National Institutes of Health
Office of Science Policy

UNDERSTANDING IMMUNE CELLS AND INFLAMMATION:

OPENING NEW TREATMENT AVENUES FOR RHEUMATOID ARTHRITIS AND OTHER CONDITIONS

Most of the 1.5 million adults in the United States who have rheumatoid arthritis (RA) take medications to control their pain and slow the damage that is occurring in their joints. RA causes inflammation and pain in the hands, wrists, knees, or other joints and, over time, leads to permanent damage. Like other autoimmune diseases, RA occurs when the immune system attacks a person's body instead of defending it against invading organisms.

NIH-funded investigators played a large role in discovering and characterizing the molecular interactions that tofacitinib acts on and in predicting the usefulness of this and related pathways as drug targets. Some of that research is described here to illustrate how knowledge about cell behavior at the molecular level can be used to improve health.

Some RA drugs protect joints by blocking interactions between inflammatory molecules and the healthy tissues that they are erroneously targeting. Others destroy the cells that produce the damaging molecules. While these disease-modifying antirheumatic drugs (DMARDs) help many people, some patients do not respond or cannot tolerate the side effects. In 2012, FDA approved another option for people with moderate to severe RA who are not helped by other treatments. This new drug, tofacitinib, fights inflammation from inside immune cells. Because it works differently than many RA drugs, it can be taken as a pill, rather than an injection.

IMMUNE CELLS AND INFLAMMATION: THEN AND NOW

THEN

Since the late 1990s, drugs that prevent inflammatory molecules called cytokines from interacting with healthy tissue have helped hundreds of thousands of people who have autoimmune diseases such as rheumatoid arthritis, but these drugs did not work for everyone.

Many of the medications need to be injected instead of swallowed.

NOW

A drug that targets a signaling pathway inside immune cells has been approved for people who have moderate to severe rheumatoid arthritis if they do not benefit from one of the older treatments.

The new drug is taken as a pill. Versions that can be absorbed through the skin are being developed to treat other diseases.

SELECTED RESEARCH-TO-PRACTICE MILESTONES IN THE DEVELOPMENT OF TOFACITINIB

For more information on the supporting evidence and research sponsors for these milestones, see the Web appendix.

FOUNDATIONAL RESEARCH

1989–1991

Researchers discovered JAK1 and JAK2. The proteins were named after the Roman deity Janus.[1]

1991–1994

Investigators around the world (some at NIH) demonstrated that JAKs respond to signaling molecules and began to determine how different JAKs are activated. Others integrated the STAT protein family into the process. These studies were some of the earliest demonstrations of how molecules outside a cell control gene expression inside a cell.[2] NIH

1994

Three research groups (two of which were funded by NIH) discovered JAK3. Unlike other JAKs, JAK3 is expressed primarily in immune cells, suggesting it may be involved in regulating the immune response.[3] NIH

1995

NIH investigators linked JAK3 inhibition to immune suppression when they discovered that children with JAK3 mutations have symptoms resembling a disease called X-linked severe combined immunodeficiency.[4] NIH

The NIH team speculated that developing phamacologic agents against JAK3 could result in useful therapies for malignancies and possibly autoimmune disorders.[5]

1996

NIH and Pfizer launched a partnership to examine how JAK3 interacts with receptors on the surface of immune cells. Over the next decade, the team characterized regions of the JAK3 protein that are important for signaling and immunity.

Working under a cooperative research and development agreement (CRADA), the team demonstrated that inhibiting JAK3 activity blocks immune responses in two animal models following organ transplantation.[7]

One compound identified during these studies became known as tofacitinib.[6] NIH

NIH

indicates NIH-funded milestones

PRECLINICAL AND CLINICAL TESTING

2007

Pfizer reported results from a clinical trial of tofacitinib for people who have rheumatoid arthritis. Pfizer began studying tofacitinib for other conditions.

In 2016, Pfizer was sponsoring 10 studies of tofacitinib for rheumatoid arthritis and other autoimmune diseases.

TREATMENT OPTIONS

2012

FDA approved tofacitinib for the treatment of people with moderate and severe rheumatoid arthritis who had not done well on an older drug (methotrexate). Patients take tofacitinib as a pill twice daily.

Depiction of tofacitinib's target, the Jak3 kinase domain.

Illustration by Emw - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=8820187

2015

NIH researchers used tofacitinib in experiments that provided insights into how gene expression is regulated.[8] NIH

2015

NIH began a clinical trial of tofacitinib for people with mild to moderately severe lupus.[9] NIH

2016

FDA approved a form of tofacitinib that people with rheumatoid arthritis can take once a day.

IMPACT OF STUDYING THE JAK-STAT SIGNALING PATHWAY

KNOWLEDGE

Discovery and characterization of the JAK-STAT pathway was one of the earliest demonstrations of how molecules outside a cell control gene expression inside a cell.

Researchers know that signals transmitted through the four JAK family members and seven STAT family members affect tens of thousands of sites in the human genome, regulating the production of thousands of proteins and other molecules.[10]

HEALTH

The finding that alterations in the JAK-STAT pathway are associated with diseases of the immune system and human cancers has led to the development of a new class of drugs, called Jakinibs.

Jakinibs that act on JAK1 or JAK2 are FDA-approved for dogs with allergic dermatitis or for people with certain blood cancers.

People who do not respond to at least one older RA treatment have a new option in the form of tofacitinib, which acts on JAK3. This is the first new oral drug approved for RA in a decade.

SOCIETY

At the beginning of 2016, a dozen compounds that inhibit JAK1, JAK2, or JAK3 signaling (alone or in combination) were in clinical trials for autoimmune diseases, including psoriasis, RA, ulcerative colitis, spondyloarthritis, juvenile idiopathic arthritis, Crohn's disease, and lupus.[11]

JAK-STAT SIGNALS CONTROL CELL BEHAVIORS, INCLUDING THE IMMUNE RESPONSE

Discovery of the JAK-STAT molecular pathway in the early 1990s was a landmark advance explaining how cells sense and respond to their immediate environment. Research teams from around the globe quickly capitalized on this finding and began exploring different aspects of the complicated signaling mechanisms. They found that when certain receptors on a cell's surface encounter signaling molecules called cytokines, at least one of the four types of JAK (Janus kinase) proteins inside the cell is activated.

The specific combination of cytokines, receptors, and JAKs dictate which member of another family of proteins, called STATs (signal transducers and activators of transcription) is mobilized. Activated STATs migrate to the nucleus, where they interact with DNA and other molecules to precisely control gene expression. Researchers have learned that changes in this process can cause disease. For example, too much JAK3 activity is associated with autoimmune diseases such as RA; too little puts people at high risk of infections.

Twenty-five years later, researchers are conducting clinical trials of molecules that alter the activity of the JAK-STAT pathway to treat autoimmune diseases and other conditions that are caused by dysregulated cell signaling. In addition to tofacitinib, two JAK inhibitors (or Jakinibs) have received FDA approval: ruxolitinib for people who have bone marrow diseases and oclacitinib for atopic dermatitis in dogs.

For references, supplementary information, and more on the impact of NIH, please visit **http://www.nih.gov/impact**.