NEW AID IN DISEASE RESEARCH:

Reprogrammed cells as a model for disease research

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In order to understand and successfully combat diseases, research must be carried out in the laboratory. In order to allow an ideal examination of the disease-specific manifestations in the affected tissues or cells, small tissue samples from diseased patients are an important resource. However, they are not available for all diseases or can only be gained under unreasonable conditions.

Disease models can circumvent these problems by enabling scientists to simulate diseases in the laboratory. Because pluripotent stem cells can also be differentiated in a cell culture dish – at least theoretically – to form any of the body's cell types, human embryonic stem cells (hES) and what are known as induced pluripotent stem cells (iPS) are increasingly being used to breed diseased cell types or even tissue types in the laboratory.

Why do we need disease models?

Whether life threatening or not, a disease can often only be successfully treated if we understand its biological basis. Disease models allow scientists to simulate certain aspects and, for example, to decode them at the molecular level. In this case, a disease model maps the misdirected biology, for example in the computer, in animals or in cells. Such models provide helpful insights into diseases. They make it possible to repeat experiments relatively simply and very robustly in order to obtain reproducible and trustworthy results. Our understanding of complex biological systems in the human organism remains limited. Different manifestations of the same disease are difficult to study and model. A first step in exploring such complex diseases is to analyze only individual cells or groups of cells in the laboratory, rather than looking at complex tissue or the whole body.

Human cells as a model for disease research

Animal models, such as laboratory mice, are well established in research and can model many aspects of human diseases. However, animals can never reproduce all aspects of human biology or disease. While treatment methods that have been effective in experimental animal models can often provide essential clues and information, they do not always work in humans. In addition, there are a number of diseases, including metabolic diseases or neuronal diseases, for which there are no meaningful animal models. Human cells were first cultured in the laboratory in the 19th century. Since then, our understanding of cells has made great progress. In particular, cancer cells have played an important role, as they are much easier to multiply in vitro than healthy tissue cells.

What advantage do stem cells have for disease models?

Stem cells can renew themselves and differentiate into different types of specialized cells. Induced

pluripotent stem cells (iPS) offer the new possibility of using pluripotent patient stem cells and of growing the relevant cell types or tissue types from them in the laboratory. The use of iPS is particularly advantageous in those diseases in which genetic components such as defective genes or certain genetic polymorphisms play a role. The reason: they possess the identical genetic make-up and generally reproduce the disease type reliably and authentically. Stem cell models have an additional benefit: many diseases are often only discovered when pronounced symptoms occur, namely, only long after the actual onset of the disease. The original development of the disease is often difficult to reconstruct and understand. Using stem cells, researchers can take a travel for a short period in time and produce every type of cell, whether in an early or a late stage of the disease.

Current and future developments for stem cell disease models

However, some diseases have a very broad genotype-phenotype correlation: Although the disease is based on the same genetic defect (genotype), the severity of the phenotype is very different in different patients. In these cases, new research approaches attempt to investigate iPS-cells from multiple patients displaying different phenotypes and to repair the underlying genetic defect in each individual patient-specific iPS-cell line using new methods of precise genome editing. Then, for each patient, the healthy and diseased iPS cell line can be examined in pairs, which allows very reliable observations. Now, if different phenotypes of the same disease are based on different mutations of the gene in question, the difficulty arises that a specific control cell line would need to be generated for each individual mutation. Given ten mutations, then, two times ten cell lines would need to be investigated. Some scientists therefore prefer to start with an intact control cell line (ES or iPS) and to then generate sub-cell lines into which the respective mutation has been inserted. Given ten mutations, then, only ten plus one cell lines would need to be investigated. In summary, ES-cells and iPS cells offer the possibility of establishing artificial but authentic disease models in vitro. They thus help to better understand a disease. Moreover, the disease models can be used to develop and test medicines and treatment methods directly on the *cell patient.*