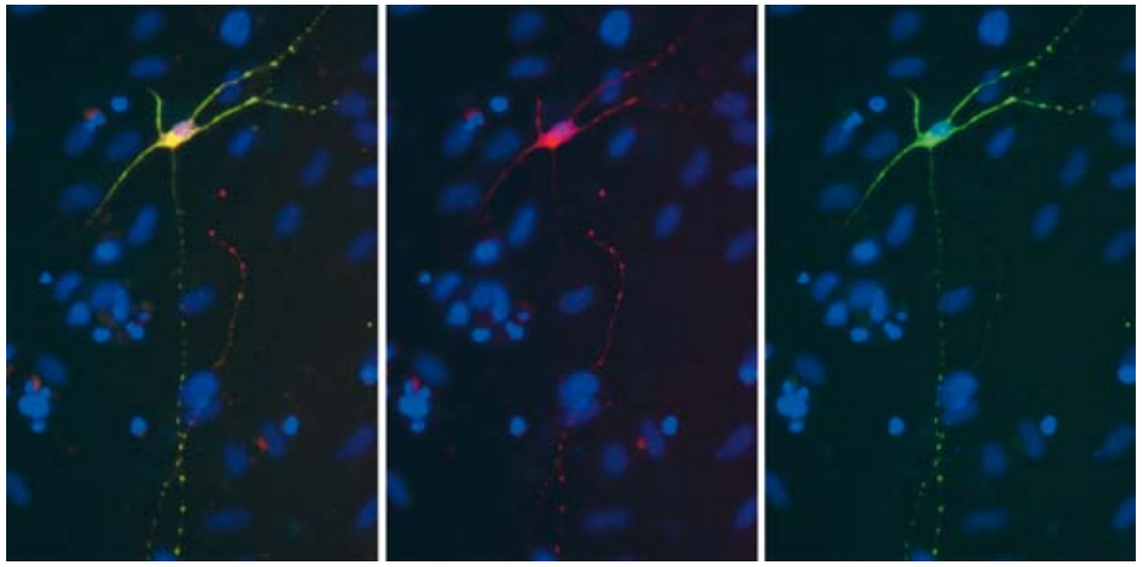
BY NATALIE VON DER LEHR

Cellular genetic makeover

The Nordic countries are well represented within the rapidly developing field of stem cell research. Two recent reports, one in Nature and one in PNAS, highlight the possibilities and challenges of this exciting field.



iN cell stained for two markers expressed in nerve cells (MAP2 in red and Synapotphysin in green).

Induced pluripotent stem cells (IPS cells) are stem cells that are derived from mature differentiated cells by reprogramming. They are promising for therapeutic applications, for example to allow the transplantation of nerve cells to patients with neurodegenerative diseases such as Parkinson's.

When the first reports of IPS cells reached the scientific community in 2008, Timo Otonkoski, a professor at the University of Helsinki in Finland, together with his research team set out to both repeat the experiments to make their own IPS cells and to characterize the cells that arose from the reprogramming method. The results of this study were published in Nature in March.

A SURPRISING FINDING

Otonkoski and his team used single nucleotide polymorphism (SNP) analyses to characterize a large amount of IPS cells and found that reprogramming is associated with inherent DNA damage. This damage was detected by genetic rearrangements and alterations of copy number variations – regions of the DNA that is either deleted or amplified on certain chromosomes. The team could also show that these alterations were due to de novo mutations, meaning that they arose during the reprogramming process rather than being inherited from the parental cells.

"The generation of IPS cells is not the most natural event and I am actually surprised that there are not more genetic alterations," says Timo Otonkoski.

Some of the mutations were lost when the cells were grown in culture for a couple of weeks, implying that they were selected against. Some mutations are however beneficial, but such cells can give rise to tumors and can thus not be used for therapy.

"Most researchers have long been aware of these problems. There is a clear need for a better understanding of the reprogramming process. This has to be developed further and evaluated carefully before we can talk about therapeutic use."

Generation of IPS cells is on the other hand a powerful tool for studying the pathogenetic mechanisms behind a disease in a particular patient. IPS cells can be derived from a skin biopsy and turned into a particular cell type for functional analysis.

"We can now study brain cells while the patient is still alive. That way we can screen for treatments that these particular cells respond to. In this context a few mutations are not a big issue," he explains.

TRANSDIFFERENTIATION

Another field that is just opening up is that of transdifferentiation – transforming one cell type into another without going through an IPS cell stage. During the past year researchers have been able to produce heart, blood and liver cells from human skin cells. Malin Parmar's research group at the University of Lund in Sweden had focused on the generation of nerve cells for a long time and picked up on the report that it was possible to differentiate skin cells into neurons in mice. The results of the efforts to do the same with human skin cells were recently published in PNAS.

In addition to being able to generate functional neurons from human fibroblasts, Malin Parmar and colleagues managed to identify the factors that are necessary to generate dopamine neurons, the type of cells that are affected in Parkinson's disease. Apart from expressing the ordinary triple gene-cocktail Ascl1, Brn2 and Myrt1l that was previously found to be necessary for the conversion of mouse fibroblasts into neurons, additional expression of Lmx1a and FoxA2 was found to give rise to cells with the typical morphology of cultured dopaminergic neurons. In order to identify exactly these two genes a cocktail of ten genes, all of them involved in midbrain patterning and the specification of dopamine neurons, was used as the starting point. When the result was positive for development of dopamine neurons Malin Parmar's team took away genes one by one until they were left with the minimum amount required.

"We were really surprised that the cells were so easily reprogrammed. We have tried the same procedure previously on other stem cells without results," says Malin Parmar.

A similar study from the research group of Marius Wernig at Stanford University was published in Nature. However, the discovery of how to differentiate cells into dopamine neurons rather than into an unspecific mixture of neural cells is what distinguishes the findings of the Swedish team.

An illustration showing fibroblasts in a Petri dish and a developing iN cell which is showing functional electrophysiological characteristics.

PHOTO: ERIKSSON/MALIN PARMAR

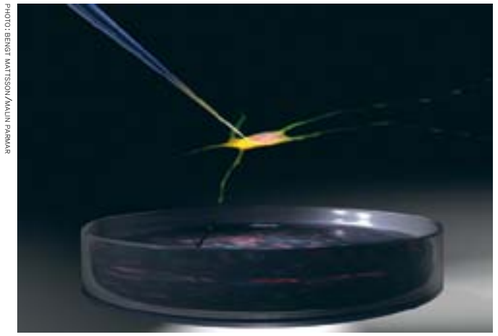


PHOTO: KATRIN STAHL

Malin Parmar.

Timo Otonkoski.

POSSIBILITIES FOR THE FUTURE

The current study is a proof of principle. For future use, especially for the clinical use of these cells, it will be important to find new methodologies. Right now skin cells are infected with viruses to make them express the genes that are necessary for reprogramming but that would not be possible if the cells are intended to be transplanted into a patient.

"In that aspect we are helped greatly by the IPS-field. They have already worked on this issue and we might be able to adapt our protocols in a similar way," Malin Parmar explains.

She has received mostly positive comments from her scientific colleagues and is looking forward to presenting her work at the 9th Annual Meeting of the International Society for Stem cell Research in Toronto.

"The reprogramming of cells represents a shift in paradigm and there will always be people who are skeptical. I find this an exciting and powerful field of research that should not be underestimated," she says.

Timo Otonkoski is also positive.

"Lineage-specific programming is very promising; the challenge will be to find ways to produce a lot of different cell types specifically. We are still at the dawn of understanding this."

Articles

Hussein et al. (2011) Copy number variation and selection during reprogramming to pluripotency. Nature, 471, 58-62 doi:10.1038/nature09871

Pfisterer et al. (2011) Direct conversion of human fibroblasts to dopaminergic neurons. PNAS June (early edition) www.pnas.org/doi/10.1073/pnas.1105135108

The new clean flows *are blowing in Kojair Tech Oy*

The year has brought several changes to Finnish Kojair Tech Oy and there is still more to come.

The year began with a new owner, Development Company Tulevaisuus Oy, taking over the company in February. The new CEO Mr. Harri Myllylä started in June and the organization was re-structured in Germany and in Sweden and Kojair recruited an experienced salesman, Mr. Lars Lundberg, to strengthen the Scandinavian sales force. All in all the company has taken giant steps forward in its over 40 year history.

But one of the most interesting happenings has been the releasing of a new safety cabinet range: Kojair BlueSeries. Kojair BlueSeries is an update of the existing product series (SilverLine and GoldenLine), but is much more than just a facelift. The first member of this new product family has been available from mid-June: the Kojair SilverLine BlueSeries. The new SilverLine BlueSeries will set the benchmark for the industry in a same way that the Kojair GoldenLine did when it launched in 2004. A new flagship GoldenLine BlueSeries with even more sophisticated features will also follow later this year.

In the development of the new series Kojair has concentrated on three key features of the safety cabinet: Safety, Silence and Saving energy.

Safety

The standard EN 12469 specifies the required air flow rates in the safety cabinet. With the specified flow rates the cabinet is safe both for the user and the environment. When environmental conditions vary the air flow management is sometimes a challenge. The sign of a high-quality cabinet is that the product is able to adapt to changing environmental conditions without sacrificing safety.

Kojair's trademark has always been safety above all else i.e. the cabinet must ensure a safe working environment throughout the whole working area. In practice, the safe operating area of the cabinet is determined according to the lowest and the fastest flow points. The closer the minimum and the maximum flow values are to each other the more stable and more secure the safety

cabinet is in all circumstances. In this case the cabinet can also be adjusted to the operating point where sound emission and energy consumption values can be optimized without risking safety.

The new innovations in the construction of laminar air flow make the new SilverLine BlueSeries cabinet the most secure safety cabinet in the world. The smoothness of the flow in laboratory tests has reached a range of ± 5%, when e.g. the limit of the maximum range set by the norm is ± 20%.

Silence

The SilverLine BlueSeries Class II microbiological safety cabinet sound levels are the lowest on the market. This is achieved by using the latest fan technology and Kojair's long experience in clean air devices and optimizing air flows. The world's lowest Class II safety cabinet sound level of 44 dB (A) was achieved in the VTT Technical Research Centre of Finland in a semi-anechoic chamber. The result is excellent, but the main advantage of the device itself for the user, however, is that the most annoying low frequencies for human ears have been minimized. The frequencies that human ears hear and the frequencies that sound level meters measure are two different things. The sound-level measuring device used in the A-weighting cuts out the low frequencies, but human ears actually hear these frequencies under normal circumstances. In the normal laboratory environment, where safety cabinets are usually placed, there are hard wall structures that reflect low frequencies easily. Therefore it is essential for the welfare of the device user and the quality of the work to minimize the most annoying sound levels emitted by the safety cabinet.

Saving Energy

The SilverLine BlueSeries Class II microbiological safety cabinet's energy consumption and heat output are the lowest on the market. The SilveLine BlueSeries safety cabinet energy consumption is as low as 170W (SL-130 size). The measured result is reached with the device adjusted according to the EN 12469: 2000 standard and with the working lights of the device on. In other words the measurements were made with normal laboratory setup. Annual financial savings are significant, because the need for air conditioning and ventilation also decreases.

Good Old Features

Despite the additional focus on new features the good, tested features like unique shadowless lights and excellent serviceability of the earlier generation of the cabinets are naturally standard features of the new models.

CONTACTS: sales@kojair.com

ADDITIONAL INFORMATION: www.kojair.com