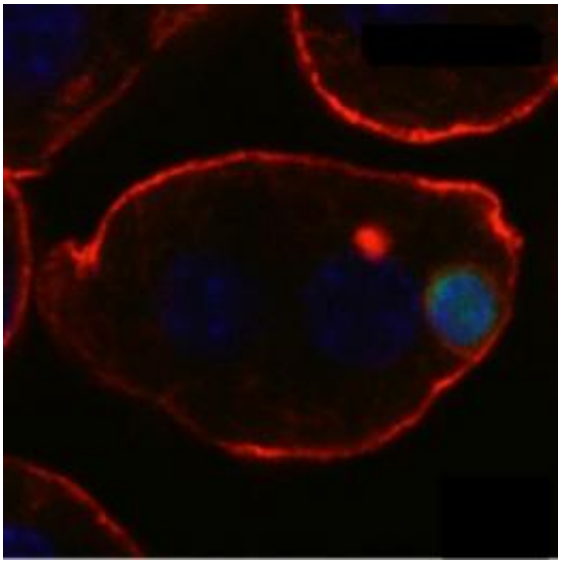
How liver kills 'killer cells'

September 19 2011



A T-cell (blue/green) is fully engulfed by a mouse liver cell (red). The two blue circles are the cell nuclei of the liver cell. Credit: Patrick Bertolino/Centenary Institute

Our livers can fight back against the immune system -- reducing organ rejection but also making us more susceptible to liver disease.

Scientists at the Centenary Institute in Sydney have seen for the first time (in mice) how the liver goes independent, engulfing and destroying the body's defence troops --T-cells.

Their discovery, published overnight in *PNAS* (Proceedings of the National Academy of Sciences), opens the way to both new approaches

to transplant rejection, and to the fight against hepatitis and other chronic liver diseases which affect over 200,000 Australians and hundreds of millions of people worldwide.

"In 2004, we discovered that healthy liver cells can engulf active immune cells, known as T-cells—and now we've seen that those T-cells are actually destroyed," says Dr Patrick Bertolino, the leader of the research team at the Centenary Institute.

"The liver is an amazing organ," Dr Bertolino says. "Most people think it just breaks down alcohol, but it's the factory of the body – breaking down substances we don't want and making the ones that we do.

"We now know liver cells also have the ability to subvert the orders of the immune system," he says, "Our discovery might explain why liver transplants have lower rejection rates than other organ transplants."

"When Patrick first told me he had evidence T-cells might be eaten by liver cells, showing a possible link to the liver's ability to dial down the immune response, I thought the idea was crazy," says lead author Volker Benseler. But Volker accepted Patrick's challenge to prove it and went on to find healthy mouse liver cells eating T-cells, which was unexpected as this 'cell cannibalism' had only previously been seen in tumour cells.

One potential benefit of the research is reducing rejection in organ transplants. About 200 liver transplants are performed in Australia each year and up to 25 per cent of cases end in rejection.

In transplantation, the new organ is seen by the body as a foreign object: the spleen or lymph nodes tell naïve T-cells to replicate and turn into killer T-cells, which are sent off to invade and kill the 'foreign' cells.

What the researchers have discovered is the liver goes around this

process: liver cells signal to naïve T-cells and digest them before they have a chance to become killer T-cells.

Centenary Institute's Liver Unit leader, Professor Geoff McCaughan, says the cocktail of immunosuppressive drugs that organ transplant patients receive reduce the odds of organ rejection but makes patients' immune systems weak, leaving them open to serious infection from otherwise minor illnesses like cold or flu. These drugs also predispose the patient to long-term heart disease and cancer. "If we can harness the way the liver controls T-cells, then long-term there is a chance that transplant patients won't need these drugs," he says.

Another spin-off of this latest work could be to find a way to dial down the liver's destruction of T-cells, increasing the liver's defence against infections like hepatitis.

In Australia, 217,000 people are living with chronic hepatitis C and it is estimated that 170 million people worldwide are infected with hepatitis C, for which there is no vaccine.

Exploiting signalling pathways between the liver and the T-cells is one possible outcome of this discovery, but first the molecular biology that underpins those pathways will need to be worked out.

"It could be another ten years plus before we see drugs derived from this work enter clinical trials," Dr Bertolino says.

However, the research opens up a new question -- why? "We don't yet know why the liver has developed this ability," says Dr Bertolino. "The discovery reminds us that we still have a lot to learn about the liver."

Provided by Centenary Institute