Somatic stem cells and development

The sources of regeneration

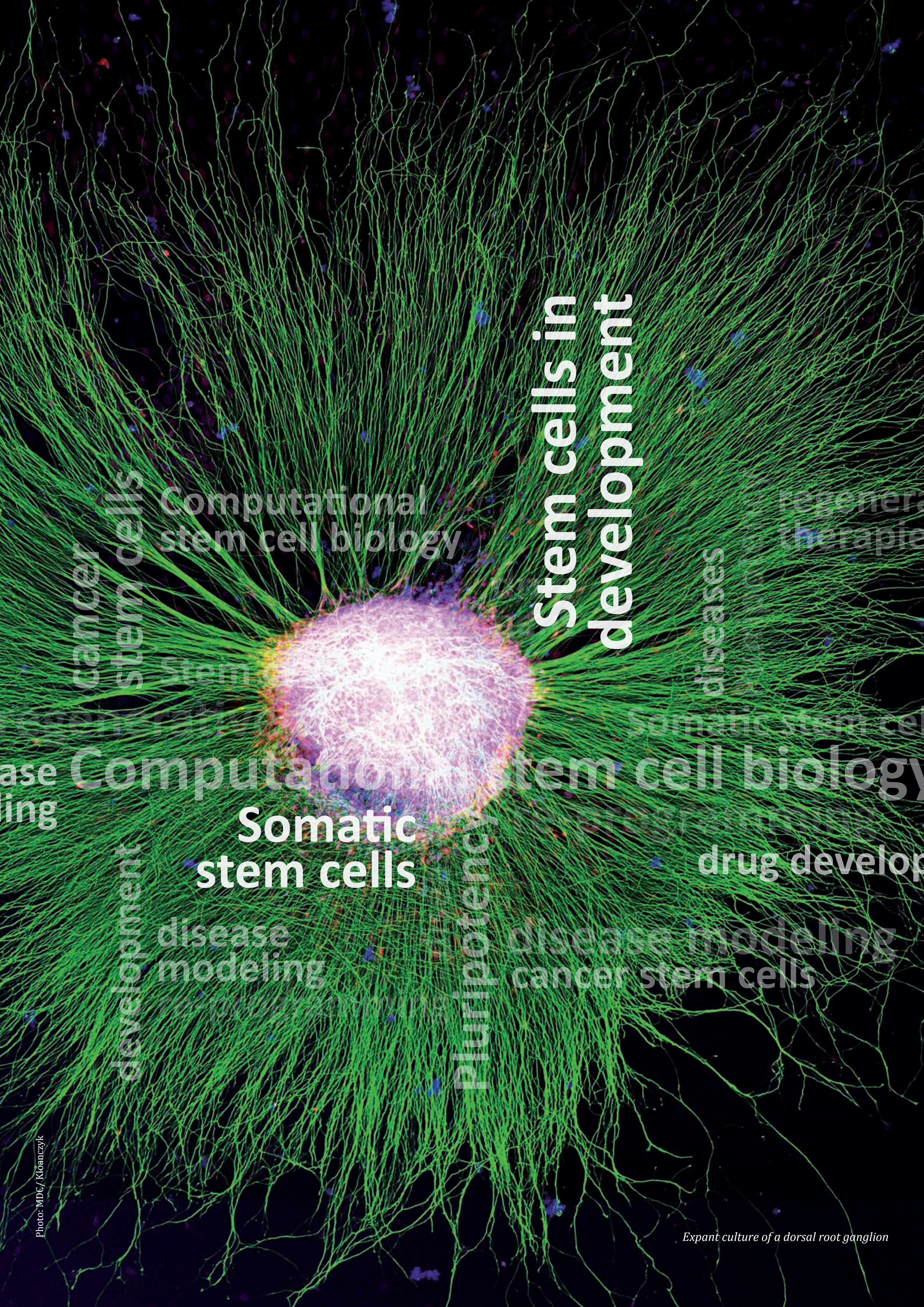
Somatic stem cells are the driving force for growth and regeneration. When there is deterioration and injury, they replenish the body with new cells. Germany has a strong tradition in developmental biology and biomedical science specialized in the study of tissue stem cells. Using model organisms, researchers explore molecular and cellular processes that provide the body with remarkable self-healing abilities. A large number of specialists in Germany are dedicated to improving our understanding of the complex nature of blood stem cells. The GSCN working group is aimed at ensuring that this expertise continues to grow together.

Adult stem cells represent an indispensable reserve for tissues and organs, making them of major interest to developmental biologists. Traditionally, Germany has a strong tradition in this discipline; including a Nobel prize for the pioneering work of German developmental biologists Hans Spemann and Christiane Nüsslein-Vollhard. The field is institutionally anchored in research organizations such as the Max Planck Society, the Helmholtz Association, the Leibniz Association, the Fraunhofer Society, and numerous universities. German laboratories have been a major source of our understanding of regeneration processes and the biology of somatic stem cells. This was emphasized at the first annual conference of the German Stem Cell Network (GSCN), where the majority of presentations came from scientists in this field of research. Another factor has been the legislative situation, which only permits work involving human embryonic stem (ES) cells to be carried out using imported lines, leading many researchers to focus on somatic stem cells instead.

Shedding light on fundamental mechanisms of regeneration requires a detailed understanding of their natural functions. Here, researchers have focused on numerous animal species with incredible regeneration abilities, namely flatworms, fruit flies, fish, amphibians and mice, all of which are common model organisms for developmental biologists working in Germany. Elly Tanaka uses the Mexican axolotl salamander, which is renowned for its ability to regrow fully functional limbs. Tanaka works at the DFG Research Center for Regenerative Therapies Dresden (CRTD) and is one of the initiators of the GSCN working group 'Somatic stem cells and development'. Tanaka and her laboratory have already uncovered some of the reasons for the axolotl's regenerative abilities.

Model organisms with fascinating abilities

One finding: In contrast to previous assumptions, an amputation site does not give rise to a clump of pluripotent stem cells but a mixture of progenitor cells. They can divide despite the fact that their developmental potential is already restricted. "Both stem cell activation and dedifferentiation play a role in the regrowth of limbs," says Tanaka. How are stem cells activated in the tissue following an injury, and how are specialized cells reprogrammed to become progenitor cells? To answer these questions, Tanaka and her team are searching for



Expant culture of a dorsal root ganglion

Axolotl

key molecules that give the starting signal for the regeneration process. The Dresden-based developmental biologists are also taking a detailed look at other mechanisms and aim to clarify the commands that cause progenitor cells to form a specific cell type.

Setting sights on muscle stem cells

Basic researchers also want to understand how to induce, facilitate and regulate regenerative processes. The experiments are motivated by the assumption that the molecules that are responsible have close relatives in humans that might also be subject to activation. This is the goal of Thomas Braun, Director of the Max Planck Institute for Heart and Lung Research in Bad Nauheim. Braun, co-initiator of the GSCN working group, is concentrating on satellite cells: adult stem cells in skeletal muscle tissue. “We have found important factors that regulate and activate the self-renewal of these stem cells,” says Braun. A particular focus of the Max Planck researchers is a muscle that is typically known for low regeneration abilities: the heart. Braun’s team has identified a population of stem cells in mice that can contribute to the renewal of heart muscle cells. Some evidence suggests that in stressful situations, new heart muscle cells can “rewind” their development program and thus regain the ability to divide. These ‘dedifferentiated’ heart muscle cells are similar in several respects to somatic stem cells. Now the Max Planck researchers have succeeded in identifying the genes required for this process. “In principle, the mammalian heart is in a position to initiate regeneration processes, although under normal circumstances it is not sufficient to cure heart damage,” says Braun. The objective now is to find means of stimulating the formation of new heart muscle cells using cardiac stem cells.

The German research landscape

Researchers in Germany are actively exploring the biology of stem cells in almost all tissue types in animals, humans, and even plants. The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) is supporting specific collaborative projects for basic research into stem cells, for example as part of the activities of the special research fields SFB 655 in Dresden and SFB 873 in Heidelberg. Funding from the Federal Ministry of Education and Research (BMBF) is particularly aimed at application-oriented research. At the European level, German stem cell researchers are involved in consortia that are financially supported by the European Commission. The progress of these projects to date are a testament to the dynamism and expertise of stem cell research in Germany.
The following overview highlights just a few of the core areas.

Stem cells in the blood

The blood – a rich source of somatic stem cells – is an important topic of stem cell research. A number of working groups across Germany focus on mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). These efforts are aimed at tapping the high potential of such cells for clinical applications (see the section ‘Stem Cells in Regenerative Therapies’).

Research teams headed by Anthony Ho and Andreas Trumpp in Heidelberg and Albrecht Müller from the University of Würzburg are studying the genetic and epigenetic profiles of MSCs and exploring their unique properties for regenerative therapies. Work by Claudia Waskow from the Center for Regenerative Medicine in Dresden CRTD led to the discovery of several different forms of blood stem cells, and the role of DNA repair in HSCs is under scrutiny by Andreas Trumpp and Michael Milsom in Heidelberg. Researchers led by Gerd Klein at the University Hospital Tübingen and Cornelia Lee

Photo: Wikimedia CC, Axolotl in der biologischen Lehrsammlung der Universität Konstanz, Faldrian

Thedieck from the Karlsruhe Institute of Technology focus on mechanisms at work in the hematopoietic stem cell niche. This niche is also the subject of investigation of a dedicated DFG Research Group (FOR 2033)coordinated by researchers in Munich. Cord blood also exhibits great potential as an alternative source of HSCs. In a BMBF joint project, researchers at RWTH Aachen University, the University of Würzburg and MHH Hannover are working on ways to improve the expansion of these versatile cells in the laboratory. At the Institute for Transfusion Medicine at the University of Essen, several research groups have joined together in a larger team under the direction of Peter Horn. Groups led by Hannes Klump and Bernd Giebel are focused on the molecular basis of HSCs and other stem cell populations.

Regeneration in organs

Heiko Lickert and his team at the Helmholtz Center Munich are studying regulators that play a key role in the formation of pancreatic β-cells. Such factors are essential for the production of insulin-producing cells and thus aim to provide a basis for a future cell replacement therapy for diabetes. These regulators are likewise a priority for Francesca Spagnoli at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin-Buch. She is investigating how liver cells can be reprogrammed into β-cells. The laboratories of Walter and Carmen Birchmeier at the Berlin MDC are specialized in the development biology of skin- and muscle stem cells and other topics.

Numerous neurobiologists in Germany are investigating adult stem cells in the brain. In recent years, they have made vital contributions to the understanding of cellular plasticity of the brain – the ability to form new neurons in the adult organ. Magdalena Götz, at the Helmholtz Center Munich, is studying neural stem cells in the forebrain that are known to play a role in so-called adult neurogenesis. Likewise, Ana Martin-Villalba at the Heidelberg DKFZ is occupied with neural stem cells in the brain and how they are locally reactivated after injury. A research focus for Gerd Kempermann at the CRTD in Dresden is adult neurogenesis and how this is influenced and triggered by behavior patterns.

How stem cells age

Even stem cells age, meaning that a tissue's ability to regenerate gradually declines over time. The phenomenon of stem cell aging is the specialized subject for a number of research groups in Germany. The team of Karl Lenhard Rudolph at the Leibniz Institute for Age Research in Jena is studying the genetic defects that cause ageing in stem cells of the hematopoietic system. A related theme is the molecular mechanisms of stem cell aging, which are thought to promote tumor development. Hartmut Geiger and his team at University Hospital Ulm are exploring signaling pathways and molecular mechanisms that lead to aging in blood stem cells. If stem cells could be rejuvenated, it could boost the regeneration process.

Ideas for joint research projects

Research activities in the field of somatic stem cells in Germany are extremely multifaceted. The GSCN working group has been established with the objective of defining common interests and facilitating information exchange through improved networking opportunities. "A number of people in the working group have already come together to form a new joint research project," says developmental biologist Thomas Braun. Although the researchers are interested primarily in fundamental mechanisms of stem cell biology, their insights will clearly improve know-how in the handling of cells in the laboratory. Learning to optimize recipes for the generation of specialized cell types in cell culture will provide a decisive impetus for the cell replacement therapies of tomorrow.

Text: Philipp Graf

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