exceed those of anti-inflammatory cytokines. This so-called "cytokine switch" has been largely attributed to a skewing in the balance between T_h1 and T_h2 cells towards T_h1 and therefore in the cytokine genes expressed by these T-cell subsets [9]. In addition to the greatly elevated level of pro-inflammatory cytokines and anabolic growth factors in RA, recruitment, adhesion and retention of macrophages as well as other inflammatory-type lymphocytes into the synovial joint space is also markedly increased [9].

Part of the central dogma that has contributed to our understanding of the pathogenesis of RA include the dominating influences of genetic factors [10] and the breakdown or loss of peripheral immune self-tolerance [11]. Thus, the combined effects of certain gene polymorphisms in susceptible individuals contribute to RA pathogenesis. These genes include specific HLA alleles such as DRB1 and other gene polymorphisms in the TNF receptor gene, TNFRII 196R, corticotrophin-releasing hormone, Toll-like receptor-4, IL-4, solute carrier family 22 (SCL22A4) and Runx1 genes, to name a few. These genetic factors in conjunction with other documented defects in T-cell-related physiology which include a reduction in T-cell receptor-induced calcium, nuclear factor of activated T-cells (NFAT) and nuclear factor-κB (NF-κB) signaling contribute to the progression of RA joint destruction. Ultimately, changes in T_{reg} cell activity may be the most significant driver of dysfunctional conventional T-cell activity [12].

In normal individuals, T_{reg} cells function to ensure immune tolerance to self-antigens. However, in RA, although T_{reg} cells are apparently sufficient in number when compared to T_{reg} cells from normal subjects, for reasons that have not been fully elucidated the function(s) of T_{reg} cells are deregulated. This form of T-cell deregulation appears to permit the aggressive and unrestrained proliferation of T-cells which contributes to B-cell hyperactivity and to autoantibody production associated with B-cell hyperactivation.

Coupled to altered cellular and humoral immune responses in RA is an apparent reduction in the frequency of cells of the immune system and activated synoviocytes to become apoptotic. Thus, "apoptosis resistance" is the mechanism proposed to be the pertinent cellular event responsible for synovial tissue hyperplasia, pannus development as well as RANKL/RANK-dependent osteoclast-mediated bone destruction [13-15]. Of note, the reduced vitality of chondrocytes may result from the combined effects of many pro-inflammatory cytokines such as the aforementioned ones, but also including IL-16, -18, and IL-22 as well as certain epigenetic changes such as those involving L1 retroelements [16].

In particular, TNF-α was shown to induce apoptosis in chondrocytes derived from both normal and osteoarthritic human cartilage *in vitro* [17]. Thus, induction of chondrocyte apoptosis may also be a significant contributor to articular cartilage destruction in RA joints. It has also been proposed that, in RA, defective apoptosis ensues in synovial tissue by virtue of the reduced activity of specific pro-apoptotic proteins [18]. This event in conjunction with the deregulation of anti-apoptotic proteins, such as the activities exhibited by a family of inhibitors-of-apoptosis proteins, including, XIAP, can provide the appropriate environment for aberrant inflammatory cell survival [19].

Against the backdrop of this constellation of significantly dysfunctional, reduced immune tolerance and chronically-induced inflammation was the decision by a group of committed biopharmaceutical companies to develop anti-RA biological drugs. These novel biological agents were principally designed not only to neutralize the activity of pro-inflammatory cytokines but also to restore defective T-cell and B-cell activity to normal [20]. Now that these biological drugs are commonly employed in clinical practice to, in effect, neutralize the effects of IL-1, IL-6, TNF-α on cells of the immune system, activated synoviocytes, osteoclasts and chondrocytes, it has become apparent that RA patients can develop refractoriness to

*Corresponding author: Charles J. Malemud, Ph.D., Professor of Medicine & Anatomy, Department of Medicine, Division of Rheumatic Diseases, University Hospitals Case Medical Center, 2061 Cornell Road, Room 207, Cleveland, Ohio 44106-5076, USA, Tel: (216) 844-7846; Fax: (216) 844-2288; E-mail: cjm4@cwru.edu

their action. Although these biological drugs are often added to the armamentarium of classical disease-modifying anti-rheumatic drugs, including non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate and anti-malarials, there is a still a continual need for the development of additional immunotherapies for RA. Thus, new small molecule inhibitors (SMIs) of the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway [21] have also recently been entered into use in the clinic for RA patients who have become intolerant to methotrexate or who have become unresponsiveness to several rounds of therapy with biological drugs. The development of tofacitinib a novel JAK SMI appears to have stemmed from compelling evidence accumulated from pre-clinical studies which showed that cytokines such as IL-6, IL-7 and IFN-γ among others activated the JAK/STAT pathway [22]. Activation of JAK/STAT was demonstrated to play a critical role in regulating in the pathogenesis of RA and in immune cell-mediated inflammation. The clinical efficacy of tofacitinib demonstrated in RA clinical trials is also likely to provide the impetus for the development of additional protein kinase SMIs which may alter the signal transduction of immune cells, synoviocytes, chondrocytes and osteocytes and in this way provide clinical efficacy in the therapy of RA. The thrust of such a drug development program could also be formulated on growing evidence indicating that shifting the defect in one signal transduction pathway involved in the pathophysiology of RA to another signaling pathway [23] may have therapeutic efficacy. Indeed, Labranche et al. [24] recently showed that tofacitinib suppressed osteoclast-mediated bone destruction in rat adjuvant-induced arthritis by decreasing the synthesis of RANKL and IL-6 levels.

This Special Issue of the *Journal of Clinical & Cellular Immunology* is devoted to "Immunotherapies and Rheumatoid Arthritis." The compilation of review articles and a primary research paper critically analyze the most recent advances in our understanding of which fundamental alterations in immune-cell mediated inflammation in RA are germane to further drug development. For example, two reviews focus on technologies designed to manipulate T_{reg} cells and dendritic cells. These novel strategies would be employed to manipulate T_{reg} cells to become antigen-specific T_{reg} cells. This technique may then permit antigen-specific T_{reg} cells to be used therapeutically to dampen abnormal immune responses in RA [25]. In another review, vaccination strategies are discussed which in one case would be designed to shift the balance between T_h1 and T_h2 towards T_h2 as well as to promote development of tolerogenic dendritic cells and functional T_{reg} cells [26]. In another, the vaccination status of RA patients receiving immunotherapies is discussed with the emphasis on a consideration that the status of these individuals for maintaining protective antibodies could be uncertain. It is suggested that routine antibody titer levels be measured in these RA patients and other strategies for earlier re-vaccination in certain cases be considered as well [27]. In another strategy paper, anti-citrullinated protein antibodies would be exploited to be employed as potential therapeutic agents [28]. Using a different approach, McGeough and Bjourson [29] discuss how identifying specific RA biomarkers could enable clinicians to measure RA disease activity and thus provide an effective clinical evaluation tool for systematically analyzing the response of patients to new and older RA drugs. Finally, recent experimental and clinical studies using the anti-IL-6 receptor monoclonal antibody, tocilizumab for the treatment of RA [30] has led to a proposal to promote tocilizumab as a "first-line" therapy for RA.

Several confounding variables in the therapy of RA with biological drugs are also discussed. In that regard, the effect of smoking on reducing the efficacy of RA treatment [31] is dealt with and a special emphasis placed on the role of smoking in reducing the effectiveness and clinical response rates of RA patients to TNF blockade. In a clinical trial analysis, the development of hypogammaglobulinemia in RA patients treated with the B-cell-depleting monoclonal antibody,

rituximab, was compared in RA patients administered rituximab in either a 6 month-fixed strategy or by a non-fixed regimen [32]. In summary, after 4 cycles, the median IgM levels were significantly lower in both groups, but only patients in the fixed pretreatment arm receiving 4 cycles of rituximab therapy had lower median IgG levels, while IgA levels remained in the normal range. Finally, a brief survey of the development of novel targeted therapies for systemic lupus erythematosus (SLE) [33] is also included. The development of targeted therapeutics for SLE should be considered in the context of immunotherapies and RA because the development of novel drugs for treating patients with SLE could take advantage of those experimental paradigms which have resulted in the success of drug therapies that have led to clinical remission in RA patients.

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