Stem cells show promise – but they also have a darker side

May 25 2017, by Jill Johnson

Credit: AI-generated image

Everyone seems to be excited about stem cells. Their excellent promise as a treatment for a range of diseases and injuries mean almost guaranteed coverage for research. While some types of stem cells are already being used in treatment – for treating diseases of the blood and leukaemia, for example, multiple sclerosis and problems in the bone,

skin and eye – there's still a lot of hype and exaggeration, with some even selling empty promises to seriously ill or injured patients.

There are many different types of stem cells in the body and they have varying abilities. When most people think of stem cells, it's often of embryonic stem cells, which have been controversial for ethical reasons, or their closely related cousins, induced pluripotent stem (iPS) cells, adult cells that have been reprogrammed to acquire stem cell-like properties. As the word "pluripotent" suggests, these stem cells have the capacity to transform into any cell type in the body, with the exception of egg and sperm cells.

There are other types of stem cells, however, that are considered to be "multipotent" – not quite as diverse in their abilities as pluripotent stem cells, but still able to turn into different cell types when stimulated in just the right way. These are mesenchymal stem cells, or MSCs, which have the capacity to differentiate into the cell types that give our bodies strength and structure: bones, cartilage, fat, muscle and tendons.

Therapies using MSCs are being touted as a great new hope for the treatment of serious chronic diseases such as colitis, diabetes, arthritis, cirrhosis, kidney disease, heart disease, chronic obstructive pulmonary disorder – the list goes on and on. In fact, there are currently over 700 MSC-based clinical trials, either ongoing or completed on the clinicaltrials.gov register.

It's clear why there is so much interest in these cells. But can they really fulfil their promise – and do they have the capacity to harm as well as help us?

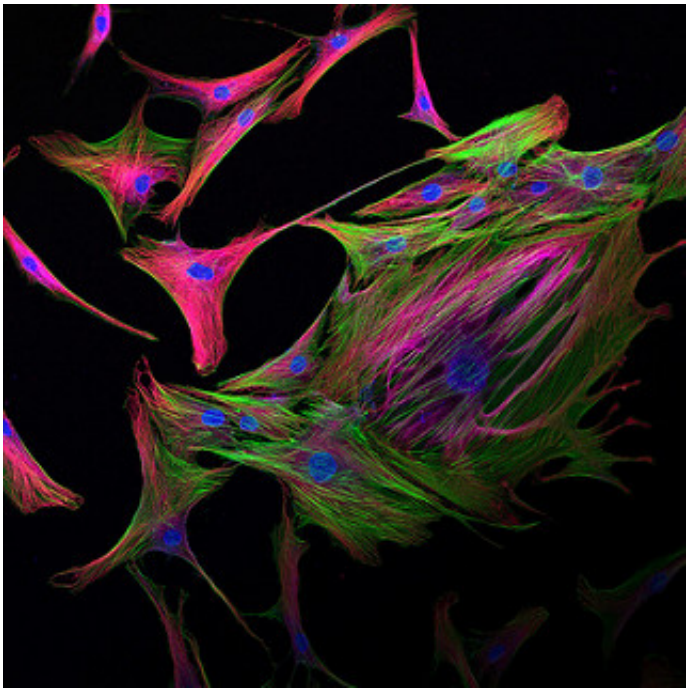
Regeneration and healing

There are two major promises that have been made when it comes to the

use of MSCs in human medicine: their "regeneration potential", that's their potential to rebuild damaged tissues, such as bone, spinal cord and heart tissue; and their "healing properties", which can reverse damage to diseased organs – for example, in arthritis and following organ transplantation.

The regenerative potential of MSCs has been studied since the late 1960s. In one of the earliest experiments with these cells, Alexander Friedenstein and colleagues showed that transplanting bone marrow to a different site of the body led to bone formation, which indicated that at least some cells in the bone marrow are able to change into bone cells – even in locations where bone would not be expected to grow.

Since then, researchers have worked out different signals that tell MSCs to change into specialised cell types. For example, the growth factor TGF-β can induce MSCs to turn into cartilage cells, which would be very helpful in repairing cartilage in arthritis sufferers.



Mesenchymal stem cells can differentiate into bone, cartilage, muscle and fat

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Studies are ongoing to determine what signals are needed to transform MSCs into bone to accelerate the healing of fractures, or into cardiac muscle cells to repair the heart after a heart attack. The POSEIDON and PROMETHEUS trials tested the benefits of delivering MSCs directly to the heart after a heart attack. Promisingly, patients who received MSCs in these trials had better heart function and less scar tissue.

Even more ambitious studies are looking into repairing whole organs, such as the lung, liver, and kidney, which are very susceptible to scar formation (fibrosis) in cases of longstanding inflammation. Needless to say, many of these treatments are still at very early stages, but progress is being made.

The healing properties of MSCs, however, are less clear. MSCs have the ability to move to sites of injury and secrete various factors that promote cell growth, reduce cell death and induce the in-growth of blood vessels in damaged tissue – all good things that promote healing. Although testing this aspect in chronic disease is still in the early stages, preliminary studies suggest that MSCs are capable of calming inflammation in chronic autoimmune diseases such as rheumatoid arthritis andmultiple sclerosis.

Scar-forming cells

One aspect of MSC biology that doesn't seem to be sufficiently considered when it comes to using these cells for the treatment of human disease is the ability of MSCs to transform into cells we don't want – scar-forming cells called myofibroblasts. A number of studies in mouse models of lung, liver and kidney fibrosis have shown that the MSCs that

normally reside in these tissues – called "pericytes" – quite readily transform into myofibroblasts and produce scar tissue, to the extent that organ function is compromised.

This phenomenon should give us pause, especially when considering the delivery of MSCs into a badly damaged and inflamed part of the body, such as an arthritic joint or the lung of an emphysema patient.

MSCs are exquisitely responsive to their environment, and if these cells are administered to a badly inflamed organ that in turn induces fibrosis, chances are the injected MSCs will transform into myofibroblasts and worsen tissue damage. Clearly, more work needs to be done to find out what signals MSCs will respond to under these conditions, and how these signals will change their biology, for better or for worse.

One of the most important aspects of stem cell treatment that still needs to be considered is their source: will they be taken from the patient who will receive them (not particularly useful for diseases with a strong genetic component) or from a consenting donor (with the added risk of the transplanted cells being rejected)?

Then there is the route of delivery: should MSCs be injected right into the injured/diseased tissue, or administered into the blood and then allowed to move to areas where they are needed? We also need to think about how effective these cells will be, how many cells need to be delivered to have an effect, and how long they stick around in injured tissue. Answers to all of these questions will be needed before we can safely use MSCs in treatment.

Despite the promise, then, there are a number of barriers that need to be surmounted before MSC therapy is a viable treatment and readily available to patients in the clinic. Along with working out the best sources of these cells, the ideal method of delivery, and harnessing their

ability to reduce inflammation, we also need to be concerned about controlling the fate of MSCs after they have been administered in order to get the best possible benefit of these cells while not causing further harm.

This article was originally published on The Conversation. Read the original article.

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