Mitochondrial genome mutates when reprogrammed

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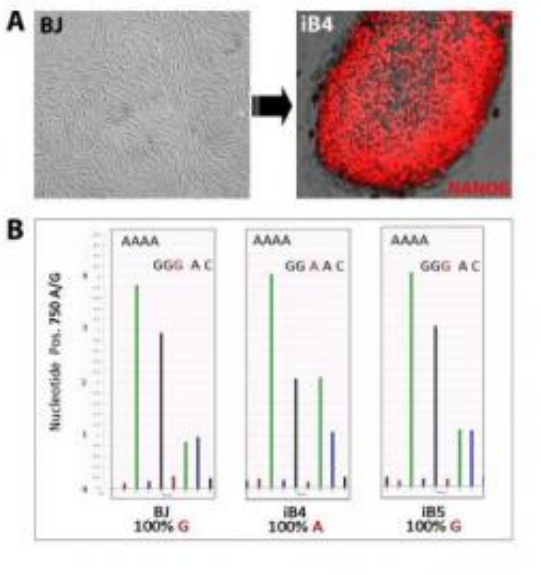

This image shows mutations in the mitochondrial genome of iPS cells. Credit: MPI for Molecular Genetics

Induced pluripotent stem cells (iPS cells) are truly talented multi-taskers. They can reproduce almost all cell types and thus offer great hope in the fight against diseases like Alzheimer's and Parkinson's. However, it would appear that their use is not entirely without risk: during the reprogramming of body cells into iPS cells, disease-causing mutations can creep into the genetic material. The genome of the mitochondria – the cell's protein factories – is particularly vulnerable to such changes.

This phenomenon has been discovered by researchers at the Max Planck Institute for Molecular Genetics in Berlin. The scientists encountered mutations in the mitochondrial genome of iPS cells. Because such genetic mutations can cause diseases, the cells should be tested for such mutations before being used for clinical applications.

A lot of hope is riding on induced pluripotent stem cells (iPS cells). Because they can be generated individually for every single person, they are expected to enable the development of tailor-made therapies that do not run the risk of triggering rejection reactions. iPS cells also offer a promising solution for drug screening, as researchers can generate different cell types such as liver cells from them, on which they can then test the effect of substances. iPS cells can be generated from adult body cells using the technique of "cellular reprogramming". The method raises no ethical concerns as it does not involve the destruction of embryos.

However, these promising cells are also associated with certain risks. Disease-causing mutations can also arise during the reprogramming of the body cells. The genetic material in the mitochondria is particularly vulnerable to changes in the genetic code. The question as to whether such mutations arise as a result of the reprogramming process had not previously been investigated.

A cooperative research study involving two research groups from the Max Planck Institute for Molecular Genetics in Berlin has now carried out a search for mutations in the mitochondrial genome of iPS cells. James Adjaye's research group recently discovered that the mitochondria rejuvenate in the course of reprogramming. Working in cooperation with Bernd Timmermann's Next Generation Sequencing research group, Adjaye's team has succeeded in showing that genetic mutations exist in the mitochondrial genome of all reprogrammed cells that were not present in the original cells. The amount of mutations varies significantly between the individual iPS cells examined. In all cases, the changes did

not involve large-scale rearrangements but rather modifications of single letters in the genetic code.

"The mitochondrial genome undergoes random reorganisation during reprogramming," explains James Adjaye. "Cell lines can arise in the process that carries disease-causing mutations. Genetic mutations in the mitochondrial genome may be responsible, for example, for various metabolic disorders, nervous diseases, tumours and post-transplant rejection reactions. Therefore, it is essential that cell lines intended for clinical use be tested for such mutations," he adds.

One of the reasons why the mitochondrial genome is so vulnerable to mutations is that mitochondria do not have the ingenious molecular repair mechanisms found in the cell nucleus at their disposal. In addition, free radicals – particularly reactive molecules that can trigger mutations – arise in the cellular protein factories during cellular respiration.

For their study, the scientists generated iPS cells from human skin cells (fibroblasts). Based on a standard procedure, they used viruses as a vehicle for the infiltration of certain regulator genes into the skin cells. These genes, which are usually only active in the embryo, transpose the cell back to a juvenile state. As a result it gains the potential to differentiate into almost all of the cell types found in the human body, in other words, it becomes pluripotent.

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reprogrammed.html