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Crohn's Disease

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 Crohn's disease and frames the context for the discussion that follows about how stem cells could help. Readers may also wish to peruse additional web resources or speak with their physicians for more information about this condition.

About Crohn's Disease

Background

Crohn's disease is incurable, unpredictable and unrelenting. As one of two chronic inflammatory bowel diseases (the other is ulcerative colitis), Crohn's can strike anywhere along the digestive tract, from the mouth the to the anus (hence the colloquial expression 'from gum to bum'). The most commonly affected sites are the ileum (lower part of the small intestine) the colon (large intestine) and the area where the two connect. The mouth, skin, joints and eyes are also commonly involved, and less so the upper digestive tract (esophagus, stomach, and duodenum – or tube leading from stomach to small intestine).

The relapsing and remitting nature of Crohn's is caused by bouts of inflammation that eat away at the digestive tract. Although the exact causes remain a mystery, researchers agree that Crohn's is a multidimensional disease.

The traditional view is that Crohn's is an autoimmune disease, where the body's own immune system turns on the digestive tract, and that the sequence of events leading to this mistaken attack is precipitated by a variety of genetic and environmental triggers. Some researchers think that the immune system becomes intolerant to the normal composition of bacteria (called flora) present in the gut, and in genetically susceptible individuals, this leads to the initial activation of inflammation which then over time becomes chronic. Infectious bacteria, including Mycobacteria, Pseudomonas and Listeria, have also been implicated in the development of this disease.

A genetic component is indisputable: 15 – 20% of individuals with Crohn's have a family member with the disease, and genome-wide analyses have implicated over 70 genetic regions. Possible environmental triggers are high fat diets, obesity, smoking, upper respiratory tract and stomach infections, and non-steroidal anti-inflammatory drugs.

As more and more research comes to light, some scientists are describing Crohn's as an immune deficiency characterized by the impaired function of immune system cells, particularly monocytes and neutrophils, leading to an inability to clear high levels of bacteria or viruses.

Crohn's typically strikes at two different ages: the first is when individuals are in their teens and twenties, and the second in the fifties and sixties. Because the symptoms often overlap with other gastrointestinal disorders, Crohn's can be difficult to diagnose and a gamut of tests may need to be ordered, starting with a physical examination and possibly including colonoscopies, endoscopies, blood tests or x-rays to narrow the diagnosis and assess the level of inflammation.

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Symptoms and Prevention

In what may represent the earliest published symptoms of Crohn's disease, scientists in 1813 documented patients with chronic diarrhea due to an ulcerated intestine. Inflammation, which has become the hallmark of Crohn's, deepens over time during three distinct phases. The initial inflammatory phase affecting the lining (mucosa) brings on diarrhea and pain. As the disease worsens and inflammation deepens, progressively more layers of the digestive tract are destroyed until the inflammation pushes through the lining of the digestive tract and into adjacent tissues. This process is called transmural (or through the wall) inflammation and it leads to the development of abnormal connections (called fistulas) between the inflamed portion of the digestive tract and adjacent tissues or organs. When the disease reaches its chronic and recurrent phase, the digestive tract may narrow (called strictures) to the point of blocking the intestine.

Daily life for individuals with Crohn's is challenging as they may be plagued by symptoms of abdominal pain, cramping, diarrhea, fever, weight loss, rectal bleeding, loss of appetite, joint pain, red eyes, skin rashes, and blood clots. Although symptoms vary considerably from person to person, diarrhea is generally thought to be the most debilitating of all as it causes a considerable reduction in the quality of one's life.

Treatment

Drug therapies for Crohn's target the immune system with the aim of dampening down the inflammatory response and providing respite or remission to patients.

Historically, anti-inflammatory drugs, such as salicylates, have been the mainstay of drug therapy but the verdict is still out as to whether they can affect long-lasting remission of symptoms. Steroids are more powerful anti-inflammatory drugs but they are administered systemically or locally with great caution due to the potential side effects. However, the widespread effectiveness of steroids is limited by the fact that many patients can become resistant to them.

Examples of non-steroid based drugs that are used to control inflammation are azathioprine, 6-mercaptorpurine and methotrexate. Despite the potential side effects, these drugs are useful for maintaining remission in patients who have received steroids or who are steroid-resistant.

In their search for more targeted therapies, researchers have developed monoclonal antibody therapies that target specific parts of the immune system. One of the most widely used is infliximab, a monoclonal antibody that inhibits a messenger molecule called tumour necrosis factor alpha (TNFa). Since TNFa normally stimulates various components of the immune system, the effect is to dampen the immune response and in so doing decrease inflammation in the digestive tract. As with the other drug therapies, this approach also has possible side effects.

Efforts to address the theory that Crohn's may be caused by intolerance to the normal bacteria in the gut have spurred researchers to test a variety of antibiotics. Some have shown no benefit as compared with standard therapy for Crohn's but others are more promising and are being tested further. The potential of using probiotics to restore the balance of 'good bacteria' in the gut is also an idea that is gaining momentum and is being actively explored. New therapies aimed at suppressing different parts of the immune system are testing whether Crohn's is caused by an abnormal immune response to bacteria normally present in the gut.

Despite the panoply of drugs available for treating Crohn's, there is still no cure for this disease. Its chronic nature means that patients are continually dealing with new areas of inflammation that may worsen to the point of requiring surgery. Over time patients might need to have so many surgeries that little of their gut remains intact. Clearly, additional therapies are needed to treat this debilitating disease.

How can stem cells help in the battle against Crohn's?

Rationale for using stem cells to treat

It is known that inflammation is central to the development of Crohn's, but the triggers that start it and keep it going are still being debated. The theories range from autoimmunity, to excessive bacterial load, genetics, environment, or immune deficiency.

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The qualities stem cells possess may be able to help. They can reset the immune system by 1) making new cells 2) regulating the immune system 3) inhibiting inflammation and 4) stimulating tissue repair.

Pre-clinical studies testing stem cells for treating Crohn's have been encouraging and some of the results are being translated to the clinical setting using mesenchymal stem/stromal cells or adipose (fat) derived stem cells, hematopoietic stem cells from bone marrow or blood, or stem cells from the placenta. Each is discussed in more detail below.

Research and clinical directions

Mesenchymal stem/stromal cells (MSCs)

Mesenchymal stem/stromal cells, or MSCs for short, have many attributes: they are easily collected from bone marrow, fat and umbilical cord; can be grown into a variety of different cell types; can modulate the immune system, inhibit inflammation, stimulate blood vessel formation, repair tissue and help stem cells to engraft. One of the most remarkable things about MSCs is that graft rejection rarely occurs when donor and recipient tissues are mismatched. In combination, these characteristics mean that MSCs could potentially be broadly applied to many different diseases.

However, it has not been so easy for researchers to study exactly how MSCs work, partly because they are not present in high numbers but also because it has been difficult to find markers that can tease them out from neighbouring cells. Despite these limitations, researchers have learned that MSCs are crucial for producing factors that construct and maintain the niche that nurtures stem cells in the bone marrow, and a growing number of early clinical trials are demonstrating that MSCs are largely safe, can provide important growth factors and can effectively suppress the immune system.

The proof that MSC therapy could benefit Crohn's patients was first observed in trials using autologous (meaning from the patient) bone marrow MSCs. The patients involved in these trials had active disease but did not respond to any of the current therapies. Enough patients reported an improvement in symptoms that subsequent trials were launched to explore using MSCs from bone marrow in more depth and to test if the same effects could be achieved using MSCs from more readily available sources, such as adipose (fat) tissue.

Although MSCs promise to be a powerful cell therapy for treating inflammatory diseases such Crohn's, many challenges lie ahead. First is demonstrating that these stem cells can work in large patient trials. Second is to understand the mechanisms that underpin how MSCs work, and third is to figure out if administering MSCs in multiple doses or in combination with other immunosuppressant drugs can maintain the health of patients with Crohn's in the short and long term.

Adipose tissue derived stem cells for treating fistula

Adipose (fat) tissue derived stem cells (ASCs) have two qualities that make them a promising new candidate for treating Crohn's: they are regenerative and anti-inflammatory. ASCs make a variety of different cell types (fat, bone, cartilage, muscle, epithelial), and also promote the formation of new blood vessels (angiogenesis). Like MSCs, ASCs can also modulate the immune system. The connection between MSCs and ASCs is curious: MSCs are found in fat tissue, and some researchers think that ASCs are MSCs.

Adipose tissue, obtained during liposuction procedures from the layer of fat that lies just under the dermal layer of skin, contains a variety of cell types including the sought after stem cells.

The first clinical trial that proved that ASCs could work for treating Crohn's involved nine patients with various types of fistula (abnormal connections between adjacent tissues and organs). In Crohn's the most common type is a connection between the anal canal and the urogenital tract or the skin around the anus. The catastrophic result of this unwanted connection is that feces are released out an opening other than the anus. Surgical interventions and medicinal therapies fall short because they are unable to provide complete healing or prevent recurrence. In addition, incontinence is an all too often side effect and this drastically reduces the quality of life for patients.

During the trial patients experienced no adverse effects and no rejection of cells. Eight weeks after autologous (from

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the patient) ASCs were injected into the fistulas, they closed in six of eight patients and partially closed in two patients. The success of this and other early trials paved the way for researchers to launch additional studies exploring the role of ASCs to treat fistulas in Crohn's and other diseases, and the outcome has been so positive that ASCs were granted approval to be marketed in Europe and the United States, under the orphan drug status regulations, for treating fistulas.

The next steps are already underway. Larger patient cohorts are being enrolled and researchers are delving deeper into the parameters of treating Crohn 's with ASCs. As an example, they are testing high versus low doses of autologous ASCs and whether allogeneic (from a donor) ASCs work as well as autologous ASCs. They are also comparing whole liposuction tissue from donor to ASCs expanded from fat tissue. Preliminary studies seem to suggest allogeneic ASCs are well tolerated without adverse effects, and that whole tissue works just as well.

Most importantly, long-term follow-up studies are assessing the longevity of ASC therapy to provide complete healing of fistulas and prevent their recurrence in patients. As these types of trials proceed, researchers are at the same time investigating the mechanisms of action of ASCs to learn how they promote healing – by suppressing inflammation, making new epithelial cells, or both.

Hematopoietic stem cells

Hematopoietic (blood-forming) stem cells, or HSCs for short, have the longest history of clinical use. The first hematopoietic stem cells transplant (HSCT) was performed in the 1950s in an attempt to cure a lethal form of leukemia. HSCs make all the red and white blood cells in the body, so the rationale was to wipe out the leukemic cells and bone marrow with radiation and then to transplant normal HSCs to rebuild the blood and immune systems. After many years of learning about donor-recipient matching and how to minimize graft-versus-host disease, HSCT has become a standard treatment for many different disease conditions.

There are two methods for transplanting hematopoietic stem cells: autologous (stem cells from the patient) and allogeneic (stem cells from a donor). In either case, the stem cells harvested may undergo manipulation in the laboratory prior to being transplanted. The advantage of using autologous HSCT is that there is no possibility of the graft being rejected and therefore no need for immunosuppressive drugs. However, not all patients are candidates for this approach, perhaps because of age, weak health, or bone marrow disorders. For them, donor (allogeneic) stem cells transplants have proven benefits. Although the ideal strategy is to 'match' a donor graft as precisely as possible to the recipient's constitution, most matches are imprecise and the transplant procedure will require the addition of prolonged use of immunosuppressive drugs to control graft-versus-host disease (GVHD).

There was an element of luck that led to the application of hematopoietic stem cells to treat Crohn's disease: leukemia patients with Crohn's got better after being treated with allogeneic bone marrow transplants.

In recent years very small clinical trials have evaluated autologous HSCT and are exploring different approaches for mobilizing HSCs to locations such as peripheral blood, where stem cells are more easily collected. But if the genetic component of Crohn's disease affects hematopoietic stem cells, then transplanting patient-specific (autologous) stem cells could eventually result in the same inflammatory condition. In this situation, using allogeneic stem cells would be a better route, especially if the donor could be screened to rule out a family history and other predisposing genetic elements of Crohn's.

Very preliminary clinical trials are testing whether the allogeneic approach could be useful in patients with severe, therapy resistant Crohn's. Researchers are making great efforts to minimize the chances of graft-versus-host disease by using matched siblings as donors, removing dangerous immune cells (T cells) from the donor graft, and not destroying the patient's bone marrow completely prior to the transplant. Taken together, this procedure is called a mini-transplant and the intended goal is to increase survival and remission of symptoms in patients with severe Crohn's disease.

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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 Crohn's.

- Crohn's and Colitis Foundation of Canada: http://www.crohnsandcolitis.ca/
- GI Society & CSIR: http://www.badgut.org/information-centre/a-z-digestive-topics/crohns-disease/

Selected Reading List

- Allogeneic Stem Cells Derived From Lipoaspirates for the Treatment of Recto-vaginal fistulas Associated to Crohn's Disease (ALOREVA) NCT00999115.
- Autologous Stem Cell Transplantation for Crohn's Disease, NCT00692939.
- ASTIC Autologous Stem Cell Transplantation for Crohn's Disease NCT00297193.
- Report of the Expert Advisory Panel on Prochymal® http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapport-eng.php
- Follow-up Study of Autologous Adipose-derived Stem Cells (ANTG-ASC) for the Complex Fistula (ANTG-ASC-211) NCT01623453.
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