Stem Cell Treatment for Achalasia?

Talk on 22 January 2019 by Conor J. McCann, Guts UK Derek Butler Fellow, Stem Cells and Regenerative Medicine, UCL Great Ormond Street Institute of Child Health

Conor had done his PhD in the transplantation of Insterstitial Cells of Cajal in the gut, and was interested in Stem Cell Therapy for Upper GI Disorders.

What is achalasia and what are the possible causes?

"A condition in which the muscles of the lower part of the oesophagus fail to relax preventing food from passing into the stomach".

The word Achalasia was coined in the early 20th century and comes from Greek, meaning 'absence of loosening [of oesophageal muscles]'

Achalasia could sometimes be caused by a virus, which can create inflammation, plus there could be a genetic susceptibility for some people. This assault on the system by the virus could have inhibited or destroyed the neurons (the relaxatory nerves – nNOS) which in turn led to digestive muscles not working properly, leading to achalasia. Chickenpox and cold sores (Herpes) were possibly implicated.

The gut is a muscular tube and along the gut there are muscles which cause the contractions and relaxation which control the way in which food is propelled through the digestive system (peristalsis). There is a large nerve network which runs along the entire length of the gut. Before birth, these nerve networks enter the digestive tract of the embryo and should travel through the whole length of the gut. But sometimes this process is incomplete, leading to gaps which cause parts of the gut to fail to work properly because of loss of nerve cells. Conor's research was trying to establish whether these lost nerve cells could be replaced.

Peristalsis and Motility

The gut has clusters of cells which control relaxation and contraction of the muscles, and in order to get this movement, you need electrical-type impulses to 'instruct' one section of muscles to relax and the next set of muscles to contract. It is a repeat cycle as food progresses through the system. Contraction is controlled by acetylecholine + nerves; relaxation by nNOS + nerves.

nNOS neurons and Gut Disease

NNOS neurons control muscle relaxation. When these have problems, it can be the cause of gastro pains, achalasia in the oesophagus, Hirschsprung disease (where a section of the bowel is unable to process / tranit faecal matter in babies), anal incontinence, intestinal pseudo-obstruction, and constipation (intractable or slow transit).

Replacing lost nerve cells

It is possible to obtain human gut nervous system stem cells from gut mucosal biopsies.
The steps for implementing stem cell transplantation would be:

1. Need to source stem cells + healthy donors & patients
2. Harvesting of cells
3. Enrichment or selection of stem cells
4. Culture
5. Manipulation/gene therapy
6. Propagation/directed differentiation
7. Collection and preparation of cells
8. Transplantation to patients

The research involved mice at present. With the mice, there have not been detrimental effects. In due course this may extend to, perhaps, rabbits and/or pigs, and eventually to humans. The research has taken stem cells from healthy mice, cultivated them and transplanted ENSC (enteric neural stem cells?) cells within nNOS neurons into diseased mice. The process involves the scratching of the surface of the gut, and placing balls of cells which will then stick to the surface. There has been evidence that these stem cells can then grow and that gut functions like transit time and motility are improved as a result.

This study provided the first evidence that stem cell transplantation can rescue gastro intestinal function within a diseased model and that diseased sections of the gut can be rescued by this method. This has so far been undertaken in part of the intestines, and it is planned to try to apply the same principle to an oesophagus shortly. There is potential for the body to attack the transplanted cells, however, as an auto-immune response.

The research is examining stem cell therapy rather than causes of conditions like achalasia

<u>Future developments</u>

There would be no clinical treatment available for at least ten years. Other groups around the world are working on other cell therapies; best practice is being shared between different research bodies

It seems like climbing Mount Everest, and still being near base camp! The climb upwards towards a clinical treatment would involve:

1. Identification of neural crest patterning in ENS (enteric nervous system?)
2. Identification of ENSC (enteric neural stem cells?)
3. Isolation of ENSC from mouse and human gut
4. Successful ENSC transplantation in normal gut
5. ENSC rescue of gut function in colon
6. Demonstrate rescue in other gut regions
7. Demonstrate rescue and safety in large animals
8. First in human trials
9. First in patient trials
10. Clinical trials

11. Licensed therapy (the Everest summit!)

As progress is made, the theoretical science arguably becomes easier; but the regulatory environment becomes more difficult and demanding.

Conclusions and discussion

Research has shown that some cell transplantation can rescue gut function.
Stem cell therapy may allow for the development of therapies for other diseases, including achalasia.
Transplantation studies to oesophagus are currently under way.
It might be possible to transplant the cells by endoscopy.
GUTS UK have been very helpful in funding the research.
Potential for DNA and genetic testing of a pool of volunteers are available from the achalasia group which would create an attractive research proposition from a patient perspective.
Stem cell therapy might be one of the ways to treat achalasia in the future?
Genome and genetic treating dispositions is slightly different from a condition being improved by stem cell therapy.
At the moment, surgery is the best option for many.
Theoretically, stem cell research could work on someone who has been operated on previously.
Theoretically one could use genetic engineering, but this is very uncertain at present.
Quite a lot of rare diseases have only 10-15 patients; achalasia is not so rare as that.
We would need people to carry out other research to build on Conor's work. Can take 12 - 18 months to set up research projects
Viruses can reside in nervous functions for many years, eg herpes cold virus. There is a window of development which is critical. In pregnancy, viral infection could lead to disruption.

There was unanimous support for Conor's research and readiness to help his project. Donations towards his research could be forwarded to GUTS UK. Website donations would be applied by GUTS UK across all their research projects. Individual cheques with letters might be directed and potentially designated towards achalasia research but this is not completely certain. GUTS UK are based at 3 St Andrews Place, Regents Park, London NW1 4LB.

Conor was thanked most warmly for his really interesting talk.

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