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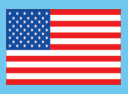

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*World Journal of Rheumatology*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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REVIEW

# Return to clinical in contrast to serologically-based diagnoses

Bruce M Rothschild

Bruce M Rothschild, Department of Medicine, Ohio Medical University, Rootstown, OH 44272, United States

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Correspondence to: Bruce M Rothschild, MD, FACR, Professor of Medicine, Department of Medicine, Ohio Medical University, 5500 Market Street, Rootstown, OH 44272, United States. spondylair@gmail.com
Telephone: +1-785-6151523
Fax: +1-724-4272707

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## Abstract

The future of rheumatology is predicated upon a return to basics. The advent and facile availability of laboratory testing led to reduction of emphasis on clinical skills. Recognition that immunologic abnormalities are not limited to individuals who clearly have related pathology provides new motivation for reorientation of training programs to assure that graduates have appropriate information gathering, diagnostic and procedural skills. Inadequate accessibility to rheumatologic care requires innovative approaches and especially training and educating those individuals who provide primary care. While the rheumatologist can elicit the patient's history remotely, telerheumatology will be feasible only when the individual interacting physically with the patient has confidence in their examination skills and when those skills have been validated. Named syndromes or diseases will be modified to avoid impugning the individual or compromising their future access to health, disability and life insurance. Interventions will be pursued in a more cost-effective, evidence-based manner. The future of rheumatology is dependent upon the rheumatologist's ability to amortize the inadequate reimbursement for direct patient interaction, depending on skills of interpretation of standard X-rays, ultrasound performance and results.

**Key words:** Laboratory test; Immunology; Procedure; Telerheumatology; Nomenclature; Radiology; Ultrasound



**Core tip:** Rheumatology started as a clinical practice, dependent on skills of eliciting pertinent history, performing complete physical examination and recognition and interpretation of radiologic findings. Laboratory testing has distracted from those origins and it is time to return to those basic skills.

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## INTRODUCTION

Rheumatology is undergoing a number of transitions, with the future representing a return to basics. Training programs will reemphasize development and validation of clinical skills. Serologic diagnostic approaches are being reevaluated with emphasis on clinical diagnosis.

### *Limitations of serology-based diagnosis*

Significance of serologic test results has been a source of controversy ever since. Sharp *et al*[1] recognized anti-RNP antibodies and identified them as the arbiter for diagnosis of mixed connective tissue disease (MCTD). The MCTD that he associated with anti-RNP antibodies presented as a well-defined syndrome, consisting of a mixture of symptoms attributable to various connective tissue/collagen vascular diseases. That combination did not represent co-occurrence of more than one connective tissue disease, and was insufficient in character and associated phenomena to define a single (up until then) recognized entity.

Sharp *et al*[1] had clearly identified a previously unrecognized syndrome. As the characteristics of the phenomenon he recognized were promulgated, rheumatologists started recognizing it in the absence of anti-RNP antibodies. Thus, some perceived presence of anti-RNP antibodies as unnecessary to the diagnosis of MCTD. More widespread testing revealed that those antibodies had less specificity than originally thought[2-4]. Clinical diagnosis of Sharp's disorder has become the more common approach.

Dr. Sharp's was but one of many attempts at standardization in rheumatology. It must be remembered that such efforts were intended to create more uniform/homeogeneous groups for scientific studies, not for clinical diagnosis[5,6]. His is not unlike DRGs, developed for a similar research purpose but subsequently "hijacked" for a national clinical coding system by non-clinicians. These attempts to establish uniform groups make the assumption that disease/symptom classifications have validity and are not simply conventions, philosophical categorizations made to help guide therapeutic approaches.

Practice of rheumatology started with establishing our own laboratories for performance of sophisticated tests, declining to accept as valid any test results performed at other facilities. At some point, such tests were delegated to various outside laboratories, with loss of oversight by the ordering physician. Whether this was a manifestation of inadequate familiarity with the techniques involved or unappreciated "interference" by insurance companies designating where tests could or could not be performed, interpretation of those tests became more complicated.

Original performance of antinuclear antibody assessment on rat or mouse liver or kidney slices had well-established normal ranges, known frequency of false positives and interpretable patterns[7]. When replaced by microscopic examination of tissue culture Hep-2 cells, similar validation of pattern implications was less stringent[8]. It can no longer be specifically attributed to the originally-associated disorders. Even presence of a positive ANA can be misleading, as it is present in 5% of the general population. Given the prevalence of lupus, 95% of individuals with a positive ANA don't actually have lupus. And 5%-30% of individuals with lupus do not have a positive ANA[9].

Similarly, serology-based practitioners have used presence or absence of rheumatoid factor as defining whether an individual is suffering from rheumatoid arthritis. The titer-based nature of the test reflects the need for sufficient sensitivity to indicate greater than normal amount of rheumatoid factor in the blood (noting that antibodies reacting with components of other antibodies are routinely present in normal individuals). This reduces specificity - for abnormal amounts in the blood, not actually for diagnosis of rheumatoid arthritis. Rheumatoid factor is elevated in other connective tissue disorders, other forms of inflammatory arthritis, malignancy, chronic infections (*e.g.,* endocarditis, rheumatic fever, tuberculosis, syphilis, viral disease, parasitic disease), rheumatic fever, pulmonary fibrosis, sarcoidosis and chronic renal disease). The tradeoff between sensitivity and specificity results in a titer cutoff that has a 5% false positive result. While that cutoff may be 1:40, it is not unusual to have 1:160 titers in normal healthy individuals. The former impression that presence of rheumatoid factor has specificity for diagnosis of a specific variety of inflammatory arthritis probably derives from lumping of all inflammatory arthritis as rheumatoid, as described below.

Perhaps the most eggarious of the serologic approaches is to diagnoses ankylosing spondylitis simply because the HLA-B27 histocompatibility antigen is present. HLA-B27 is present in 90% of individuals with ankylosing spondylitis and 50% of individuals with other forms of spondyloarthropathy, but is also common in healthy individuals. A recent Turkish study found HLA-B27 present in 18% of the general population, while the prevalence in Caucasians is 13% and in African Americans, 4%[10]. Given that ankylosing spondylitis is only present in 0.2% of the population, 98% of HLA-B27 positive individuals will not have the disease. Thus, the reversion from serologic to clinical diagnostic approaches will eliminate the patient's psychic trauma resulting from receiving such a misdiagnosis and facilitate the clinician who must subsequently disabuse that patient of the perceived life-style and morbidity implications of a disease they don't have.

### *Reinvestment in clinical skills*

In the transition from clinical diagnoses to those based on testing by outside laboratories, a standard rheumatology procedure became similarly outsourced, actual examination of joint fluid. Examination by the rheumatologist originally provided an approximation of white and red blood cell content, allowing verification of

outside laboratory actual counts[11]. Loss of cells in clots or other handling misadventures were recognized and the reliability of results provided by outside laboratories, independently assessed. This was a "side benefit" of rheumatologist-performed polarizing examination for crystals. It was also difficult to find a reference laboratory with acceptable reliability[12-15]. Concern with this issue apparently fell by the wayside, perhaps related to changes in training program priorities. Clinically oriented individuals recognize the importance of their performance of this evaluation, but serologically-oriented individuals have delegated this to outside laboratories. The future of rheumatology involves restoration of its practice by rheumatologists and re-establishing their expertise in its performance[13].

Perhaps one of the major factors stimulating renewed attention to clinical evaluation is the availability of so many effective biologic agents (*e.g.,* acting on tumor necrosis factor, interleukins 1 and 6, T cells)[16-18]. These target the inflammatory process, but have no direct effect on mechanical sources of pain and morbidity. It has become much more critical for the rheumatologist to be able to distinguish inflammatory components of a patient's complaints and limitations from those of mechanical origin[11,19]. Pain and limited ambulation (and sometimes swelling) resulting from ligamentous laxity producing knee instability may be misinterpreted as a component of the patient's inflammatory arthritis, if the responsible knee instability is not recognized. Similarly, distinguishing wrist pain related to tendonitis [often of mechanical origin (*e.g.,* DeQuervain's tenosynovitis)] is critical in its resolution, and in avoiding more aggressive anti-inflammatory and biologic therapies - for a problem that will not yield to such intervention[11,19], but will subject the patient to potential toxicity.

One of the most important lessons is for the clinician to have the patient point to the site of pain[11]. The complaint of hip pain is a classic example. This term is commonly used to identify pain in the buttock, back or lateral aspect of the pelvis, rarely for the groin - which is actually the anatomical location of the hip. While pain in the buttock or back may lead to investigation for fibromyalgia or sacroiliitis, it is pain in the lateral aspect of the pelvis which affords the rheumatologist the rare opportunity to safely provide immediate relief. That area is home to a series of bursae[20]. Previously referred to simply as trochanteric bursitis, it has now been realized that there are actually four bursae that are typically involved as a group - and that treatment of only one usually is ineffective. All four bursae (gluteus medius, gluteus minimus, subgluteus medius and subgluteus minimus) need to be injected with a water insoluble corticosteroid. Water soluble steroids simply diffuse to the whole body, while non-soluble ones remain localized to the affected area. They expose the patient to less systemic complications. The lidocaine in the injection provides immediate relief and verifies the accuracy of the diagnosis, while the corticosteroid provides lasting benefit. Of course, for this disorder and for others (*e.g.,* epicondylitis, DeQuervain's tenosynovitis), it is important to examine clinical history for activities of daily life and occupational derivations - issues which need resolution, if recurrence is to be avoided.

Clinical skills of physical examination are also being reemphasized, especially the importance of assuring the examination is complete and inclusive[11]. Uniformity is critical, to reduce interobserver variability[21,22]. This includes assuring ability to perform arthrocentesis of all joints. The "no touch" joint aspiration technique was recognized and promoted a third of a century ago. It is predicated upon understanding joint anatomy, a subject typically not addressed in medical school. Renewed access to the anatomy laboratory provides the opportunity to dissect and identify surface markers that allow facile joint access joint[11]. Much of this has been relegated to utilization of ultrasound for needle placement, allowing clinical skills to deteriorate, rather than utilizing ultrasound images to refine those clinical skills.

### *Role of procedures*

Rheumatology has been a field badly in need of a procedure. Reimbursement for time spent with patients has been woefully inadequate, while procedures are typically well compensated. Closed muscle biopsies, fat and synovial membrane biopsies have been pursued, but are not major revenue generators. Rheumatologists will have difficulty maintaining the level of our services if we cannot amortize the inadequately reimbursed clinical examinations.

An early consideration was developing endoscopy (gastroscopy) skills, as it was thought that rheumatologists should be able to evaluate the ulcers caused by the medications we prescribe. Assessing significance of gastrointestinal complaints is complicated as most symptomatic individuals actually do not have endoscopic evidence of damage, while many non-steroidal anti-inflammatory drug-related ulcers are not symptomatic. A mechanism existed in the 1980's to establish just such training. It was, however, abandoned because hospital credentialing at that time was usually limited to those who had completed a gastroenterology training program, with general surgeons grudgingly allowed to perform the procedure. Rheumatologists were not getting credentialed, despite appropriate training.

Infusions have been touted as revenue-generators, leading to a potential conflict of interest between patient and practice revenue. Performance and examination of X-rays would seem the most appropriate procedure for rheumatologists to add to the armamentarium. Thus, training in radiologic techniques will be emphasized as well as developing skills necessary for skeletal radiologic evaluations[11]. Because some rheumatologists practice in an environment where the organization/hospital has an agreement with a radiology group for sole performance of X-ray examinations, there has been a perception that stream of revenue is totally lost. However, training in skeletal radiology provides the opportunity to bill for

reexamination of X-ray images, whenever there are findings that general radiologists have not recognized. The generalist has a search image and pattern of review that is different than that of the skeletal radiologist (*e.g.,* rheumatologist trained in skeletal radiology), so each has significant contributions to patient care and it is appropriate for both to bill.

Attempting to find a fully billable procedure has led rheumatologists to consider diagnostic ultrasound. While an excellent and informative technique[23-25], it is quite time-expensive, although shortcuts with limited examinations have been pursued[26]. It has been used for needle localization for arthrocentesis for those without confidence in their clinical skills to localize the joint[27-29], but does have a value in recognizing calcium pyrophosphate deposition disease and gout, as well as distinguishing synovial effusions from synovial proliferation and recognizing erosions[27,28,30,31]. There has been significant controversy as to whether it is more sensitive than the clinical examination for recognition of effusions, most of which seems to relate to examination skills. It may be one of the best radiologic techniques for recognizing and identification of shoulder pathology[32], a 20 min examination which unfortunately is not sufficiently recompensed for that time allocation.

### *Diagnostic appellations*

We've also learned to examine what's in a name: An identification helpful to patients or a diagnosis that can be used to discriminate (*e.g.,* by insurers). Names often have unintended deleterious effects, stigmatizing people, industries or communities and can misdirect therapy[33,34]. This is exemplified by changes in utilization of the diagnostic appellation, rheumatoid arthritis. The criteria originally proposed by Ropes *et al*[5] were modified by a committee of what was then the American Rheumatism Association modification of criteria for rheumatoid arthritis in 1987[35].

Diagnosis of rheumatoid arthritis has been predicated on committee-derived criteria which subsequently expanded its purview and deleted past exceptions[36-39]. The resulting patient cohort may be more inclusive, but specificity is problematic. This has commonly resulted[40-42] in lumping as rheumatoid arthritis additional patients with predominantly non-axial disease[43-45]. Expansion of these criteria was accompanied by the requirement that there be no "alternative diagnosis that better explains the synovitis". The latter assumes adequate diagnostic skills to recognize other disorders. Spondyloarthropathy and calcium pyrophosphate deposition disease are the major disorders that share clinical presentations with that of rheumatoid arthritis[46-48], It is critical to recognize the symmetrical pattern, marginal localization of and axial joint sparing characteristics of rheumatoid arthritis[49-51], if these alternative diagnoses are to be recognized.

Examination of the archeologic record reveals two distinct patterns, thus challenging the specificity incurred when utilizing the 1987 criteria for diagnosis of rheumatoid arthritis. Predominant metacarpal phalangeal joint involvement, distribution of erosions to the bare areas of peripheral joints and periarticular osteopenia characterizes the arthritis present in seven populations, with joint ankyloses conspicuously absent[38,39,49,52].

Erosions in skeletons from other archeologic sites involved fewer joints and were typically localized to the areas originally covered by cartilage (subchondral)[53-57]. Joints were often fused[46,48,50,54,56,58-62]. Radiologic examination revealed periarticular osteopenia in less than half, in contrast to its universal presence in the first gro up[46,48,50,54,56,58-62]. Why are the patterns and distribution of joint involvement so different in these populations? "Osseotropism" and "rheumotrophism" have been suggested to help characterize the phenomena[57]. It seems useful to examine how individuals with this second pattern of arthritis compare with those more universally recognized as having spondyloarthropathy, those with axial joint disease[46,48,54,57,62,63]. Vertebral centra bridging in the form of syndesmophytes and sacroiliac joint and zygapophyseal erosions or fusion through their articular surfaces are definitive for the diagnosis of spondyloarthropathy[46,48,54,57,62,63]. It is the latter form of fusion through the articular surface of sacroiliac joints that provides insights to the subchondral propensity of erosion localization in peripheral joints. Fusion requires that the integrity of the subchondral cartilage be compromised, such that trabeculae can bridge what was originally a synovial lined space. This propensity is not found in individuals with rheumatoid arthritis.

The biomechanics of the two diseases are also quite different[53,64]. As might be expected, a disorder that disrupts articular surfaces should produce joints which glide less easily than one in which the joint surface is smooth. One method to quantify such variation is use of an accelerometer, which characterizes as vibration intensity/power the joints resistance to transitional movement[64,65]. High vibration/power was noted in individuals with subchondral erosions, independent of presence or absence of peripheral joint fusion or axial joint disease, in contrast to low vibration/power in individuals with marginal erosions lacking peripheral joint fusion or axial joint disease, the group classically recognized as having rheumatoid arthritis[64,65]. There was no overlap of vibration/power "signatures" between the groups.

Critical examination of the zoologic record also provides clarity. Previous diagnosis of rheumatoid arthritis in pigs and dogs[66-69] was apparently related to lack of familiarity with alternative (to rheumatoid arthritis) diagnoses, as the classic subchondral erosions and peripheral joint fusion of spondyoarthropathy were present[51,54,62,70,71]. Systematic assessment revealed frequent evidence of the above-noted patterns associated with spondyloarthropathy, but none of those associated with rheumatoid arthritis, among more than 30000 mammals examined in zoological collections around

the world[46,50,72]. The animals have a disorder clearly distinguishable from classic rheumatoid arthritis.

Peripheral joint fusion clearly represents a pathophysiology distinct from that of natural course of rheumatoid arthritis[38]. The term "natural" is used, as corticosteroid therapy has many complications, including altering disease course to allow joint fusion. The biomechanics and epidemiology (both archeologic and zoological) of erosive arthritis clearly separate rheumatoid arthritis and spondyloarthropathy. Those studies further note that isolated wrist and ankle affliction is indicative of spondyloarthropathy and not rheumatoid arthritis. The lumper-splitter controversy, wherein lumpers considered most inflammatory arthritis as part of the rheumatoid arthritis syndrome, is being superceded by the splitters[6,73,74].

### *Therapeutic intervention*

While methotrexate and tumor necrosis factor inhibitors might be considered the "boutique" treatments for inflammatory arthritis[75], because of less insurance company obstruction to their use and expansion of available biologic agents, therapeutic intervention also is returning to the basics and perhaps more cost-effective agents. Use of one of the older agents, hydroxychlorquine (plaquenil), is undergoing resurgence, with renewed recognition of its efficacy[76]. Sulfasalazine is another example. It originally was developed specifically for treatment of rheumatoid arthritis because of the perspective that it was infectious in origin[77,78]. At the time of its conception, antibiotics were predominantly sulfa-based. Combining that antibiotic with the anti-inflammatory effect of salicylate was therefore logical but proved to be ineffective - in the short term. It was subsequently recognized that sulfasalazine had delayed benefit, requiring months for its efficacy to manifest. Renewed consideration of sulfasazine therapy resulted from recognition of inflammatory arthritis of the spondyloarthropathy variety in gorillas[79]. How do you treat a 600 pound individual with an attitude? Eye contact is considered a threat gesture and they don't cooperate in the same manner as chimpanzees for the vascular access necessary to assure medication safety. Anesthetizing gorillas at frequent intervals is not an option, because of anesthesia-related mortality. A medication was required which did not require the close laboratory monitoring so necessary with methotrexate and the ophthalmologic evaluations required with hydroxychloroquine use[80,81]. Sulfasalazine seems the safest of the disease modifying (DMARD), has documented efficacy in gorillas, and is actually now standard veterinary treatment for the disease (except perhaps in dogs, where some develop dry eyes from the drug)[79]. Recognition of its efficacy across the vertebrate spectrum[79], led to reexamination of its use in humans and recognition that it offers a safe alternative (without the cancer risk) to methotrexate.

### *Telerheumatology*

Telemedicine or remote provision of services has been suggested as a new approach, especially in underserved areas[82]. Working with physicians and physician extenders, this has proven a useful approach in Alaska[83]. If needed for cardiology (for which extensive education and experience are provided in medical school and residencies), how much more so that might seem for rheumatology. However, that very difference in training and experience is fundamental to the difficulty of providing rheumatology services in such a manner[84]. It would require establishment and validation of physical examination (not limited to the joints) and history taking skills, assurance that those skills are maintained

Those history taking skills require attention to nuances and vocabulary variation in different geographic and ethnic populations. There are major discrepancies between patient-completed questionnaires and their verbal response to essentially the same questions (*e.g.,* attention to hesitancy in responses, suggesting they are thinking about the question. If so, it is useful to have patient verbalize what they are considering and often dismissing - precluding access to important diagnostic information. "Absenting substantial revision of medical school and post-graduate education and training, telerheumatology does not seem feasible"[84], not ready for prime time.

## CONCLUSION

The future of rheumatology is predicated upon patient advocacy as always, but now more proactive with those who make the laws/regulations that insurance companies are obligated to follow[81]. This derives from insurance companies with oxymoronic names stonewalling evidence-based appeals and even FDA-approved usages in favor of medicines unapproved for a given indication. The future direction is illustrated by the change in the American College of Physicians' journal name from Arthritis and Rheumatism to Arthritis and Rheumatology. Rheumatism was an old term for aches and pains. Rheumatology deals with much more than arthritis and now recognizes derivation of those aches and pains. It has changed from simply recording symptoms to identifying their causes. That is the future of rheumatology, pursuing a more scientific, evidence-based approach, examining and testing preconceived notions to provide appropriate care with an approach that maximizes efficacy and safety.

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MINIREVIEWS

# Role of leptin in the progression of psoriatic, rheumatoid and osteoarthritis

Jessica Mounessa, Iryna Voloshyna, Amy D Glass, Allison B Reiss

Jessica Mounessa, Iryna Voloshyna, Amy D Glass, Allison B Reiss, Winthrop Research Institute and Department of Medicine, Winthrop-University Hospital, SUNY Stony Brook School of Medicine, Mineola, NY 11501, United States

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Correspondence to: Allison B Reiss, MD, Winthrop Research Institute and Department of Medicine, Winthrop-University Hospital, SUNY Stony Brook School of Medicine, 101 Mineola Boulevard, Suite 4-004, Mineola, NY 11501, United States. areiss@winthrop.org
Telephone: +1-516-6633455
Fax: +1-516-6634710

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## Abstract

Leptin, an adipokine responsible for body weight regulation, may be involved in pathological processes related to inflammation in joint disorders including rheumatoid arthritis (RA), osteoarthritis, and psoriatic arthritis (PsA). These arthropathies have been associated with a wide range of systemic and inflammatory conditions including cardiovascular disease, obesity, and metabolic syndrome. As a potent mediator of immune responses, leptin has been found in some studies to play a role in these disorders. Furthermore, current potent biologic treatments effectively used in PsA including ustekinumab (an interleukin 12/23 blocker) and adalimumab (a tumor necrosis factor-alpha blocker also used in RA) have been found to increase leptin receptor expression in human macrophages. This literature review aims to further investigate the role leptin may play in the disease activity of these arthropathies.

**Key words:** Psoriatic arthritis; Rheumatoid arthritis; Leptin; Ustekinumab; Tumor necrosis factor-alpha



**Core tip:** Leptin is an adipokine well known for its role in metabolism and body weight regulation. More recently, it has gained recognition as a potential contributor to the pathogenesis of inflammatory disorders. Numerous studies reveal elevated leptin levels in rheumatoid arthritis patients. Similarly, a link between severity of osteoarthritis and leptin levels has been suggested. At the same time, little research on the role of leptin in the pathogenesis of psoriatic arthritis has been conducted. Further investigation on these relationships could provide for better-targeted treatment of these rheumatic diseases and their systemic manifestations.

Mounessa J, Voloshyna I, Glass AD, Reiss AB. Role of leptin in the progression of psoriatic, rheumatoid and osteoarthritis. *World J Rheumatol* 2016; 6(1): 9-15 Available from: URL: http://www.wjgnet.com/2220-3214/full/v6/i1/9.htm DOI: http://dx.doi.org/10.5499/wjr.v6.i1.9

## INTRODUCTION

Approximately one in five adults in the United States reports having the medical diagnosis of arthritis[1]. Arthritis and other rheumatic conditions (AORC) were found to cost equivalent to 1.2% of the 2003 United States gross domestic product, and this number is estimated to increase in the coming years[2]. While dozens of different types exist, three of the most common are rheumatoid arthritis (RA), osteoarthritis (OA), and psoriatic arthritis (PsA).

While the pathogenesis of each type of arthritis is unique, as a whole, AORC are associated with a number of comorbidities and chronic conditions including hypertension, physical inactivity, hyperlipidemia, obesity, and smoking[3]. Other inflammatory diseases including atherosclerosis and cardiovascular disease also occur at a higher rate[1]. In recent years, numerous studies have investigated such relationships.

More specifically, leptin is an adipokine derived from adipose tissue that has recently been suggested to contribute to the pathogenesis of RA, OA, PsA and their systemic manifestations[4-6]. It is a 167-amino acid peptide with a four-helix bundle motif similar to that of a cytokine. Leptin receptors belong to the class Ⅰ cytokine receptor family.

Although six isoforms of receptor have been identified, only two are known to be involved in intracellular signaling. Binding of leptin to its longest receptor isoform activates numerous intracellular signals following JAK2 activation, which have been associated with a wide variety of biological actions in different tissues[7]. The leptin receptor has been postulated to play a role in signal transducer and activator of transcription 3-dependent T cell differentiation, by influencing the downstream pro-inflammatory milieu of IL-23, which includes interferon-gamma, tumor necrosis factor (TNF)-alpha, and IL-17[8].

Numerous studies have also aimed to identify leptin's potential role in the progression of these arthropathies (Figure 1). Most of these studies, however, focus on RA and OA, but not PsA. To date, these findings also seem conflict, and no clear conclusions have been reported. In this article, we aim to explore whether or not a link exists between leptin and RA, OA, or PsA disease activity.

## LITERATURE STUDY

A review of literature was performed on Cochrane and PubMed databases using the keywords "leptin" and "arthritis." Study inclusion criteria were: (1) studies conducted between 01/01/1990 through 10/01/2015; (2) studies on human subjects with either RA, OA, or PsA; (3) studies available in English; (4) randomized controlled trials or clinical trials with total $n \geqslant 20$ and $P < 0.05$; (5) studies reporting on leptin and disease activity; and (6) studies with original data. Studies that did not meet these criteria, including case reports, duplicate studies, studies with $n < 20$, and studies without significant or original data were excluded. Studies that meet criteria, but are not in English are described separately as they are evaluated based on the abstract in English.

## RESULTS AND DISCUSSION

A total of 34 publications met the criteria listed above. Of these, 24 studies pertained to RA, 9 to OA, and one to PsA. The studies were further categorized into whether the studies identified: (1) no relationship between leptin and disease activity; (2) a positive correlation between leptin and disease activity; and (3) a negative correlation between leptin and disease activity (Table 1).

### *Leptin in RA*

The largest number of studies pertained to the role of leptin in the disease activity of RA ($n$ = 24). About 50% of the studies suggested no association ($n$ = 12), while 29% of the 24 studies suggested a positive correlation between leptin and RA disease activity ($n$ = 7), and 21% of the studies suggested a negative correlation ($n$ = 5).

Numerous publications report no significant change in serum leptin levels in RA patients treated with common anti-rheumatic drugs including adalimumab and infliximab. A study on 32 Caucasian RA patients revealed that after 12 wk of anti-TNF treatment with adalimumab, typical measures of inflammation (swollen joints, tender joints, global assessment of pain, IL-6 serum levels) markedly decreased, while serum leptin levels did not[9]. This was also found to be true in another study after 16 wk of adalimumab treatment[10]. A 2012 report investigating the effect of one year of treatment with the chimeric anti-TNF-alpha monoclonal antibody infliximab on plasma leptin concentration further revealed that while treatment with infliximab resulted in enhancement in leptin concentration, there was no significant correlation between disease activity and plasma leptin concentration[11].

Several studies have also reported no significant correlation between radiographic progression of RA and serum leptin levels[12-14]. In one study on 253 patients with RA from the Early Arthritis cohort, no association was found between serum leptin, visfatin, resistin, adipsin, IL-6, or TNF-alpha levels and RA disease progression after correcting for age, sex, treatment strategy, body mass index (BMI), and the presence of anti-cyclic citrullinated peptide antibodies[13]. Interestingly, they all suggest that a link between serum adiponectin levels and radiographic progression of disease exists. Patients with high levels of adiponectin at baseline were also found to have significantly higher odds of radiographic progression when compared to those with high levels of leptin or resistin[15].

In an investigation of the association between circulating leptin and adiponectin levels and cardiovascular risk factors in patients with RA, it was suggested

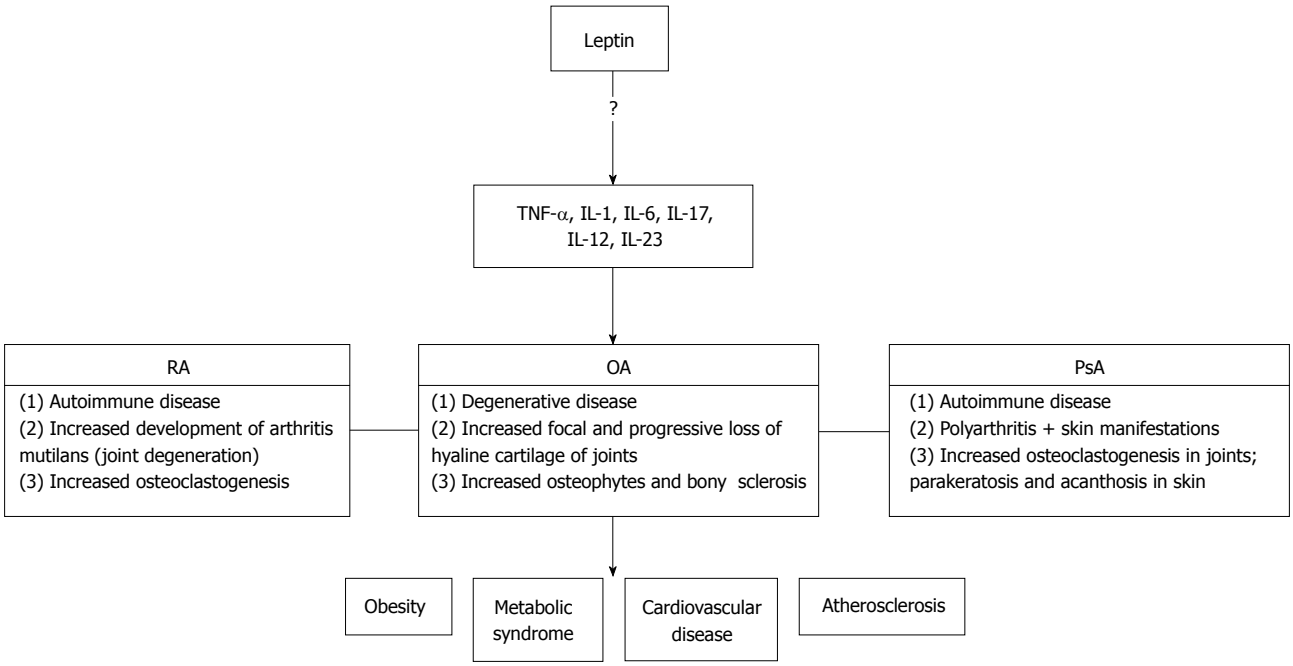


**Figure 1 Schematic representation of possible role of leptin in the pathogenesis of psoriatic, rheumatoid and osteo-arthritis.** Leptin levels regulate release of pro-inflammatory cytokines: IL-1, IL-6, IFN-γ, TNF-α, and IL-23/IL-17, very well-known pro-inflammatory mediators affecting joint cartilage, chondrocyte loss and apoptosis. RA: Rheumatoid arthritis; OA: Osteoarthritis; PsA: Psoriatic arthritis; TNF-α: Tumor necrosis factor-α; IL: Interleukin; IFN: Interferon.

that leptin and adiponectin are markers of fat mass rather than independent metabolic risk factors for cardiovascular disease[16].

On the other hand, a larger number of studies point to the harmful role leptin may play in the pathogenesis of RA or its systemic manifestations. A 2003 report examining 76 RA subjects revealed that RA patients had significantly higher leptin production when compared to 34 healthy controls[17]. At the same time, they were found to have significantly lower synovial fluid leptin levels, perhaps suggesting *in situ* consumption of this molecule in the progression of RA[17].

Interestingly, Härle *et al*[18] showed that patients with RA exhibited a negative correlation between serum leptin and androstenedione levels, suggesting a link between chronic inflammation and a hypoandrogenic state.

In 2006, a comparative analysis of 31 RA patients and 18 controls revealed that patients with RA had considerably higher plasma levels of leptin, adiponectin, and visfatin, when compared to healthy controls[19]. Another study added that leptin levels were linked to higher fat mass in RA patients[20]. A 2011 study revealed that higher serum leptin levels found in RA were positively associated not only with BMI, but also with C-reactive protein (CRP) levels (an inflammatory biomarker for RA)[21]. Most recently, Xibillé-Friedmann *et al*[22] found that higher leptin levels at baseline predicted higher disease activity severity at six months.These studies identify a possible role leptin may play in the body composition and disease severity in RA patients.

More specifically, a South Korean study of 242 RA subjects found that persistent LDL cholesterolemia in synergy with serum leptin contributed to radiographic progression of RA in patients over the course of two years[23]. RA patients with hypertension were also found to have increased levels of leptin and homocysteine, after adjustment for age, sex, race, smoking, BMI, and corticosteroid and nonsteroidal anti-inflammatory drugs use[24].

Furthermore, the multi-biomarker disease activity (MBDA) score is a recently developed tool used to assess disease activity and response to treatment in RA patients in numerous studies. The MBDA score is calculated using the concentrations of twelve biomarkers, one of which is leptin. The relationship between MBDA score was found to significantly correlate with disease activity, radiographic disease progression, and remission rate in 37 patients with RA, including 31 women and 6 men[25].

At the same time, other studies identify a potentially protective role of leptin in the progression of RA and its associated systemic diseases. In 2005, an evaluation of 31 patients with active RA in The Netherlands demonstrated that baseline plasma leptin levels inversely correlated with the degree of inflammation as determined by CRP and IL-6 levels[26]. Anti-TNF treatment with adalimumab did not change plasma leptin concentration in this study or in a later study[27].

In 2010, Rho's group obtained coronary calcium scores on 169 patients with RA and found that in leptin concentrations were significantly associated with a decreased risk of coronary calcification related to insulin resistance[28]. That same year, a sub-study of

**Table 1 Summary of findings**

| RA | | | | OA | | | | PsA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ref. | Negative correlation ($n^1$) | Positive correlation ($n^1$) | No correlation ($n^1$) | Ref. | Negative correlation ($n^1$) | Positive correlation ($n^1$) | No correlation ($n^1$) | Ref. | Negative correlation ($n^1$) | Positive correlation ($n^1$) | No correlation ($n^1$) |
| [25] | 37 | - | - | [42] | 117 | - | - | [43] | - | 41 | - |
| [26] | 31 | - | - | [34] | - | 193 | - | - | - | - | - |
| [29] | 40 | - | | [38] | - | 543 | - | - | - | - | - |
| [30] | 167 | - | - | [29] | | 18 | - | - | - | - | - |
| [31] | 515 | - | - | [40] | - | 20 | - | - | - | - | - |
| [17] | - | 76 | | [41] | - | 219 | - | - | - | - | - |
| [18] | - | 30 | - | [35] | - | - | 172 | - | - | - | - |
| [19] | - | 31 | - | [36] | - | - | 2477 | - | - | - | - |
| [21] | - | 141 | | [37] | - | - | 44 | - | - | - | - |
| [22] | - | 127 | - | - | - | - | - | - | - | - | - |
| [23] | - | 242 | - | - | - | - | - | - | - | - | - |
| [28] | - | 169 | - | - | - | - | - | - | - | - | - |
| [9] | - | - | 32 | - | - | - | - | - | - | - | - |
| [10] | - | - | 33 | - | - | - | - | - | - | - | - |
| [11] | - | - | 16 | - | - | - | - | - | - | - | - |
| [12] | - | - | 197 | - | - | - | - | - | - | - | - |
| [13] | - | - | 253 | - | - | - | - | - | - | - | - |
| [14] | - | - | 152 | - | - | - | - | - | - | - | - |
| [15] | - | - | 119 | - | - | - | - | - | - | - | - |
| [16] | - | - | 791 | - | - | - | - | - | - | - | - |
| [20] | - | - | 38 | - | - | - | - | - | - | - | - |
| [27] | - | - | 58 | - | - | - | - | - | - | - | - |
| [32] | - | - | 52 | - | - | - | - | - | - | - | - |
| [33] | - | - | 12 | - | - | - | - | | - | - | - |
| Total | 5 | 7 | 12 | 9 | 1 | 5 | 3 | 1 | - | 1 | - |

[1]Number of subjects in treatment group. Relationship between leptin and disease activity of RA, OA, and PsA. RA: Rheumatoid arthritis; OA: Osteoarthritis; PsA: Psoriatic arthritis.

the Swefot (Swedish Pharmacotherapy) study reported that markers of bone resorption were significantly decreased in patients randomized to both anti-TNF and sulphasalazine/hydroxychloroquine treatment groups at one year, and leptin concentrations significantly increased at two years. Anti-TNF agents were interestingly found to cause a significant increase in fat mass at two years, when compared to the other treatment group (3.8 kg *vs* 0.4 kg) despite reduction in disease activity[29].

In terms of radiographic findings, a 2009 publication by Rho *et al*[30] evaluated 167 RA patients and 91 control subjects and suggested that leptin concentrations were negatively correlated with radiographic joint damage. It is important to note, however, that the significance of this finding disappeared after adjustment for BMI. More recently, a 2013 study found that RA patients with poor radiographic outcomes had significantly higher baseline CRP levels and significantly lower baseline leptin levels[31].

In addition to those published in English, two human RA studies not in English are noted. A prospective, cross sectional study of 52 RA patients from Poland showed lower serum leptin in RA patients than in controls and no relationship between serum leptin and BMI or CRP and no influence of gender or treatment[32]. A study of 49 RA patients from Japan found leptin level correlated to BMI in both RA and healthy subjects, no difference in leptin level between RA and healthy subjects and no correlation of leptin to CRP or RA stage[33].

### *Leptin in OA*

A total of 9 studies on patients with OA met the criteria for inclusion in this paper. Of these, one-third suggested no role for leptin in disease activity. Fifty-six percent of studies identified a positive correlation between leptin levels and disease activity, while only 11% supported a negative correlation.

In a cross-sectional study of patients with hip OA, it was found that serum leptin levels did not correlate with the severity of osteophytes[34]. Another study further suggested that no correlation exists between synovial fluid inflammation and serum leptin levels in 172 patients with severe knee OA[35]. Finally, when a sample of 2477 subjects with OA in the Third National Health and Nutrition Examination Survey (NHANES III) were investigated, it was found that once again, no significant association between serum leptin and OA status existed[36].

Numerous studies have also reported a potentially harmful role for leptin in the pathogenesis of OA and its systemic manifestations. In 2012, Massengale's group investigated the relationship between adipokine concentrations and hand X-rays in patients with arthritis, and revealed that leptin, BMI, and a history of coronary artery disease were linked with higher rates of chronic hand pain[37].

In 2013, participants in the Michigan Study of Women's Health Across the Nation underwent bilateral knee radiographs that were associated with leptin levels

at baseline and followed up over the course of ten years. Women with OA were found to have significantly higher serum leptin levels compared to those who did not have knee OA at baseline and at the ten-year follow up[38]. In another study, synovial fluid collected from 18 patients with end-stage knee OA and 16 control donors was analyzed for 47 cytokines, chemokines, and growth factors and revealed that leptin, IL-12, macrophage-inflammatory protein (MIP-1B), and soluble CD40 levels were higher in patients with OA[39]. A cross sectional study of patients with end stage OA of the hip ($n$ = 123) and knee ($n$ = 96) confirmed an association between joint pain and synovial fluid leptin concentration[40].

Furthermore, when total RNA from knee lateral tibial and medial tibial plateaus was isolated in a 2013 study, immunohistochemical staining showed that protein expression of leptin was strong in osteoarthritic lateral tibial regions where significant degeneration was found[41].

On the other hand, a study examining the relationship between adipokines and biomarkers of bone and cartilage metabolism revealed that baseline leptin was significantly associated with increased levels of bone formation biomarkers including osteocalcin and PINP (amino peptide from type Ⅰ procollagen) over two years. However, it is important to note that soluble leptin receptor (sOB-Rb) was linked to a significant reduction in the cartilage biosynthesis marker PIIANP (amino peptide from type IIA procollagen), increased cartilage defects score, and increase loss of volume over the course of two years[42].

### *Leptin in PsA: Open to exploration*

There has been limited research regarding the role of leptin in the pathogenesis of PsA. In 2012, one study revealed that patients with PsA had higher osteoclast numbers, which were positively associated with increased serum levels of TNF-alpha, RANKL, and leptin. These 41 patients were found to have increased erosion, joint-space narrowing, osteolysis, and new bone formation. The opposite relationship was seen with adiponectin, as levels were decreased in PsA patients[43].

Several recent studies have investigated the roles of commonly used anti-psoriatic drugs on leptin level. In one study, patients who received six months of treatment with the biologic anti-TNF agent adalimumab were not found to have any significant changes in their serum leptin levels when compared to baseline. In a different study, patients treated with TNF-alpha inhibitors for the same amount of time were actually shown to have lower leptin levels after treatment. These findings are in contrast to a study done by our group, which compares the impact of adalimumab and ustekinumab (an IL-12/23 inhibitor) on leptin and leptin receptor expression in THP-1 human macrophages[44]. In our hands, both drugs up-regulated expression of leptin in THP-1 macrophages. Ustekinumab was also found to enhance the expression of leptin-receptor in a dose dependent manner. Our work is macrophage-specific and does not reflect other cell types that may contribute to serum leptin levels.

Obesity is common in patients with psoriasis or PsA and so are obesity-related complications[45]. Anti-TNF therapy may aggravate this problem by causing further weight gain[46]. Excess leptin produced by macrophages in PsA patients given biologic medications may contribute to obesity-related inflammation. This controversy is ongoing and needs resolution so that PsA can be treated optimally.

Further studies identifying the mechanism of action of leptin as well as the pathway through which ustekinumab and anti-TNF agents alter expression of leptin and its receptor could lead to new preventive measures to avoid systemic disease manifestations and ultimately decrease morbidity and mortality.

## CONCLUSION

Leptin, an adipokine derived from adipose tissue, has a well-established role of maintaining metabolic homeostasis and regulating body weight. Recently, its role in the progression of inflammatory and rheumatic diseases has been an area of active research. The present paper highlights that although numerous studies have investigated its role in RA and OA, results are conflicting. In total, nearly 80% of the studies suggest either no role or a potentially harmful role for leptin in the pathogenesis of RA, OA or PsA. The underlying reason for discrepancies among the studies is unclear, but may be related to small sample size, unknown metabolic factors such as diabetes or thyroid disorder, circadian rhythm effects, leptin receptor levels or differences in genetic background or leptin sensitivity of various populations or other factors not considered. Clearly, these suggestions are speculative and resolution requires large-scale prospective studies.

It is important to note the lack of research published on leptin's role in the pathogenesis of PsA. While RA, OA, and PsA share common symptomologies and features, they are pathologically distinct. RA is characterized by an auto-immune increase in osteoclast formation and joint derangement. OA is a degenerative joint disease with focal and progressive loss of hyaline cartilage of the joints, osteophytes, and bony sclerosis. In PsA, auto-immune skin and poly-arthritic joint disease are seen.

All three of these diseases are associated with inflammatory mediators and systemic manifestations including metabolic syndrome, diabetes, and atherosclerosis. At the same time, it is uncertain whether leptin functions in a similar or different manner in these pathologies. In other words, leptin's role in RA or OA cannot be directly transferrable to its role in PsA.

The major biologic treatments for PsA include the TNF-alpha inhibitors and the interleukin-12/23 inhibitor ustekinumab[47]. Future research on whether leptin participates in the pathogenesis of PsA could allow for better understanding of the impact of these treatments on leptin and the creation of more effective treatments

that could specifically address the adipokine.

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MINIREVIEWS

# Roles of plasmablasts in IgG4-related disease and various immune-based diseases

Syuichi Koarada, Yoshifumi Tada

Syuichi Koarada, Yoshifumi Tada, Department of Rheumatology, Faculty of Medicine, Saga University, Saga 849-8501, Japan

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Correspondence to: Syuichi Koarada, MD, PhD, Department of Rheumatology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan. koarada@cc.saga-u.ac.jp
Telephone: +81-952-342367
Fax: +81-952-342017

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## Abstract

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory disease with multiple organ disorders. Recently, in IgG4-RD, increased circulating plasmablasts have been found. The subsets of plasmablasts are negative for RP105 (CD180). A large population of B cells lacking RP105 (RP105-negative B cells) are found in patients with active with systemic lupus erythematosus and other systemic autoimmune diseases, including dermatomyositis, and Sjögren's syndrome. In other conditions, such as neuromyelitis optica, Kawasaki's disease, primary biliary cirrhosis and aging, RP105 expression on B cells and monocytes also alters. We review the basic science and clinical significance of RP105-negative B cells including plasmablasts in various immune-based diseases. RP105-negative B cells, especially plasmablasts, play crucial roles in both systemic and organ-specific autoimmune and inflammatory disorders.

**Key words:** Plasmablast; CD180; IgG4-related disease; Autoimmune disease



**Core tip:** RP105 (CD180) is associated with B cell function, survival and death. RP105-negative B cells, especially plasmablasts, take part in pathophysiology of various immune-based diseases.

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## INTRODUCTION

IgG4-related disease (IgG4-RD) is a novel systemic fibro-inflammatory disease with multiple organ disorders[1,2]. IgG4-RD affects the various organs, including pancreas, kidney, aorta, lung, lymph node, salivary gland, lacrimal gland, prostate, pericardium, and so on. The elevated serum IgG4 levels are associated with the pathophysiology of IgG4-RD. B cell depletion therapy using rituximab (RTX) is an effective and alternative

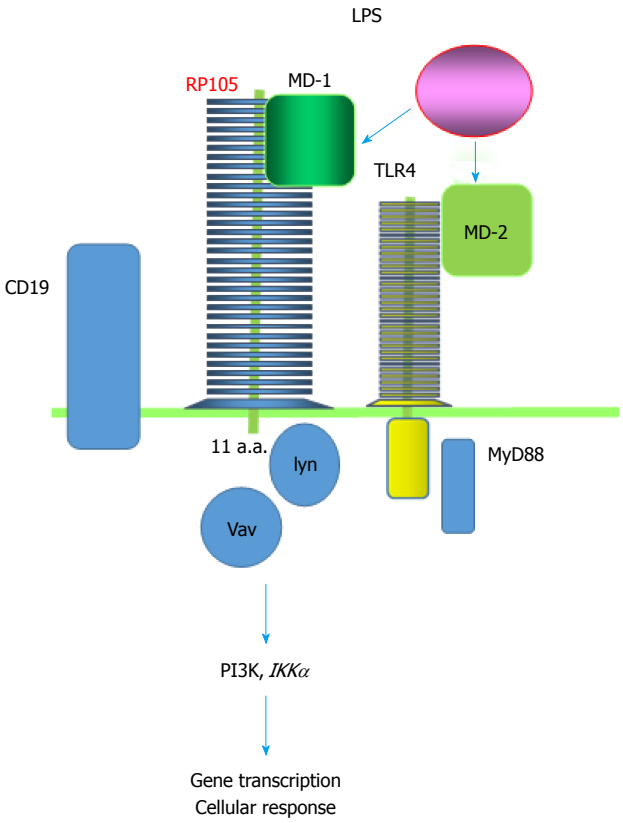


**Figure 1 P105 consists of extracellular leucine-rich repeats and a short cytoplasmic tail.** LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; IKKα: IκB kinase α; PI3K: Phosphoinositide 3-kinase.

therapy of refractory IgG4-RD[3]. These results suggest that B cells play important immunological roles in the disease. The diagnosis of IgG4-RD is performed by biopsy-proven characteristic histology and immunohistochemistry features. Although, to date, the etiology and B cell biology in IgG4-RD have not been fully elucidated, recent studies suggest that late B cells, especially plasmablasts, play a pivotal role[4,5]. In patients with IgG4-RD, increased circulating plasmablasts and IgG4+ plasmablasts were found[6].

Toll-like receptors (TLRs) are important components of innate immune system that trigger antimicrobial responses. TLRs recognize various pathogens such as lipopolysaccharides (LPS), lipopeptides and CpG-DNA. RP105 [radioprotective, 105 kDa (MW); CD180], TLR associated molecule, is principally expressed on mature B cells[7]. Interestingly, a large population of B cells lacking RP105 (RP105-negative B cells) are found in patients with active systemic lupus erythematosus (SLE)[8] and other systemic autoimmune diseases, including dermatomyositis (DM), Sjögren's syndrome (SS) and so on[9]. Moreover, in organ-specific autoimmune diseases, for example, in neuromyelitis optica (NMO), an inflammatory disease affecting the optic nerve and spinal cord, increased circulating RP105-negative B cells were reported[10]. Recently, in IgG4-RD, increased RP105-negative B cells, especially the subsets of plasmablasts, have been described[11-13]. Moreover, in various conditions, such as Kawasaki disease (KD), primary biliary cirrhosis (PBC) and aging, altered RP105 expression on B cells and monocytes was found. We review the basic science and clinical significance of plasmablasts and RP105-negative B cells in various immune-based diseases.

## STRUCTURE AND FUNCTION OF RP105 (CD180)/MD-1

### *Structure and expression of RP105*

RP105 is a pathogen receptor of the leucine-rich repeat (LRR) family with homology to TLR-4. It was first reported that RP105 is mainly expressed on murine naïve and memory B cells[7]. The human homologue of RP105 was identified in 1998[7,14]. Although RP105 was originally discovered as a surface marker of B cells both in mice and humans, the molecule is also expressed on monocytes, macrophages, and DCs.

Virtually, all human B cells express RP105 strongly but not on plasma cells[15]. RP105 consists of extracellular LRRs and a short cytoplasmic tail (Figure 1). The LRRs involve in protein-protein interaction[16]. Extracellular LRR motifs of RP105 are similar to the other TLRs. RP105 forms a heterodimer complex with MD-1[17-19]. In the same manner as MD-2 for TLR-4, MD-1 is essential for expression of RP105 on the cell surface. Because RP105 has a very short cytoplasmic tail, 11-amino-acids, RP105 lacks the conserved intracellular signaling domain, Toll-IL-1 receptor (TIR) domain. TIR domain is required for TLR-signal transduction *via* adapters such as MyD88. Therefore, RP105 may be associated with a coreceptor transducing a signal into the cell.

The molecules with LRRs take part in the recognition of exogenous pathogens and activation of the immune system[20,21]. Historically, TLRs were first identified in Drosophila[22]. The molecules having LRRs are also important in the defense against pathogens in humans. The structural similarity of the extracellular LRRs of RP105 to TLRs suggests that RP105 also senses pathogen invasion, such as LPS[18].

### *Signaling of RP105*

Although signaling molecules binding to cytoplasmic tail of RP105 are not fully identified yet, there are multiple signaling pathways of RP105. RP105 signals separate from MyD88 and use CD19 as a coreceptor to signal through lyn, Vav, phosphoinositide 3-kinase (PI3K), AKT and IκB kinase α[23,24]. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and PI3K inhibitors control TLR4/RP105/LPS signaling in the $CD19^+$ B cells and pan PI3K inhibitors reverse the lymphoproliferative phenotype *in vivo*[25].

### *Functions of RP105*

The differential function of RP105 on macrophages/monocytes and B cells has been reported. RP105 has a negative regulatory function for TLR-4/MD-2 signal in macrophages and monocytes[26,27]. Recently, the unique

role of RP105 in macrophages to TLR ligands has been reported. The function of TLR2 and TLR4 in activated macrophages could be associated with RP105[28,29]. In B cells, RP105 may have enhancing role of TLR-signals. Anti-RP105 monoclonal antibodies induce polyclonal B cell proliferation and immunoglobulin production of IgG1 and IgG3[30]. RP105 may regulate signals and functions of TLR-7 and TLR-9 to limit activation of autoreactive B cells[31]. In mice, RP105 plays a role in regulation of B cell growth and death. Although, in humans, the function of RP105 in B cells is still controversial and undefined, RP105 affects activation and regulatory function of B cells.

## ACTIVATING ACTION OF RP105

### *Anti-RP105 antibodies*

Cross-linking of anti-RP105 antibodies transmits an activation signal leading to B cell proliferation strongly, provides resistance against radio- and glucocorticoid-induced apoptosis, and expresses CD86, a co-stimulatory molecule, in mice[19]. RP105/MD-1 is functioning in concert with TLR4, controlling B cell recognition and signaling of LPS from Gram-negative bacteria[14].

### *Agonists of RP105; lipoprotein and LPS*

RP105 physically interacts with TLR2, and both RP105 and TLR2 are required for macrophage activation by *Mycobacterium tuberculosis* lipoproteins[32]. RP105 is also involved in activation of macrophages by gram-positive bacteria, *Staphylococcus aureus*[28] and by Pam3CSK4 through TLR2 signaling[29]. In activation of macrophages by LPS and Pam3CSK4, TLR2 signaling overcomes RP105-mediated regulation of TLR4 signaling[29].

In RP105- and MD-1-deficient mice, activating function of B cells, including antibody production, CD86 expression and proliferative response to LPS, was reduced. However, because RP105 or MD-1-deficient mice do not lack LPS responsiveness completely, there may be functional associations between TLR4/MD-2 and RP105/MD-1[17].

### *Inhibiting action of RP105*

On the other hand, because, unlike the TLRs, RP105 has a short cytoplasmic protein and lacks an important signaling domain, RP105 may function as a competitive negative regulator of TLR signals structurally. RP105 plays a physiological role of negative regulation of TLR-4 signaling in dendritic cells (DCs) and macrophages[25-27]. We have also investigated the inhibitory role of RP105 in the development of collagen-induced arthritis (CIA)[33]. Onset and severity of arthritis were accelerated in RP-105-deficient DBA/1 mice. In this model, RP105 regulates the antigen-presenting cell function and regulatory T cell (Treg) development. As a result, RP105 induces the attenuation of the cell-mediated immune responses and suppression of the development of CIA.

RP105-activated B cells after cross-linking of surface IgM show growth arrest and apoptosis[24,34]. This result suggests that RP105 can function as a negative regulator of B cell activation. RP105 regulates proliferation and survival of B cells in response to various stimulation.

### *Population of RP105-negative B cells in human and murine diseases*

Up to the present time, expression of RP105 on B cells and monocytes from patients with various diseases has been examined (Table 1). The numbers of RP105-negative B cells vary considerably according to the diseases. Especially, RP105-negative B cells are increased in SLE, SS, DM and IgG4-RD in which pathophysiologically B cells are significantly involved[1,11]. Also, in NMO, an organ-specific autoimmune disease, increased RP105-negative B cells were found[10]. Some NMO patients have elevated serum anti-nuclear and anti-SS-A/SS-B antibodies, and then NMO might share common pathological mechanism with systemic autoimmune diseases to some extent.

### *SLE*

Although normal mature B cells express RP105, RP105-negative B cells are dramatically increased in active SLE patients[8]. The disease activity of SLE, SLE Disease Activity Index (SLEDAI) scores, is correlated with the percentages of RP105-negative B cells. Also, serial analysis of the ratio of RP105-negative B cells from the same SLE patients was performed individually and RP105-negative B cells decreased as the disease turned inactive. The serum IgG levels were also correlated with the percentages of RP105-negative B cells. These results suggest that RP105-negative B cells in the peripheral blood are closely associated with activity and function of B cells of SLE. Being similar to RP105-negative B cells, $CD27^{high}CD38^{+}$ B cells producing high-affinity IgG are increased in the peripheral blood of SLE patients with correlation to disease activity[35,36]. RP105-negative B cells and CD27highCD38+ B cells should be phenotypically identical[9].

RP105-negative B cells disappeared in the peripheral blood from patients treated with corticosteroids and seem to be more sensitive to corticosteroids than RP105-positive B cells *in vivo*. The effect of dexamethasone on apoptosis of RP105-negative B cells was confirmed *in vitro*. Although RP105-negative B cells underwent spontaneous apoptosis more easily compared to RP105-positive B cells, dexamethasone induced apoptosis of RP105-negative B cells, but not RP105-positive B cells. This result illustrates the rapid clearance of RP105-negative B cells from peripheral blood by the treatment with corticosteroids in SLE patients.

### *ANA-negative SLE (seronegative SLE)*

Because, in patients with SLE, antinuclear antibody (ANA) in serum is a primary hallmark, ANA-negative SLE is very rare[37]. Although, in clinical practice, ANA-negative

**Table 1 Altered expression of RP105 (CD180) and the human and murine diseases**

| Human | Disease | Ref. |
|---|---|---|
| Increased RP105-negative B cells | | |
| | SLE | [8] |
| | ANA-negative SLE | [48] |
| | Sjögren's syndrome | [56,57] |
| | Dermatomyositis | [58] |
| | IgG4-related disease | [13] |
| | ANCA-associated vasculitis | [submitted] |
| | Neuromyelitis optica | [10] |
| | Aging | [64] |
| Increased RP105-negative B cells; low levels | | |
| | Rheumatoid arthritis | [56] |
| | Systemic sclerosis | [56] |
| | Behçet's disease | [56] |
| | Mixed connective tissue disease | [56] |
| | Polymyositis | [56] |
| Increased RP105 on B cells | | |
| | Kawasaki disease | [63] |
| Decreased RP105 on stimulated monocytes | | |
| | Primary biliary cirrhosis | [65] |
| | BWF1 | [52] |

SLE: Systemic lupus erythematosus; ANA: Anti-neutrophil cytoplasmic antibody.

SLE patients exist as a subpopulation of SLE, the diagnosis of seronegative SLE can be difficult in patients showing no immunological abnormalities[38-46]. The numbers of RP105-negative B cells were increased and correlated with disease activity even in ANA-negative SLE patients[47]. Without significant serological markers for SLE, examination of B cell population may be useful in evaluation of activity. Later, these patients turned out to be serologically positive, including ANA, anti-dsDNA and anti-Sm antibodies.

### *Human SLE*

RP105-negative B cells produce autoantibodies, including IgG and IgM class anti-dsDNA and single stranded DNA antibodies *in vitro*[48]. Especially, IgG class anti-dsDNA antibodies are specific and profoundly associated with pathogenesis of SLE. RP105-negative B cells have characteristic phenotype compared to RP105-positive conventional B cells[49,50]. Collectively, RP105-negative B cells are assigned as autoantibody-producing pathogenic B cells.

### *Murine models of SLE*

In addition, recently RP105-negative B cells have been found in a murine lupus model, the first filial generation of New Zealand Black (NZB) and White (NZW) mice (BWF1)[51]. Although the parental strains (NZB and NZW mice) do not show the phenotype of SLE, BWF1 mice develop autoimmunity with diffuse proliferative nephritis and production of anti-DNA antibodies. In BWF1 mice, splenic or peripheral RP105-negative B cells are increased with progression of renal lesions and aging.

### *RP105-negative B cells in NMO*

NMO is an inflammatory neurological disorder with recurrent attacks of severe optic neuritis and myelitis[52]. In NMO, anti-aquaporin-4 (AQP4) water channel protein antibodies are pathogenic autoantibodies and can be used as a disease marker[52,53]. Because anti-AQP4 antibodies alone do not cause the disease, cellular immunity works in concert with anti-AQP4 antibodies in pathophysiology in NMO[54]. Although RP105-negative (CD19intCD27highCD38highRP105-) B cells are increased in the peripheral blood of anti-AQP4 antibody-positive NMO patients compared to normal subjects or patients with conventional form of multiple sclerosis (CMS), the frequencies of naïve and memory B cells are not changed. The frequency of RP105-negative B cells is correlated with the serum levels of anti-AQP4 antibodies[10]. Serial analysis of paired samples from the same NMO patients during relapse and in remission shows that RP105-negative B cells increased during relapse.

### *RP105-negative B cells in various immune-mediated diseases*

Among various systemic rheumatic diseases, RP105-negative B cells are also increased in SS[55,56], DM[57], IgG4-RD[13] and ANCA-associated vasculitis [submitted]. In the patients with rheumatoid arthritis, systemic sclerosis, angiitis syndromes except for granulomatosis with polyangiits, Behçet's disease, mixed connective tissue disease, and polymyositis (PM), the numbers of RP105-negative B cells are increased compared to normal subjects. However, the levels are not very high[55].

### *DM/PM*

DM and PM are clinically similar diseases each other. Difference between two diseases is not only the presence of skin manifestations, but also etiological findings, the

involvement of humoral immune mechanism in DM and cellular immunity in PM. The proportion of RP105-negative B cells is increased in patients with DM compared to PM patients or normal subjects[57]. The increase of RP105-negative B cells reflects B cell activation in DM but not in PM. This finding is similar to the difference between NMO and CMS, as increased RP105-negative B cells are only found in NMO but not in CMS[10].

The different distribution of RP105-negative B cells between in the peripheral blood and the target organ is also interesting. Bronchoalveolar lavage fluid from a DM patient contained larger number of RP105-negative B cells than the peripheral blood. RP105-negative B cells may be preferentially located in the impaired organs, such as lung.

### SS

In SS patients, polyclonal hyperactivation of B cells exists[58]. Increased RP105-negative B cells are also found in SS patient. RP105-negative B cells from SS patients produced IgG and IgM spontaneously *in vitro*[56]. In some of salivary glands with lymphoid follicles in SS, germinal centers mainly consisted of RP105-negative B cells. B cells infiltrating the area other than lymphoid follicles were RP105-negative. RP105-negative B cells may be associated with the inflammation and tissue damage of the target organs in SS.

### IgG4-RD

IgG4-RD is a rare and novel systemic inflammatory disease characterized by tumefactive lesions with infiltrating IgG4-positive plasma cells[1,2]. IgG4-RD affects various organs. The elevated serum concentration of IgG4 has been believed as a hallmark of IgG4-RD. B cell depletion therapy using RTX is an effective and alternative approach in refractory IgG4-RD[3]. B cells play an important role in the pathophysiology of IgG4-RD.

RP105-negative B cells increase in IgG4-RD[11]. Because RP105-negative B cells consist of mainly plasmablasts and early plasma cells, precursors of plasma cells are increased in peripheral blood in IgG4-RD. Serial analysis showed that RP105-negative B cells decreased in parallel with disease activity.

Wallace *et al*[12] reported that plasmablast is a biomarker for IgG4-RD, independent of serum IgG4 concentrations. Patients with active, untreated IgG4-RD have elevations in their circulating plasmablast counts. Increased RP105-negatvie plasmablasts are associated with disease activity and the number of organ involvement[11,12]. Existence of RP105-negative B cells may reflect the dysregulation of differentiation and localization of late B cells in patients with IgG4-RD. Moreover, in patients with IgG4-RD, CXCR5 is expressed on the later B cell subsets.

### KD

KD is one of the vasculitis syndromes in childhood and an acute febrile illness with the formation of aneurysms in coronary arteries[59]. The percentages of RP105-positive B cells are higher in patients with KD than normal subjects. The levels of RP105 expression are also high in children with KD. RP105 expression at both protein and messenger RNA levels was enhanced in B cells stimulated with poly inosinic-cytidyric acid [poly(IC)], a synthetic double-stranded RNA *in vitro*. Similar mechanism may be involved in the up-regulation of RP105 expression on B cells in KD and viral infections.

### Aging

In the elderly people, RP105-negative B cells are increased compared to the young[60]. In normal young persons, RP105-negative B cells are seldom (1.7% ± 1.1%)[8].

### RP105 expression on monocytes in PBC

Altered monocyte response to ligands for TLRs was reported in patients with PBC[61]. Peripheral blood mononuclear cells and monocytes from PBC patients were stimulated with LPS. The level of TLR4 expression was increased with LPS stimulation on PBC monocytes compared to controls. Conversely, the expression of RP105 on PBC monocytes was decreased in comparison with controls.

## CONCLUSION

RP105 molecule is deeply associated with B cell function, survival and death. RP105-negative B cells produce autoantibodies and take part in pathophysiology in various diseases. RP105-negative B cells play a crucial role and are useful as a disease marker in both systemic and organ-specific immune-based diseases. As RP105 has complicated function, different mechanisms of the increase in RP105-negative B cells may function in each disease. To clarify these mechanism, further studies should be required.

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