HSS Rheumatology Research News

New Discoveries. Latest Studies.

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The kidney disease lupus nephritis is the most common severe manifestation of systemic lupus erythematosus (SLE). It confers an increased risk of end-stage renal disease and death.

One of the key cytokines that signals for an inflammatory response in the body – type I interferon (IFN-1) – is found at elevated levels in patients with lupus.

Now, a new HSS study has discovered that high IFN-I activity in the plasma of patients with lupus indicates higher likelihood of disease activity, particularly increasing the chances of the patient developing future lupus nephritis.

Furthermore, patients with higher plasma IFN-I activity at study initiation maintained elevated levels at future visits.

Higher IFN-I activity in the plasma of patients with lupus may serve as an important disease monitoring biomarker and help identify patients at risk for lupus nephritis.

Above: Kyriakos A. Kirou, MD, DSc, Assistant Attending Physician and Mary K. Crow, MD; Joseph P. Routh Chair, Physician-in-Chief
Netrins are a class of proteins called chemorepulsants that can chemically affect the movement of other cells. Netrins are known to guide axons during fetal brain development. Netrins are also thought to suppress inflammation and affect migration of the immune system’s macrophage cells.

A recent collaborative study between HSS and NYU Medical Center asked whether netrins might be involved in the development of osteoclasts, the cells responsible for dismantling old bone cells to make way for new bone. The answer is yes. Without netrin1, the body cannot properly create new osteoclast cells.

The study found that netrin1 is required for osteoclast differentiation and stimulates that process by an autocrine mechanism.

New Discovery in Bone: The Protein Netrin1 is Required for Osteoclast Differentiation
Stimulating Cholinergic Neurotransmitter Receptors Modulates Inflammation in Lupus

There are neurotransmitter receptors on the immune cells that cause inflammation in lupus. A new HSS study, sponsored in part by the Lupus Research Institute, has revealed that stimulating these cholinergic neurotransmitter receptors resulted in less immune complex-induced inflammation in cultured human cells and less organ damage in mouse models.

The team plans to investigate ways to turn this discovery into treatment. Possibilities include using existing drugs that directly activate cholinergic receptors or cause production of more cholinergic neurotransmitters. Another avenue may be electrically stimulating the vagus nerve, which carries a wide assortment of signals to and from the brain, and governs many reflex responses, to calm inflammation and limit tissue damage.

Patients may also benefit from activities that naturally stimulate the vagal nerve, like aerobic exercise, meditation, acupuncture, and relaxation training.
An interdisciplinary HSS research team has found that statin drug therapy can protect against pulmonary embolism (PE) although not total venous thromboembolism (VTE) following hip or knee total joint replacement.

The team reviewed 16,183 returned 6-month questionnaires from patients who had total hip or knee replacement at HSS. 40% of the patients were on statin therapy.

Other findings included that patients on statins were older (68.9 vs 63 years), heavier (BMI 29.6 vs 28.3), more commonly male (49.2% vs 38.5%), had a longer length of stay (5.0 vs 4.9 days), and were more commonly discharged to a rehabilitation center (46.9% vs 37.9%).
First Large Outcomes Studies to Focus on Joint Replacements for Patients with Psoriatic Arthritis

Two large studies by an interdisciplinary HSS research team reviewed outcomes in total knee replacement and total hip replacement for patients with psoriatic arthritis (PsA).

Despite worse pre-operative health status, having PsA or cutaneous psoriasis with osteoarthritis (PsC+OA) were not independent risk factors for poor outcomes.

Using the large HSS patient registries, the team was able to identify 289 patients with psoriasis (69 with PsA and 167 PsC+OA) for the hip replacement study and compared their results to 771 patients with OA, alone. The knee replacement study compared 253 patients with psoriasis (76 PsA and 155 PsC+OA) to 547 patients with OA, alone.

In both studies, in 3-to-5 year follow-ups, the patient groups had equally good outcomes in pain and function scores, and were equally satisfied with the results.

HSS:
Lisa A. Mandl, MD, MPH
Rebecca Zhu
Wei-Ti Huang, MS
Michael M. Alexiades, MD
Mark P. Figgie, MD
Susan M. Goodman, MD

(from left)

Susan M. Goodman, MD
Associate Attending Physician

Mark P. Figgie, MD
Chief, Surgical Arthritis Service

Lisa A. Mandl, MD, MPH
Assistant Attending Physician
Ear, nose, and throat (ENT) involvement is the most prevalent manifestation of granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis.

Reviewing data from 99 patients and 975 office visits, RTX was found superior to conventional immunosuppressives for ENT manifestations of GPA.

The drug Rituximab (RTX) has proven effective in treating severe GPA involving vasculitic manifestations, but its effectiveness in treating ENT manifestations in GPA has been less certain.

Reviewing data from 99 patients and 975 office visits, RTX was found superior to conventional immunosuppressives for ENT manifestations of GPA.

**HSS:**
Lindsay S. Lally, MD
Robert Lebovics, MD
Wei-Ti Huang, MS
Robert F. Spiera, MD

Dr. Lally presented this study at the 2013 ACR Annual Meeting, where she received the Distinguished Fellow Award.
Adult bodies form new blood vessels from existing ones through a process called *angiogenesis*. During pregnancy, a woman’s body grows many new blood vessels to support the developing fetus. The biological molecules involved in the growth processes are called *angiogenic factors*.

A recent study has found that specific alterations in angiogenic factors early in pregnancy are strongly associated with preeclampsia and other poor outcomes in pregnant patients with lupus or antiphospholipid antibodies (aPL).

Increased levels of sFlt1 (an *anti-angiogenic factor*) and/or decreased levels of placental growth factor or PlGF (a *pro-angiogenic factor*) suggest that a pregnancy may be destined for complications.

Using levels of angiogenic factors as biomarkers, doctors can identify pregnancies at risk before 15 weeks, allowing early intervention and revealing novel targets for treatment.
ADAM17, a crucial regulator of cell-to-cell interaction in inflammation, has been found to control cellular signaling in terminal differentiation of chondrocytes, a key process of new bone growth.

The long bones of the skeleton are formed through a complex process called endochondral ossification, in which the matrix made by cartilage cells known as chondrocytes is transformed into hard, new bone. Terminal differentiation refers to the final maturation process of chondrocytes, which allows these cells to synthesize a matrix that can be mineralized as part of the formation of new bone.

A recent HSS-led study has shown that ADAM17 controls cellular signaling during terminal differentiation of chondrocytes in the growth plate of long bones, specifically along the growth factor TGFα/EGFR axis.

Mice bred without ADAM17 in their endochondral chondrocytes did not have proper ossification or normal long bone growth because the cellular signaling that ADAM17 would normally send to regulate the differentiation of chondrocytes and permit the deposition of new bone was disrupted in these animals.
Social Isolation Increases the Risk of Persistent Pain After Hip Replacement

A large outcomes study of 223 patients with *rheumatoid arthritis* (RA) and 561 with *osteoarthritis* (OA) who underwent total hip replacement at HSS shows that being socially isolated is associated with almost three times the odds of experiencing painful results after surgery.

Furthermore, social isolation appears to be more significant in OA, which comprises the vast majority of hip replacement cases.

**HSS:**
Danielle Ramsden-Stein, MD
Susan M. Goodman, MD
Michael M. Alexiades, MD
Wei-Ti Huang, MS
Rebecca Zhu
Mark P. Figgie, MD
Lisa A. Mandl, MD, MPH
Comparing 28 patients with lupus to 25 healthy control patients, a research team of HSS scientists and rheumatologists found that the patients with lupus had increased activity of proteins called rho-associated kinases – or ROCKs. This enhanced activity was associated with differentiation of the Th17 cells of the immune system.

In lupus, inflammation can be triggered by signals from two key cytokine messengers – interleukin 17 (IL-17) and interleukin 21 (IL-21). To produce these cytokines the body requires a transcription factor called IRF4. The ability of IRF4 to drive cytokine production is controlled by ROCKs – which phosphorylate IRF4.

Drugs that inhibit ROCK activity are already used to treat cardiovascular and other diseases. In previous studies, using lupus mice, the HSS team showed drugs that inhibit ROCKs could reduce inflammation. In this new study, using human T cells, ROCK inhibitors reduced production of IL-17 and IL-21. These results support the idea that ROCKs could be promising therapeutic targets for treating lupus.
Two exciting studies at HSS have shown that inactive rhomboid protein 2 – or iRHOM2 – is a promising target for new therapies to treat rheumatoid arthritis (RA). Currently, biologic drugs used to treat RA block the cytokine tumor necrosis factor alpha (TNF-α) from signaling for inflammation. New iRHOM2 therapies would intervene earlier in the inflammatory process.

TNF-α is released into signaling action by a process known as shedding. A kind of molecular scissors called TACE, or tumor necrosis factor-α converting enzyme, snips the tether that holds TNF-α on the membranes of macrophage cells of the immune system. TNF-α “sheds” into the bloodstream. However, any drug that blocked TACE system-wide to prevent shedding would also block TACE’s other important functions like protecting skin and the intestinal barrier.

Now, HSS-led research has found that iRHOM2 regulates TACE’s shedding functions. Essentially, iRHOM2 wraps around TACE to help it shed TNF-α. Further, these studies suggest the exciting possibility that monoclonal antibodies could be developed to prevent iRHOM2 from allowing TACE to shed TNF-α, but not stop TACE’s necessary and helpful functions.

Experiments at HSS with special mice who had no iRHOM2, found that the mice, when challenged to develop inflammatory arthritis, remained healthy. New iRHOM2 therapies could potentially cause less side effects than anti-TNF drugs, and benefit patients with conditions that anti-TNF drugs do not currently help.
Doctors Using Excessive Medical Jargon Can Seem Unprofessional to Patients

Rheumatology fellows training in New York recently learned some important news with implications for all clinicians, not just fellows: excessive use of medical jargon makes a doctor seem less professional.

Since 2004, fellows from many NYC hospitals participate in a structured, clinical exam called New York City Rheumatology Objective Self Assessment Clinical Exam or NYC-ROSCE. Real-life patients with rheumatic conditions are recruited and trained to be examined by the fellows, simulating many different rheumatic issues and patient temperaments, while a board-certified rheumatologist observes.

The patient-actors and observing MDs give immediate oral feedback, then later fill-in written evaluations and questionnaires. The fellows also rate their own performances. Discussing the results helps the fellows become better doctors.

This year, an evaluation was added to see which particular skills correlated highest with professionalism. Results: clear communication matters. Both the patient-actors and MD-evaluators correlated jargon reliance inversely with the ratings of professionalism. The patients considered ability to minimize medical jargon to be one of the most important markers of professional competency.
Patients with early rheumatoid arthritis (RA) who reach the treatment target of low disease activity (LDA) at 6 months show less joint damage and functional ability after two years than those who do not achieve the target. LDA means joint pain, swelling, and other markers of inflammation are markedly reduced.

These important findings are from a study using data from the Canadian early ArThritis Cohort (CATCH), an ongoing multi-center project which has been collecting information on patients with early inflammatory arthritis in Canada since 2007. HSS Associate Attending Rheumatologist Vivian Bykerk, MD, is chair and director of CATCH.

Of the 833 patients in the study, 56% achieved LDA at 6 months. Dr. Bykerk believes there is a window for RA treatment within the first three months of developing joint inflammation. During the window, patients with RA have a better chance of getting the disease under good control, with many needing less intense therapy over the long run.
A multi-center collaboration has revealed new information about the differences between girls and boys who have *systemic lupus erythematosus* (SLE). Gathering data from several hospitals allowed the team to study a large group of pediatric patients with lupus that included 29 boys and 138 girls.

Statistical analysis showed that compared to girls in the study, boys had a higher age of disease onset, lesser disease duration, and greater disease activity. Differences in disease damage and immunosuppressive medication use between the two groups were not statistically significant.

Lupus is more common in females, but males have more severe disease.
The combined DNA and proteins inside the nucleus of a cell is known as chromatin. Chromatin can restructure depending on the cell’s life stage and activities.

Using genome-wide analysis, a recent HSS study identified several molecular mechanisms involving chromatin that act synergistically during the inflammatory process. The linked actions occur between signaling mechanisms that call for increased inflammation and epigenetic actions required to prepare genes for increased transcriptional activation. Highlights include:

- **Interferon-gamma** (IFN-γ) primes the chromatin of key promoters and enhancers of inflammation – including TNF, IL6, IL12B – so their genes are ready for transcription.
- The primed chromatin enables increased response to the signaling for more transcription coming from toll-like receptors.
- The priming is mediated by pathways and mechanisms used in inflammatory signaling. These include a stable STAT1 and IRF1 occupancy and histone acetylation.
- Priming makes cells more susceptible to inhibition by two categories of drugs termed Jak inhibitors (already used for RA) and BET inhibitors. This suggests new therapeutic approaches to suppress inflammation.

Understanding the deeper connected complexities of how the immune system orchestrates inflammation will continue to help HSS uncover potential new therapies to stop the tissue-damaging processes.