Mice with human body's defenses

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Therapeutic antibodies can be an efficient alternative when common drugs do not work anymore. However, antibodies obtained from blood of animals such as mice could not be used: The human immune system recognizes them as foreign and rejects them.

In an international cooperation, scientists from the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany have now succeeded in developing a promising approach to solve this problem; with the help of human stem cells they generated mice with a human immune system, which were then vaccinated to produce human monoclonal antibodies. These fully human antibodies could help in the research and therapy of human diseases. Their results have now been published in the current online issue of the scientific journal *PLoS One*.

Antibodies are small proteins, produced by B cells during an immune response. They bind at and thus mark invading pathogens so that scavenger cells recognize and destroy them. "The task of our immune system is to distinguish between self and non-self structures," says Professor Carlos A. Guzmàn, head of the department of "Vaccinology and Applied Microbiology" at the HZI. "This means also that only human antibodies come into question for an antibody therapy", since the human immune system fights antibodies from mice – a threat for the patient. Furthermore, it is cumbersome to humanize murine antibodies for human treatment or to generate human B cell clones producing high quantities of antibodies.

The scientists used an already established method to give a human

immune system to mice, which were then exploited to solve this problem: they injected human stem cells into young mice that due to a genetic defect lack an immune system. The stem cells migrate into the bone marrow, proliferate, differentiate and lead to the generation of a human immune system. "In our in-depth investigations we were able to detect all important types of immune cells in these mice," says Dr. Pablo Becker, scientist in the HZI department "Vaccinology and Applied Microbiology".

To validate the new approach, mice with a human immune system were vaccinated against Hepatitis B or Tetanus. The scientists then isolated human antibody producing B cells from the mice and treated them so that they survive outside the body in a cell culture dish and continue producing antibodies. Then, the researchers took a deeper look at the antibodies. The results give hope: "Antibodies from mice with a human immune system showed good properties in our tests, but the model still needs to be improved for broad implementation in biomedicine," says Pablo Becker. "However, we were able to demonstrate for the first time that it is possible to produce human monoclonal antibodies using humanized mice." Now it is important to improve this mouse model to use it one day for the development of advanced therapies against human diseases. "In the future this approach might represent the most powerful tool to develop therapeutic antibodies for clinical use," hopes Becker.

More information: Becker PD, Legrand N, van Geelen CMM, Noerder M, Huntington ND, et al. 2010. Generation of Human Antigen-Specific Monoclonal IgM Antibodies Using Vaccinated "Human Immune System" Mice. PLoS ONE 5(10): e13137. doi:10.1371/journal.pone.0013137

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