A breath of fresh air could improve drug toxicity screening

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A team led by Massachusetts General Hospital (MGH) researchers has developed an innovative way to culture liver cells for drug toxicity screening. In a report to be published in *Proceedings of the National Academy of Sciences* that has been released online, the investigators describe how liver cells grown in a high-oxygen environment and in a culture medium free of animal-derived serum quickly begin to function as they do within the liver.

Better and faster ways to screen drugs for toxic side effects could significantly reduce the cost and expense of bringing new drugs to market, along with reducing unexpected adverse events that can occur when new agents move from the clinical trial stage into wider use, the authors note. Since the liver plays a key role in the metabolism and clearance of drugs, screening for liver toxicity is an essential step in assuring the safety of new agents. But studies in animals are not always successful in predicting toxic liver effects, and freshly cultured liver cells quickly lose their metabolic competence under standard culture methods.

"Finding a better way to culture liver cells has been a major stumbling block in the development of predictive drug-discovery tools," says Yaakov Nahmias, PhD, of the MGH Center for Engineering in Medicine (CEM), the paper's senior author. "We needed to develop an environment in which liver cells behave as they do in the body."

Earlier studies by the CEM team and others suggested that animal-

derived serum, commonly used in cell cultures, may interfere with the metabolism of cultured liver cells. Since one of the key stresses involved in moving cells from an in vivo environment into culture is a tenfold drop in oxygen levels, the researchers theorized that a high-oxygen, serum-free culture environment might be the answer.

Their experiments first confirmed that serum interferes with the metabolism of cultured rat and human liver cells. They then found that liver cells grown with endothelial cells in a serum-free culture with 95 percent oxygen quickly resume normal metabolic activity, including gene expression and cell function. These cultured cells successfully predicted the clearance rates for both rapid- and slow-acting drugs and maintained a high level of metabolic activity for several weeks.

"This is a significant achievement," says Martin Yarmush, MD, PhD, director of the MGH Center for Engineering in Medicine and a co-author of the PNAS study. "Oxygen had been thought to affect cell survival but not gene expression or the function of cultured liver cells. This all changed when we started looking at new formations of culture media." Yarmush is the Helen Andrus Benedict Professor of Surgery at Harvard Medical School, where Nahmias is an instructor in Bioengineering.

The new culture system is being licensed to HμREL Corporation of Beverly Hills, Calif., a company developing human-relevant models of drug metabolism. Future work will explore extending these results to other cell systems and clinical applications, such as transplantation of liver cells.

Source: Massachusetts General Hospital (news : web)