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Originally published by the Stem Cell Network April 2014

Arthritis

Research is a dynamic activity that creates new ideas. It provides a forum for generating observations and testing why they occur. Because people and their diseases are so diverse, clinical trials are the ONLY WAY it is possible to test whether new ideas about how to diagnose or treat human disease will work. But the process of taking research from bench to bedside is a lengthy one and demands not only vision but also years of teamwork and dedication on the part of scientists, physicians and patients. This document presents basic information about arthritis and frames the context for the discussion that follows about how stem cells could be used to better understand and eventually treat this condition. Readers may also wish to peruse additional web resources or speak with their physicians for more information about arthritis.

About Arthritis

Background

Arthritis is a descriptive term that literally means 'inflammation of the joints'. With over 100 different conditions that fall under this heading, there are many causes but common underlying symptoms: chronic pain in the joints, muscles and bones, stiffness and swelling. The resulting disability can be mild as in the case of tendinitis or crippling as with rheumatoid arthritis.

Arthritis is broadly classified as either degenerative and/or inflammatory. Osteoarthritis (OA), the most common form, is degenerative (worsens over time) and is caused by wear and tear on the joints. There are two types: Primary OA occurs mostly in patients of advanced age and is associated with genetic or familial factors; Secondary OA is associated with mechanical stresses such as deformity, misalignment of limbs or acute injury.

Rheumatoid arthritis (RA) is the classic and most common example of inflammatory arthritis. It is caused by an autoimmune attack on the lining of the joints. The resulting inflammation and swelling is also thought to involve genetic and environmental components. Other types of inflammatory arthritis are lupus, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, and gout.

Arthritis is not discriminating: it can affect people of any age, at any time and any ethnic background. However, the hardest hit group is the elderly (over 60). They most often suffer from osteoarthritis, which is on the rise in the West in part due to the aging population and the increase in obesity, a major risk factor because it increases the load joints must carry, alters limb alignment, gait, and systemic metabolic factors. The joints most commonly involved in osteoarthritis are found in the hand, spine, hip, knee and feet.

The burden of arthritis is growing at an alarming rate. The Arthritis Society estimates that in Canada alone over 4.6 million adults have arthritis and the number is expected to rise to 7.5 million – or 1 in 5 by 2036. The cumulative healthcare and loss of productivity costs are estimated at $33 billion per year and that figure is expected to double over the next 18 years. Because there is no cure for arthritis and the condition tends to worsen over time, early diagnosis is very important for providing an opportunity to limit long-term disability and improve the quality of life for individuals.

What is cartilage and how does it work?

Cartilage is a marvelous anatomical buffer. Without it, the friction between opposing bones would lead to excruciat-

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ing pain. Lubricated by a liquid called synovial fluid, the cartilage matrix is a paper-thin connective tissue that covers the ends of joints that move, or articulate, against each other. A sac of liquid encapsulates every articular joint and the associated nerves, muscles, tendons, ligaments and bones adjust to the mechanical load imposed on our joints as we move during normal daily life and intense activity.

There are two main constituents of the cartilage matrix. Both are proteins. Type 2 collagen lends strength, and aggrecan lends stiffness by retaining water within the tissue. Cartilage lacks blood vessels and nerves but it does contain a single cell type called chondrocytes. In a normal joint, these cells are responsible for making the matrix proteins and remodeling the cartilage during the never-ending cycle of breaking it down and building it up. Anything that interferes with that natural remodeling process or that negatively affects the strength of stiffness of cartilage sets the stage for the possibility of arthritis.

Treatment

All the treatments for arthritis converge on a single goal: to alleviate pain for patients and minimize the loss of function in the affected joints. The simplest, least invasive approach is to avoid or reduce activities that cause pain, and if possible to exercise in a way that improves strength and conditioning of the muscles surrounding the joint. However, this approach is not always enough and drug treatments, taken orally, topically or injected into the joint, may be necessary to reduce inflammation and control pain. Failing the success of this second tier approach, surgical procedures that realign or redesign the damaged joint or that replace the joint outright with an artificial version are available.

In the past 10 years, researchers have explored the possibility of cell-based therapies for repairing arthritic joints. The first attempt at this involved drilling holes and scraping the joint to create a channel to the underlying bone and bone marrow. This seemingly brutal approach is actually a way of inducing injury to create inflammation in the joint. Inflammation acts as a beacon to various cell types, including mesenchymal stem cells, to seek out the inflamed area. When that happens, the mesenchymal stem cells eventually make chondrocytes, which make new cartilage. The downside to this approach as that it works for only small areas of injury and the new cartilage is not as mechanically strong as the original tissue and therefore can wear out.

These limitations prompted researchers to develop a technique called ACI (autologous chondrocyte implantation) that is now widely used for regenerating cartilage in arthritic joints. In this procedure, a biopsy of cartilage is taken from a non-load bearing portion of a joint and the patient's chondrocytes are extracted and expanded in the laboratory. Then the new chondrocytes are transplanted back into the patient at the load-bearing site of the arthritic joint. ACI is able to reliably provide short- and mid- term relief to patients, but there are limitations. Mature chondrocytes are tricky to grow and a huge number of them are required to patch just a small area of a damaged joint. Improvements in growing cells and the creation of bioengineered surfaces that help grafted chondrocytes to integrate have made some headway, but the long-term effectiveness of ACI is still being evaluated.

The obvious gap in enduring treatments for arthritis leaves the door open for researchers to explore new approaches that take advantage of the power of stem cells.

How are stem cells being used to help with arthritis?

The clinical application of stem cells to cure arthritis is still many years away, but there is a sound premise for exploring their use for this purpose.

Cartilage lining the head of the joints that move (called articular cartilage) lacks both blood vessels and nerves, and so is very slow to repair itself following acute injury or chronic inflammation. Furthermore, cartilage tissue has a very low cell content, with chondrocytes accounting for only ~5% of the tissue (the remainder is extracellular matrix and water).

Stem cells can make chondrocytes and chondrocytes make cartilage, so finding ways to harness this power would be very beneficial. The stem cell field is ready to move forward: there are now better cell culture techniques for growing stem cells into chondrocytes, and bioengineered scaffolds to expand chondrocyte numbers and help them to engraft.

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Researchers have also learned that some stem cells possess anti-inflammatory properties that might buffer against the immune components contributing to arthritis. More information about stem cells and their application to arthritis is discussed below.

Research directions

Mesenchymal stem/stromal cells (MSCs)

MSCs have tremendous flexibility to make a variety of different cell types, including bone, fat, muscle, cartilage, bone marrow stroma and tendon. MSCs are also able to modulate the immune system, inhibit inflammation, stimulate blood vessel formation, repair tissue and help transplanted stem cells to engraft. For the purpose of donor transplantation, these stem cells are very versatile and do not lead to extensive graft rejection even when the donor and recipient tissues are mis-matched. Many tissues in the human body contain MSCs, and in adults they are easily collected from bone marrow, fat, and umbilical cord.

In combination, these characteristics have led MSCs to be broadly studied as potential therapeutics in many different diseases. Despite the fact that they aren't present in high numbers in the body and biomarkers distinguishing them from neighboring cells are lacking, researchers have devised ways to harvest MSCs, expand them the laboratory, and stimulate them to make chondrocytes. They have also developed a method for engineering a layer of cartilage by seeding MSCs onto a three-dimensional scaffold that can be used to replace damaged tissue.

Positive results from pre-clinical studies transplanting MSC-derived chondrocytes into animals with osteoarthritis and rheumatoid arthritis have proven benefits, and the evolution to clinical trials in this field is promising. A recent publication reviewed 844 procedures involving bone marrow expanded MSCs for repairing cartilage and treating osteoarthritis in patients. The minimal adverse effects, mostly having to do with pain/swelling or dehydration after the bone marrow procedure are encouraging.

The other way that MSCs are being used is as anti-inflammatories to support the regeneration of cartilage in affected joints, and emerging safety data from early phase clinical trials are positive. Some researchers are also packaging MSCs as "extra strength" anti-inflammatories by loading them with genes that block inflammation. This approach is being tested in animal models of rheumatoid arthritis.

Although MSC therapies are very promising, many variables still remain to be worked out. One very curious observation is that not all MSCs are equal in their abilities and this has researchers working hard to understand the possible reasons. Some preliminary results suggest that stem cells harvested from synovial fluid in the joints are better able to make chondrocytes than MSCs harvested from bone marrow, skeletal muscle, or adipose tissue. Scientists are also exploring novel, easy access, sources for obtaining MSCs, such as the gums (gingiva) in the mouth.

Going forward, the field agrees that for designing better clinical trials, it will be crucial to be able to distinguish various MSC populations, in terms of their tissue of origin, biomarkers, and functionality across different laboratories, animal models and patients. Being able to use donor (allogeneic) MSC transplants is also on the agenda of many scientists who are working out the conditions first in animal models of arthritis.

Adipose-derived stem cells (ADSCs)

Adipose (fat) derived stem cells (ADSCs) are similar to bone marrow MSCs in their ability to make different types of cells. ADSCs make fat cells, bone, cartilage, muscle cells, and even promote the formation of new blood vessels (angiogenesis). ASCs can be isolated through minimal liposuction techniques from fat tissue and then put through a series of isolation and purification steps in the laboratory. In preclinical testing, a single dose of ADSCs injected into animals with osteoarthritis has been able to suppress the inflammatory events that cause cartilage destruction and damage to the ligaments holding the joints together. Clinical trials testing whether the same holds true for human joints with osteoarthritis are underway.

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Originally published by the Stem Cell Network April 2014

Embryonic stem cells (ESCs)

Applying embryonic stem cells to the problem of arthritis is still at pre-clinical stage and much work will be needed to evaluate the safety of the ESC-derived chondrocytes before they can be approved for human use. The ultimate goal is to use ESCs to make 'off the shelf' chondrocytes to be used as donor (allogeneic) transplants for many different patient populations.

Web Resources

Readers may wish to peruse the recommended sites or review the selected reading list below for more information about the application of stem cells to treat arthritis.

- The Arthritis Society: http://www.arthritis.ca/
- The Arthritis Society: Facts and Figures: http://www.arthritis.ca/facts
- Arthritis Research Centre of Canada: http://www.arthritisresearch.ca/

Selected Reading List

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