Human immune cells -- in mice

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(PhysOrg.com) -- In 1796, English physician Edward Jenner decided to investigate a tale he had often heard -- that milkmaids infected with cowpox became immune to smallpox, a much more dangerous affliction. To test this theory, Jenner inoculated an eight-year-old boy with pus from the blisters of a milkmaid who had caught cowpox. Two months later, Jenner injected the boy with material from a smallpox lesion. The boy did not become ill, nor did the 22 people on whom Jenner later performed the same procedure.

Jenner had just made one of the most significant discoveries in medical history — a vaccine against smallpox, one of the greatest scourges humans have faced. But, his methodology would not make it past the ethical review boards that now govern research on human subjects.

Today, scientists testing experimental vaccines usually rely on laboratory experiments, measuring the immune responses of cells grown in Petri dishes, or animal studies, which don't always offer an accurate picture of the human immune response. Once vaccines become promising enough to test in humans, researchers can vaccinate volunteer subjects but can't purposely expose them to the pathogen. For example, in a recent study of an AIDS vaccine, researchers administered either the vaccine or a placebo to more than 16,000 volunteers in Thailand, then followed them for three years to see how many became infected.

That kind of study is useful but doesn't allow researchers to fully control the experimental conditions. Now, researchers at MIT and elsewhere are trying a new tactic — recreating the human immune system in a mouse. With mice that have human immune cells, you can "study immune response to pathogens that you can't give to people," says Jianzhu Chen, the MIT biology professor leading this effort.

Chen and his colleagues recently reported that they have engineered, for the first time, strains of mice that produce several types of human immune cells. Though the mice still do not express the full complement of immune cells, the work, published in December in the *Proceedings of the National Academy of Sciences,* represents a big advance in generating so-called "humanized" mice, says Andrew Tager, an immunologist who works on humanized mouse models for HIV.

Chen's new technique offers "a big advantage in terms of really filling a glaring hole in the human immune system in humanized mice," says Tager, an assistant professor at Harvard Medical School, who was not involved in this research.

Such humanized mice could be used to test potential vaccines against HIV and other human diseases such as tuberculosis, malaria and Dengue fever.

A complicated system

The human immune system is a vastly complicated network with multiple layers of defenses, exquisitely suited to combat the huge range of pathogens — bacterial, viral and fungal — to which humans can be exposed. Reproducing that complex system is no easy task.

Most of the critical players are white blood cells. B and T cells roam the bloodstream looking for specific pathogens, and launch an attack when they encounter a bacterium or virus that match receptors on the immune cell surfaces. Natural killer (NK) cells seek out and destroy cells that have been infected with a pathogen, and macrophages and dendritic cells engulf pathogens and recruit other immune cells if necessary.

To get a comprehensive picture of the body's immune response to a pathogen or vaccine, you need all of those components. All of those cells originate from hematopoietic stem cells (HSCs), which are hard to come by; the most plentiful and easily obtainable source is umbilical cord blood.

In the early 2000s, scientists induced mice to create B and T cells by injecting them with human HSCs from cord blood, but the mice lacked human NK cells and other cells important to the immune response.

In 2008, Chen and his colleagues at the Singapore-MIT Alliance in Research and Technology (SMART) set out to create mice with not just B and T cells, but also NK cells, macrophages and red blood cells. The team realized that in order to get mice to produce those humanized cells, they would have to express human cytokines that promote stem cell differentiation into NK cells and myeloid cells such as macrophages.

Rather than injecting the mice with cytokines, a laborious process that would have to be done daily to have any effect, Chen's team delivered a

single injection containing genes for human cytokines, which were taken up and expressed by the mouse livers. Within two to three weeks, the mice were producing human cytokines and significant numbers of human NK cells.

The team also engineered mice that can generate human macrophages, dendritic cells and red blood cells.

Chen's team is now working on a new way to boost the number of hematopoietic stem cells generated from a single umbilical cord, which now only provides enough cells for about 10 mice. Their new technique increases the stem cell population by 20- to 150-fold, allowing them to generate enough genetically identical mice to do the large-scale studies necessary for vaccine testing.

Though any vaccine developed and tested in humanized mice would still need to be studied in humans before approval, this kind of model would allow researchers to select only the most promising candidates before moving to human trials, which are expensive and time-consuming, says Tager. "That would be tremendously helpful to vaccine efforts," he says.

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