Understanding what happens after a paracetamol overdose

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What is the problem?

Paracetamol overdose is a leading cause of liver injury. It is the cause of more emergency hospital admissions than heart attacks (see Figure 1).

To diagnose paracetamol toxicity, blood samples are taken and analysed for markers of liver injury. The current marker (a protein called ALT) has its limitations, which has led to a search for alternative diagnostic tests. A new liver injury marker, microRNA-122 is a possible candidate.

MicroRNAs are important in the body because they block the production of messenger RNA (mRNA), a molecule involved in protein synthesis that acts as an intermediary between DNA sequences encoded by genes, which provide the instructions to make proteins, and the resultant proteins. By blocking mRNA, microRNAs inhibit protein synthesis.

Reason for emergency admission	Number of emergency admissions (England)
Paracetamol overdose	41,778
Hip fracture	42,616
Heart attack	26,967

Figure 1 Numbers of emergency hospital admissions in England (data from National Poisons Information Service UK).

What am I interested in?

MicroRNA-122 is normally found in the liver at very high concentrations, with little to none found in other organs. After paracetamol injury, it is released from the liver and its concentration increases 100 fold in the circulating blood. I want to find out **where it goes** after it is released from the liver and if it is protective against other organ damage.

What did I do?

I genetically altered mice, so that I could stop a protein called DICER being produced in the liver. DICER is responsible for the production of microRNA, including microRNA-122. I tested the mice to determine whether DICER and microRNA-122 were found in a variety of organs (brain, lung, heart, liver, kidney and spleen) and in what quantities. I used a technique called qRT-PCR (quantitative PCR) to measure the amount of mRNA and microRNA in the different organs.

What did I find?

I showed that I was able to stop DICER being produced in the liver of the genetically altered mice, as I'd hoped! I found that the levels of microRNA, including microRNA-122 were decreased in the liver compared to normal mice (see Figure 2).

In other organs, DICER was still found in the genetically altered mice. However, microRNA-122 levels decreased over time in the kidney and the spleen in the genetically altered mice compared to the normal mice. MicroRNA-122 levels did not change in the other organs (brain, heart and lung).

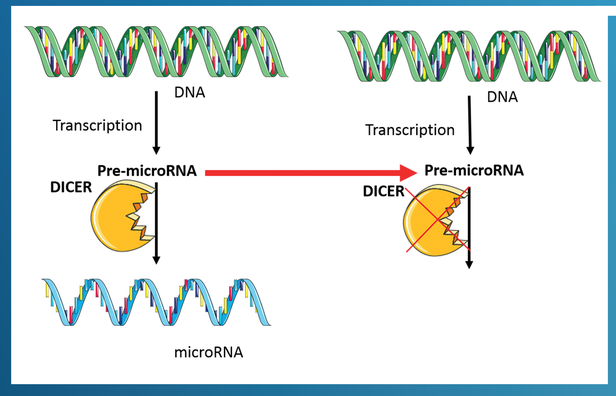

Figure 2 Without DICER protein, microRNA is not produced in cells.

What does this mean?

My findings suggest that when microRNA-122 is released from the liver into the blood, it is taken up by the kidney and spleen to be broken down. This was shown by microRNA-122 steadily decreasing in the kidney and the spleen, within 4 weeks of stopping DICER and microRNA-122 production in the liver.

My next step is to use this mouse model to investigate what happens to microRNA-122 when the mice undergo paracetamol injury.

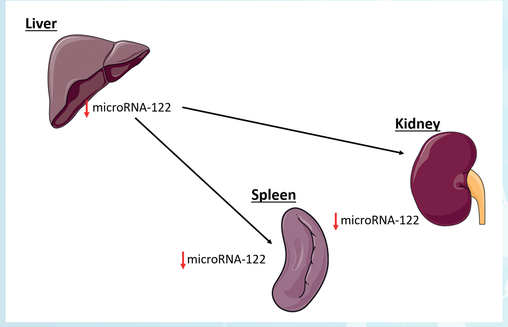

Figure 3 When the amount of microRNA-122 in the liver is reduced, the amount of microRNA-122 is also decreased in the spleen and kidney.

Who am I?

I am a 3rd year PhD student. I started my PhD after my undergraduate study of Pharmacology at the University of Liverpool. I really enjoyed the toxicology side of my degree as I found I could study a range of diseases and organs. Due to this, this PhD caught my eye and my application was successful!

Olivia started her PhD project entitled *"Hepato-renal signalling of miRNA-122"* in 2016 and while principally based at the University of Edinburgh, supervised by Dr James Dear, she is also working closely with AstraZeneca.