Mechanisms of Psoriatic Arthritis

By:

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This thesis is dedicated to Ryan and Chloe whose support, encouragement, and smiles kept me going through the tough times.
Psoriasis (Ps) is the most common chronic autoimmune disease in the United States. The immune system releases proinflammatory cytokines and growth factors that accelerate the growth of skin cells which accumulate and form thick red patches of skin on various parts of the body. About 25 percent of psoriasis patients develop inflammatory arthritis in which inflammation progresses to joints and entheses. Psoriatic Arthritis (PsA) patients exhibit joint pain, stiffness, and swelling which can affect any part of the body. PsA occurs when the immune cells release cytokines that act on healthy cells and tissues to induce skin and joint inflammation. Genetic and environmental factors interact to trigger the cellular pathways that promote skin and joint disease.

Research studies on the pathophysiology of psoriatic arthritis have revealed that alterations in both immune cells and resident cells in the skin and joint characterize this disease. Dr. Christopher Ritchlin’s research focuses on the links between skin and joint inflammation. His laboratory is examining the mechanisms of bone resorption and formation, the effect of anti-TNF agents on dendritic cell differentiation, and the mechanisms of bone marrow edema (a finding on MRI of the joints) observed in PsA and rheumatoid arthritis.

His current research demonstrates a mechanism for the destructive pathology in psoriatic joints. The purpose of my thesis is to illustrate Dr. Ritchlin’s research. It will be a 2-dimensional animation explaining normal bone remodeling and the bi-directional attack on PsA joints. Accompanying the animation is a voice over explaining what is happening on screen.
INTRODUCTION

I chose this topic for my thesis for personal reasons. As a person suffering from psoriasis, I have a twenty percent chance of developing psoriatic arthritis. I was not even aware of this disease until speaking with Dr. Ritchlin. After speaking to rheumatology patients, I was informed they do not understand what is happening within their bodies. I hope that this animation will educate patients with high school science knowledge.

After viewing the animation, the learner will be able to:

1. State what psoriasis is
2. List the symptoms of psoriatic arthritis
3. State the events of normal bone remodeling
4. State the events of the outside-in mechanism
5. State the events of the inside-out mechanism

I contemplated creating a traditional print piece rather than an animation. This is a complex subject and I believe an animation is easier to explain it. With an animation I am able to show several steps without overwhelming the viewer. The labels used are large but because they disappear, they do not crowd the image plane. The voice over also helps to reiterate ideas that are being shown on the screen. The script explains step-by-step what is happening with in the animation.
WHAT IS ARTHRITIS?

Arthritis literally means “joint inflammation” and describes over 100 conditions affecting joints and their surrounding tissues. Because the term does not describe the cause or type of joint inflammation, it is qualified with an adjective such as rheumatoid, osteo-, or psoriatic (Scott, 1980). Arthritis also involves the degradation of cartilage, which protects the joint and allows it to move smoothly. Without the cartilage, the bones rub together causing inflammation and stiffness. The two most common types of arthritis are osteoarthritis and rheumatoid arthritis (RA). Osteoarthritis causes pain, stiffness and inflammation most often in the hips, knees and hands, while rheumatoid arthritis usually affects the hands and wrists. People suffering from these two diseases often exhibit stiffness, swelling, and pain in the joints.

WHAT IS PSORIASIS?

Psoriasis is a chronic inflammatory skin disease that affects up to 3% of the population (Menter et. al., 2008). There are several forms including chronic plaque psoriasis, erythrodermic psoriasis, pustular psoriasis, inverse psoriasis and guttate psoriasis. Chronic plaque psoriasis (psoriasis vulgaris) is the most common type and is present in over 90% of patients with psoriasis. There are two types of chronic plaque psoriasis:

Type I: occurs in adolescents with a family history of psoriasis and is the most common type.

Type II: manifests in patients between 50 and 60 years of age with no family history.

Psoriasis most commonly affects the scalp, nails, extensor surfaces of limbs, elbows, knees, umbilicus, genital, and sacral regions. The major characteristics of psoriasis are scaling, thickening and inflammation.

Psoriasis occurs when the immune system sends out faulty signals that tell the skin to grow quickly, forming thick red patches of skin (Scott, 2012). This is a chronic autoimmune disease that is not contagious. There are several triggers that cause psoriasis to flare: trauma, infections, stress, medications, alcohol, smoking, obesity and estrogen (Menter et. al., 2008).
WHAT IS PSORIATIC ARTHRITIS?

Psoriatic arthritis is an inflammatory autoimmune joint disease distinguished by extensive bone resorption (Ritchlin et al., 2003). The body attacks its own tissues and sends white blood cells to the synovium eventually inflaming the tissue. The inflammation causes the synovium to thicken which results in a swollen joint. As the synovium continues to thicken into the pannus, it begins to invade the cartilage, which then begins to erode. This causes bones to rub together causing joint damage (Ludlam, 2012). Joint damage occurs early in the disease so early diagnosis is important.

About twenty percent of people suffering from psoriasis develop psoriatic arthritis. In seventy five percent of cases, psoriasis precedes PsA. Psoriatic arthritis generally goes undiagnosed and untreated and is often confused with rheumatoid arthritis. According to Ritchlin, there are several musculoskeletal features that characterize PsA: tendonitis, enthesitis, dactylitis, and arthritis (2007). There are also five clinical patterns of PsA for classification (Menter et al., 2008):

1. Distal arthritis
2. Asymmetric oligoarthritis
3. Symmetric polyarthritis
4. Arthritis with axial disease
5. Arthritis mutilans

The most commonly affected joints are the spine and distal interphalangeal joints (DIP joints) of the hands and feet. Involvement of the DIP joints is common in patients with nail disease (Menter et al., 2008). The rheumatoid factor (an antibody) is present in 80% of patients with RA and up to 10% of patients with PsA making the two diseases hard to distinguish. RA is more common in women and involves symmetrical joint inflammation. PsA affects men and women equally and all joints of a single digit are affected, specifically the DIP joints. PsA joints are less erythematous, less tender, and more fibrous. Enthesistis is also present in PsA patients.
Mechanisms of Psoriatic Arthritis

There are five types of psoriatic arthritis (Levesque, 2010):

1. Symmetric: affects the same joints on both sides of the body; milder than rheumatoid arthritis
2. Asymmetric: affects one to three joints in the body; non-matching pairs
3. Distal interphalangeal predominant: affects the small joints in fingers and toes closest to the nail
4. Spondylitis: affects the spinal column and may cause stiffness in the neck, lower back, spinal vertebrae, or pelvic region; may also attach ligaments
5. Arthritis mutilans: severe and destructive form of PsA that affects the small joints in the fingers and toes and also the lower back and neck; very uncommon
DR. RITCHLIN’S RESEARCH

Dr. Christopher Ritchlin of the University of Rochester Medical Center has focused his research on understanding the mechanisms of pathologic bone resorption and new bone formation in both psoriatic arthritis and rheumatoid arthritis. His lab is also working with Dr. Eddie Schwarz (also of URMC) to understand the mechanisms of bone marrow edema that shows on MRI images of inflammatory arthritis. Dr. Ritchlin is also performing studies on the effect of tumor necrosis factor (TNF) inhibition on the frequency of osteoclast precursors and enhancing bone marrow edema in PsA.

There are four types of cells that make up bone: osteoprogenitor cells, osteoblasts, osteoclasts and osteocytes. Osteoprogenitor cells (OPCs) are immature cells located in bone marrow and the periosteum that mature into osteoblasts. Osteoblasts are bone cells responsible for bone formation. Osteoclasts are responsible for the breakdown of the bone matrix. Osteocytes are mature bone cells.

Bone remodeling is the process of bone matrix breakdown by osteoclasts. Osteoclasts attach to the bone surface and form a leak-proof seal at the edges with their ruffled border. They release protein digesting lysosomal enzymes and acids. The enzymes digest collagen fibers and the acid digests bone mineral. Several osteoclasts carve out a tunnel and degraded proteins and matrix minerals enter the osteoclast by endocytosis. Osteoclasts depart the bone and osteoblasts move in and bone remodeling begins. Osteoblasts synthesize and secrete collagen fibers and other matrix building tissues (Tortora, 2003).

According to Ritchlin “the presence of marked bone resorption coupled with adjacent new bone formation (often in the same digit) suggests a disordered pattern of bone remodeling in the psoriatic joint” (2003). The purpose of his research is to explain how osteoclast precursors (OCPs), RANK (receptor activator of nuclear factor kappa-B), RANKL (receptor activator of nuclear factor kappa-B ligand), and osteoprotegerin (OPG) cause osteolysis in PsA. Dr. Ritchlin found that the number of OCPs is increased in PsA patients, but this number was not significantly different from the number found in RA samples.

The results of this study propose a bi-directional attack on the joints, known as the “inside-out” and “outside-in” mechanisms. First, TNF-α increases the number of circulating OCPs. In the
inside-out mechanism osteoclast precursors enter the synovial membrane from the bone marrow and migrate to the site of inflammation. High levels of osteoprotegerin expressed by endothelial cells suppress osteoclastogenesis. Undifferentiated osteoclast precursors migrate through the pannus and target the bone. At the bone-pannus junction, osteoclast precursors bind to RANKL on the surface of synoviocytes. In the presence of TNF-α, osteoclast precursors undergo osteoclastogenesis and become osteoclasts. The osteoclasts then begin bone remodeling.

In the outside-in mechanism of bone remodeling osteoclast precursors enter the subchondral environment via the periosteal vessels from the inflamed synovial tissue. The osteoclast precursors translocate through the endothelium of the blood vessels. They are then exposed to TNF-α induced RANKL on the surfaces of osteoblasts and stromal cells. This exposure causes generation of osteoclasts that line cutting cones devoid of synovial tissue. The mature osteoclasts resorb bone matrix in the subchondral bone and at the pannus-bone interface (Ritchlin, 2003).

In normal bone remodeling, lining cells along the bone matrix differentiate into osteoblasts. The osteoblasts move apart to expose the bone surface and begin to express RANKL. RANKL binds to RANK located on osteoclast precursor cells, which are derived from monocytes. Multiple osteoclast precursors fuse to form multi-nucleated osteoclasts. RANKL continues to bind to RANK on mature osteoclasts. Osteoclasts move to the bone surface and form a leak proof seal with their ruffled border. They begin to excrete enzymes and acids, which break down the bone matrix resulting in the formation of deep pits. Osteoclasts then leave the bone to allow osteoblasts to move in and fill the pits with new bone matrix.
PROCESS

After deciding on the subject of arthritis I contacted several rheumatologists in the Rochester area. Dr. Christopher Ritchlin responded to me with enthusiasm. I met with him, discussed his research, and began brainstorming ideas. After reading his article titled “Mechanisms of TNF-α and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis” I decided on animating this process (Ritchlin, 2003). He uses the following image in his article:

To me, this image is very confusing. When I first looked at it I felt overwhelmed by everything depicted. Although patients ultimately may not fully understand his research, I feel they should be educated on what is happening in their bodies, and I believe this animation will do that.

Using this article and image as my main source, I began to decipher the different components of the synovial joint and osteoclastogenesis. I determined the animation should consist of four parts: introduction, normal bone remodeling, outside-in mechanism, and inside-out mechanism. I think it is imperative for the viewer to understand normal bone remodeling to ultimately understand what happens during bone remodeling within a person suffering from PsA. I researched bone remodeling extensively in order to fully understand the different cells involved in the process and what happens to joints.
I began to illustrate osteoclasts, osteoblasts, and RANKL using different programs because I was not sure if I wanted to create a 2D or 3D animation. I was always leaning toward a 2D animation due to my knowledge of these programs, but I found several 3D animations online that were very nice. I made the cells in Photoshop, Illustrator and Maya, because I was not sure which way I was going to go.

### Osteoclasts

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### Osteoblasts

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### RANK

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During the beginning of my process, I experimented with all three of these programs, trying to determine which one would ultimately be best to create my animation. I began watching tutorials on Maya and After Effects on Lynda.com. I knew if I wanted to create a two-dimensional animation it would need to be done in After Effects rather than Flash, so it would display on Apple products. Tablets, especially the iPad, have become more popular for both personal and professional use, and I want viewers to be able to use their tablet to view my animation. Another determining factor for the type of animation was time. Although I have used Maya to model, I had never used it to animate. I did not feel as though I had enough time to learn this in order to create a successful piece. I felt much more comfortable with using After Effects and that my time would be used more wisely.

Once I decided on the animation program, I began to draw storyboards. During most of my thesis I created and re-created storyboards to determine the best way to execute this animation. Once I came up with a general idea of what I wanted to create, I began to experiment in After Effects. I imported .psd files (from Photoshop) and began to animate the osteoblasts moving, but because they are raster images, things became pixelated. That is what finally led me to use only Illustrator files within the animation (moving objects only) and use Photoshop for the static images. I created the figure, hand, and x-ray images using Poser and Photoshop, and the trabeculae and synovial joint using only Photoshop.

\[Trabeculae \text{ static image}\]
I knew that in order for viewers to understand what was happening within this animation, I needed labels and a voice over. For the labels I decided that each time a new cell appears on the screen it would have a label. Because this animation is geared toward an audience with high school science knowledge, I thought these labels would help explain things better.
Throughout the illustration process I was also working on a script (see Appendix). After thoroughly reading and re-reading Dr. Ritchlin’s research, I was able to write the process of bone remodeling in a way for viewers with high school science knowledge to understand. I sent the script to Dr. Ritchlin for final approval. After receiving edits from him, I recorded trial sounds and began working on the animation. I did not record the final voice over until late into my process, which was a mistake. I found that it was much easier to animate with the finished voice over due to timing. If I had to do this again, I would write and record the script before animating.

There is also background music accompanying the voice over. After viewing other medical animations online, I found that the ones with both a voice over and background music were most pleasing.
CONCLUSION

This animation has taught me several lessons as a medical illustrator. I have expanded my knowledge of rheumatology and learned about a disease that I knew nothing about. My abilities as a two-dimensional animator have improved to the point that I am now able to envision animation opportunities that I had previously not considered. I now have a better understanding for the entire animation process as well.

This animation explains the concept of Dr. Ritchlin’s work in a simple way. I hope that he can use this piece for patient education and to generate public knowledge of this disease. I would love to continue working with him as his research progresses and elaborate the animation.
APPENDIX

Voice over script

Psoriasis is an autoimmune disease that results in inflammatory cell infiltration in the deeper layers of the skin, which promotes rapid growth of cells in the superficial layers. This results in the formation of red, scaly plaques. It is thought to be sustained by faulty signals that speed up the growth of skin cells.

About twenty percent of patients with psoriasis develop psoriatic arthritis.

Psoriatic arthritis is an inflammatory musculoskeletal disease that causes pain, stiffness, and swelling at the joints. Psoriatic arthritis can affect the lower back, wrists, and ankles but typically causes dactylitis, or swelling, of the fingers and toes.

Bone remodeling is a key factor in damage that is observed in the joints and x-rays of patients with psoriatic arthritis.

In normal bone remodeling, lining cells along the bone matrix differentiate into osteoblasts. The osteoblasts move apart to expose the bone surface and begin to express RANKL. RANKL binds to RANK located on osteoclast precursor cells, cells which are derived from monocytes. Multiple osteoclast precursors fuse to form multi-nucleated osteoclasts. RANKL continues to bind to RANK on mature osteoclasts. Osteoclasts move to the bone surface and form a leak proof seal with their ruffled border. They begin to excrete enzymes and acids, which break down the bone matrix resulting in the formation of deep pits. Osteoclasts then leave the bone to allow osteoblasts to move in and fill the pits with new bone matrix.

Joint erosion in psoriatic arthritis is caused by a bi-directional attack on the joint. There are two mechanisms for this attack: outside-in and inside-out.

In the outside-in mechanism of bone remodeling osteoclast precursors enter the subchondral environment via the periosteal vessels. The osteoclast precursors translocate through the endothelium of the blood vessels. They are then exposed to TNF-α induced RANKL on the surfaces of osteoblasts and stromal cells. This exposure causes generation of osteoclasts that line
cutting cones devoid of synovial tissue. The mature osteoclasts resorb bone matrix in the subchondral bone and at the pannus-bone interface.

In the inside-out mechanism osteoclast precursors enter the synovial membrane from the bone marrow and migrate to the site of inflammation. High levels of Osteoprotegerin expressed by endothelial cells suppress osteoclastogenesis. Undifferentiated osteoclast precursors migrate through the pannus and target the bone. At the bone-pannus junction, osteoclast precursors bind to RANKL on the surface of synoviocytes. In the presence of TNF-α, osteoclast precursors undergo osteoclastogenesis and become osteoclasts. The osteoclasts then begin bone remodeling.
GLOSSARY

Cutting cone
Groups of osteoclasts that attach to bare bone surfaces and dissolve the organic and inorganic matter

Osteoblast
Bone-building cell

Osteocyte
Cell that makes up bone tissue

Osteoclast
Cell responsible for the breakdown of bone matrix

Osteoclastogenesis
The development of osteoclasts

Osteoprogenitor cell
Immature cells located in the bone marrow that mature into osteoblasts

Osteoprotegerin
A cytokine that inhibits osteoclastogenesis

Pannus
Thickened synovial tissue that covers cartilage

RANK
Receptor activator of nuclear factor kappa B; a protein expressed on the surface of osteoclasts

RANKL
Receptor activator of nuclear factor kappa B Ligand; found on osteoblasts and activate osteoclasts
Rheumatoid factor
The antibody most prevalent in rheumatoid arthritis

Subchondral bone
Bone located below the articular cartilage

Synoviocyte
Cell of the synovium

TNF-α
Tumor necrosis factor; a cytokine involved in systemic inflammation
REFERENCES


