Exploring the role of the immune system in polycystic liver disease

AIMS

- Introduction:

  Polycystic liver disease (PLD) is a genetic disease in which the liver develops large, fluid-filled cysts throughout the liver. It is estimated that up to 5,000 individuals within Scotland are afflicted with PLD. Patients are born with a DNA mutation yet do not show symptoms of disease until midlife. Although the liver can still perform its normal jobs when cysts are present, the growth of cysts causes the liver to become bigger – and in some cases, extremely large – which causes stomach and back pain/discomfort from the liver compressing on other organs in the body. Additionally, liver cysts are at risk of rupturing and becoming infected, which can lead to sepsis. Overall, individuals burdened with PLD experience a poor quality of life and **there are no approved medicines that can stop PLD**. Research is needed to halt or reduce cyst growth, improving patient quality of life.

  We know from other diseases, like cancers, that immune cells – those cells that normally protect our bodies against infections from bacteria and viruses – are incredibly important in controlling how disease progresses. Interestingly, in the context of cancers, using medicines that can activate or inactivate specific immune cells has been shown to improve disease outcome. The

role of immune cells in PLD has not been explored and therefore could present as a potential way in which we could begin to control the disease.

- Aims:
  To understand (i) what type of immune cells sit in the livers of patients with polycystic liver disease; and (ii) how/if these immune cells talk to cysts and support cyst growth.

KEY FINDINGS

- Before this study, there was no comprehensive characterisation of the immune cells that are present within the livers of patients with PLD. Here, we found many different cells types of the immune system are found win the livers from polycystic liver disease (PLD) patients. When compared to patients that have normal liver tissue, there are a lot of a particular immune cell type called **T cells**, which can control how cancers grow – while there are loss of other immune cell subtypes.

- Different genes can become faulty to cause PLD. To understand whether the genetic cause of disease has an influence on what immune cell subtypes are present in the livers of PLD patients, this study made use of samples from different patients with different mutated genes. Our results identified that regardless of the faulty gene that causes PLD among patients, the immune cells that are within cystic livers are the same.

- To further understand how cysts within the liver interact with immune cells, this study looked at the spatial distribution of cystic cells and immune cells within the liver. We discovered that although there are lots of immune cells within the livers of patients with PLD, these immune cells do not sit in close proximity to large cysts. Large cysts create physical barriers (made up of large, complex proteins) that prevent immune cells from getting in close proximity.

WHAT DID THE STUDY INVOLVE?

Polycystic liver disease (PLD) is common within Scotland, the UK and the globe more generally. A lot of the research focus to date has been on cystic cells only, and not considered the role of other cells in the tissue. We know from cancer that tumour cells do not work in isolation; rather, they interact with a wide range of different cell types, including immune cells. While immune cells typically help us to fight off infections (e.g., from bacteria and viruses), they are much more complex and in the case of cancer have the ability to both stop and encourage tumour growth. This project set out to understand the role of immune cells in PLD – something that we had very little understanding of.

To fully define the different type of immune cells within PLD, this project made use of a new scientific technique within biomedical sciences termed ***spatial biology*** that has quickly developed and improved over the last 5-10 years. Spatial biology can make use of archived, preserved tissues to image cells within a tissue, and then use DNA sequencing to understand how they communicate with one another and more about their role in disease. Additionally, their placement within 3-dimensional space can be assessed to predict how small ***micro-environments*** of cells exist within diseased tissues.

The spatial distirbution of cells is important in understanding how they communicate within one another. Cell communication can be performed under two main ways: (1) cells present molecules to one another that require close interaction (e.g., like velcro strips); (2) cells send small, chemical molecules to one another and do not have to be within close proximity because the molecules travel throughout tissue. We know that in order for immune cells to cause cells (e.g., bacteria, viruses or even cancer cells) to die or slow down their growth, they need this first type of interaction where both cells that are communicating are close to one another. Here, this research study aimed to understand more of the interactions between cystic cells and immmune cells.

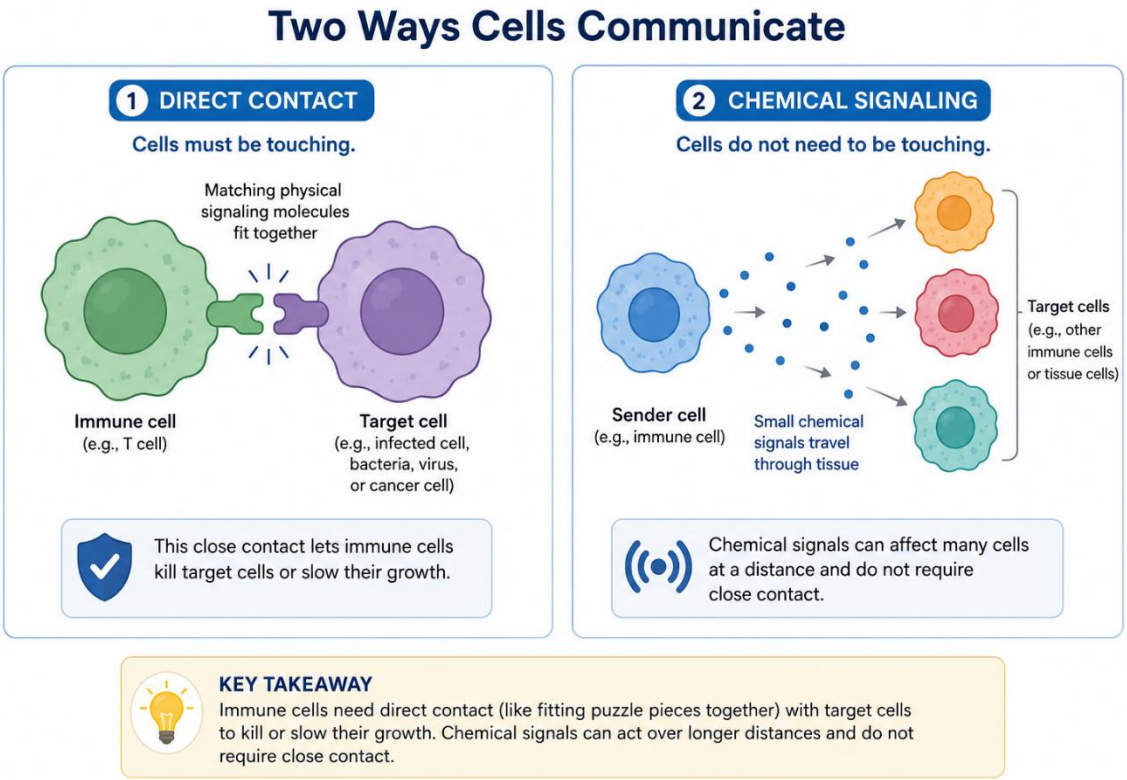


Figure 1 Cell-cell communication. Cells typically depend on: 1 – Direct Conctact for communication with other cells, in which both cells must present physical signalling molecules that fit together; or 2 – Chemical Signalling, in which cell do not need to be close as the chemical molecules can travel through tissues.

Two different spatial biology methods were used to study PLD tissues from 7 different patients – each with different genetic causes of PLD – and 4 non-PLD tissues ('normal' livers). The inclusion of different patient tissues with different genetic causes is important to ensure representation of patients with the most commmon faulty genes and those that are more rare in the population. Overall, this is the first work of its kind, exploring the complete cellular make-up of PLD tissue beyond just looking at cystic cells.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Our analyses to date have identified specific immune cells that exist within livers from PLD patients. There are a lot of different types of immune cells, but most immune cells found in cystic livers are called **T cells**. T cells are important cells in several diseases and play many different roles, including killing harmful cells (e.g., bacterial cells, tumour cells), controlling how other immune cells behave and remembering previous infections/insults in the body (e.g., preventing people from usually getting chickenpox more than once).

Interestingly, despite T cells being the most common immune cell in cystic livers, they do not sit very close to cysts. Instead, they are in closer proximity to small, **injured bile duct cells** that are not cystic, but are found in other examples of liver disease where they help the liver repair and regenerate. Work from others in the liver field has shown that important interactions occur between injured bile duct cells and T cells to help the liver repair.

In PLD, this implies that cystic cells are able to keep immune cells far away, and prevent immune cells from attacking the cyst; while injured bile ducts do communicate with immune cells and try to encourage the liver to repair.

From this work, we can now begin to explore approaches that are used in other liver diseases that have shown promise in stopping these diseases. Research into immune cells has been explored in a similar disease of the kidneys, called polycystic kidney disease; going forward, we will compare our findings with those already described in the kidneys and understand how cystic disease makes use of the same interactions with immune cells in either organ.

WHAT IMPACT COULD THE FINDINGS HAVE?

While this work serves as basic science, it builds a strong case to impact across patients, policy and practice:

- Patients

  This project is focused on understanding the underlying biology of polycystic liver disease (PLD)

so that new treatments can eventually be developed. By uncovering how the immune system contributes to the disease, this research aims to open up new possibilities for treatment, including the potential use of medicines that are already available for other conditions, such as cancer.

As this is the first study to fully explore the role of the immune system in PLD, any direct benefit to patients is expected to be long term, likely within 10–15 years. However, this foundational work is essential. Without a clear understanding of the disease mechanisms, it is not possible to develop safe and effective treatments that could improve quality of life for people living with PLD.

- Policy

  In the medium term (around 7–12 years), this research could begin to influence health policy if it leads to successful pre-clinical and clinical trials of medicines that target immune cells in PLD. At present, PLD can be diagnosed but there are no treatments that cure or actively control the disease, except for liver transplantation in a small number of patients. If this research demonstrates that immune-targeting medicines can slow or manage disease progression, it could shift policy away from a “watch and wait” approach. Instead, treatment strategies could be introduced earlier, aiming to manage the disease from the point of diagnosis and reduce long-term complications and poor quality of life.

- Practice

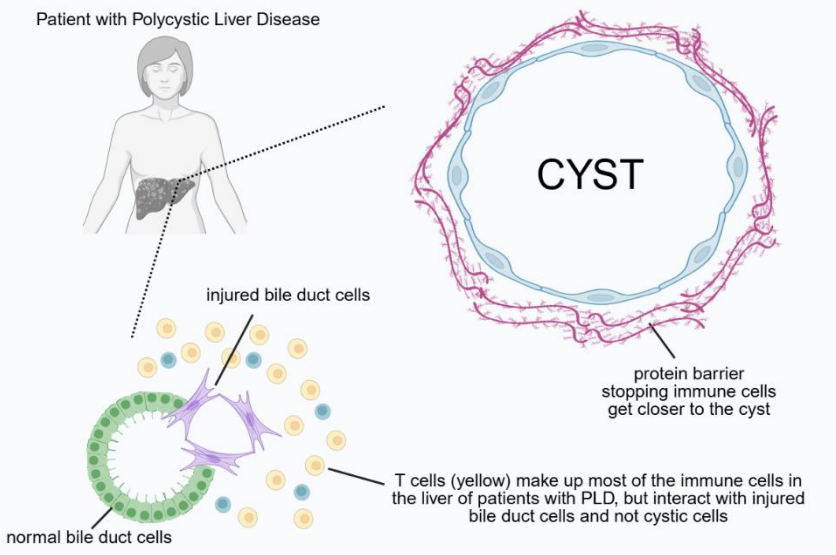
  In clinical practice, these findings could lead to the development of new treatments, or the repurposing of existing medicines used in other diseases to manage PLD. Such treatments could be offered to patients soon after diagnosis and potentially continued throughout their lifetime.

  This would also change how patients are monitored, with more regular follow-up to ensure that treatments affecting the immune system are safe and effective. In addition, improved understanding of the disease may lead to changes in how PLD is diagnosed, including greater use of genetic testing to identify at-risk family members earlier and provide appropriate advice and support.

Liver cysts shield themselves from the immune system:

In polycystic liver disease (PLD), normal, injured and cystic cells sit within the liver. Injured bile ducts (non-cystic cells) work with immune cells to try repair the liver.

Cystic cells surround themselves with a protein coat that stops immune cells that could stop cyst growth.



HOW WILL THE OUTCOMES BE DISSEMINATED?

Throughout the duration of this fellowship, findings from this work have been disseminated through oral and poster presentations at international conferences. Additionally, work specifically detailing the protein barrier that shields cysts from immune cells has been shared with patients on a webinar organised by the Polycystic Kidney Disease Charity (PKD Charity), as well as its publication in *Science Translational Medicine*. Further work detailing the immune cells in PLD is ongoing and it is anticipated that a manuscript for publication will be complete by the end of 2026.

CONCLUSION

PLD is a genetic disease and little work to date has focussed on the role of the immune system in this disease. Here, tissue from PLD patients has been used to understand how immune cells sit within cystic livers, and results demonstrate that while there is evidence for injured bile duct cells and immune cells to interact to promote repair of the liver, cysts protect themselves from the immune system by making a protein coat that acts as a barrier. This project is ongoing and further analyses and findings will be made to help complete our understanding of the immune system in PLD.

RESEARCH TEAM & CONTACT

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