Adult stem cells for the treatment of adults

Scientists and physicians at the Medical Hospital II in Tübingen are investigating adult stem cells and their potential for therapeutic applications. They are pursuing a two-fold strategy: The experimental laboratory deals with basic findings, the clinical stem cell laboratory focuses on applications.

For many decades, a number of departments at the University Hospital in Tübingen have been exploiting the regenerative potential of stem cells for the treatment of leukaemia patients. At the beginning of the 1990s, the first extensive register for donor stem cells derived from bone marrow and blood was set up. This led to the establishment of the German Bone Marrow Donor Centre (DKMS), which is the largest stem cell donor data bank in the world.

Unfortunately it is still not possible to destroy just leukaemia cells in patients undergoing high-dosage radiation or chemotherapies. Such treatment always also affects all haematopoietic cells, including healthy ones. The organism is not viable without haematopoietic stem cells, which continuously produce immune system cells.

Destroying disease-causing cells and regenerating healthy cells

A suitable method of restoring blood generation (haematopoiesis) is the transfer of stem cells from the bone marrow or blood from a donor. Previously, the tissue characteristics of donor and recipient had to be a virtual 100% match to ensure that the recipient did not reject the foreign cells. It is now a different story. Scientists at the University Children's Hospital in Tübingen succeeded in developing an efficient method that enabled them to give children stem cell transplants from their parents or siblings (haploidentical donors). The method relies on the removal of incompatible cells from the blood that has been donated (see "Stem cells – tailor-made transplants", see link in the top right-hand corner).

The method is also used at the Medical Hospital II and has been adapted for use in adults. Dr. Robert Möhle, head of the experimental stem cell laboratory at the UKT, and Dr. Christoph Faul, head of clinical stem cell transplantation, described the obstacles that had to be overcome in order to be able to transfer the method to adults. "The stem cell dosage, which is vital for the success of a haploidentical transplantation, is calculated on the basis of the recipient's body weight. In children, the doctors use 10, 20 or even 30 million stem cells per kilogram body weight. In terms of quantity, this is difficult to achieve in adults because an extremely large amount of donor material would be necessary. However, we found out that a correct preparation of the donor cells reduces the amount of cells required for the regeneration of haematopoiesis to six million per kilogram body weight."

Current members of the experimental stem cell laboratory at the UKT: Dr. med. Robert Möhle, Dr. rer. nat. Gabriele Seitz and Andreas Lächele (MTA). (Photo: Medical Hospital II, UKT)

More therapeutic options with haploidentical donors

Now that this method has been successfully adapted for use in adults, the question might well be asked as to why doctors are still looking for matching donors. Dr. Faul explains why: "There are two different issues. Haploidentical cells are used in cases when no suitable donors are available. We first look for suitable donors among the patient's relatives. If we are unsuccessful, we look for suitable donors in the worldwide registers. If this turns out to be unsuccessful as well, then we will use donors from the patient's relatives that do not fit or only match 50% (haploidentical) of the recipient's tissue features.

Working at the clean bench in the clean room of the stem cell laboratory. (Photo: Medical Hospital II)

In cooperation with other UKT departments, Möhle and Faul are investigating the regeneration and regulation of haematopoiesis. They also hope to find out why leukaemia recurs to a lesser degree in patients transplanted with allogeneic stem cells than in patients who only undergo chemotherapy. "We are slowly coming closer to understanding how the therapeutic effect occurs," said Möhle explaining that the composition of the transplant is of major importance. "The regeneration of haematopoiesis depends mainly on the amount and quality of the stem cells," said Faul, also emphasising the important role of other cell types that are isolated along with the donor blood for the long-term therapeutic effect and the prevention of recurrences.

The immune system is key in this process

The natural killer cells of the donated blood are what is particularly required. These cells continue their work in the recipient's blood as part of the immune system and assist the therapy. T-lymphocytes, which also attack leukaemia cells, are not initially required in haploidentical transplants and are therefore removed from the transplant in the laboratory. They must regenerate slowly so that the transplant is not rejected. The researchers are looking for other cells and factors that might have a potential positive therapeutic effect. "In our clinical studies we are investigating how we are able to better use and regulate immunological components," said Faul.

Dr. Christoph Faul heads up stem cell transplantation at the Medical Hospital II of the UKT. (Photo: Medical Hospital II, UKT)

The scientists hope to eventually be able to generate immune cells that can take over specific tasks in the recipient. For example, they might be able to attack viruses that could spread when the immune system is destroyed following chemo- or radiotherapy. "There are T-lymphocytes that are active against adenoviruses or cytomegaloviruses," said Faul. Such cells are produced in the laboratory. Cultivated T-lymphocytes are stimulated with viral constituents. Particularly sensitive cells are kept in culture and prepared for transplantation.

Mobilisation, isolation and use of stem cells

Another approach involves the preparation of autologous stem cells prior to a high-dosage therapy. The patient receives cytokines which leads to the mobilisation of as many stem cells in the bone marrow as possible. Once an increased amount of stem cells is circulating in the blood, they can be isolated in a procedure known as leukapheresis, frozen and returned to the patient after high-dosage therapy. This strategy protects the stem cells from the damaging effect of the therapy and the haematopoietic system of the patient is able to self-regenerate. The scientists have also made promising advances in this field. "Stable haematopoiesis develops approximately two weeks after transplantation," said Faul.

It would be even better if it were possible to propagate the stem cells outside the body and return them to the patient for regeneration. However, this is still associated with many problems and no clinical benefit is yet achievable despite the addition of growth factors," said Möhle. The lack of success in this field was one reason why the team abandoned the field of stem cell expansion a few years ago. "It is far more important to understand how stem cells are mobilised and why they are able to return to the bone marrow from the blood," said Möhle.

Stem cell transplants are thawed with this device (Barkey Plamatherm). (Photo: Medical Hospital II, UKT)

Focusing on the nature of stem cells

The team is now concentrating on the characterisation of stem cells. "For example, it is still not known how human stem cells can be reliably differentiated from other cells," said Möhle who hopes that the results will eventually contribute to the ability to completely regenerate tissue and generate different cell types. In this particular field of research, Möhle and Faul are working together with Dr. Hans-Jörg Bühring, who is head of the stem cell characterisation work group. Bühring is constantly looking for unknown surface structures that might enable us to better define stem cells," said Möhle. The researchers are not only investigating haematopoietic stem cells but also mesenchymal stem cells that can differentiate into fatty, cartilage, tendon or muscle cells. "A lot less is known about mesenchymal stem cells than about haematopoietic stem cells. However, we are able to cultivate them and they also seem to have immunoregulatory effects," said Faul who, along with his colleagues from Tübingen, is working on the characterisation of these cells at the same time as looking for clinical cooperation partners.

leh - 3 April 2007

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