Higher or lower? A sugary implication to antibody structure, and its relation to IgA nephropathy

Owen Vennard1, Dr Karen Molyneux1, Professor Stephen Perkins3, Dr Jonathan Barratt1

1Department of Infection, Immunity & Inflammation, University of Leicester, UK
2Structural Immunology Group, Biochemistry, UCL, UK

Background

The Kidneys

Our kidneys do an amazing job. Think of them as small but powerful filtration plants which keep your blood clean and the body’s chemical balance maintained – filtering 180 litres of blood each day! This filtering is done by two million nephrons, all containing fine, tangled blood capillaries called the glomerulus. This works to filter the blood before passing it further on, where the kidneys continually work to adjust to your body’s chemical needs. What is needed by the body is returned to the bloodstream; what’s not needed is excreted as urine.

IgA Nephropathy

IgA nephropathy (IgAN) is well recognised as the most common cause of glomerulus inflammation worldwide, whereby the antibody (Fig A) IgA is abnormally deposited in the fine filtering capillaries of the kidney (Fig B). Over time, this antibody in the kidney ultimately results in kidney failure, with up to 30% of patients needing dialysis within 20 years of diagnosis. It therefore represents as a major health and lifestyle problem in these patients.

Methods

Neutron and X-rays

Small angle solutions scattering provides views of proteins in their natural liquid home.

There are two variations of solution scattering, this can be done by using neutrons (SANS) and X-rays (SAXS). Both of these highly specialised techniques provide different information for a molecule such as IgA in solution. (see Table A). This is the first time that this technique has been applied to IgA from patients with this disease, allowing us to identify if the lower sugar content seen in IgAN patients affects their normal shape.

Analytical ultracentrifugation

Analytical ultracentrifugation (AUC) is a powerful tool used to characterise the size and shape of molecules such as IgA in solution – where they are normally found.

AUC measures molecules at very high speeds and provides us with a great deal of relevant shape information - such as whether the traditional ‘Y’ shape antibody is in fact more ‘T’ shaped due to reduced sugar. This will help us to identify the precise antibody type which causes disease.

Biological modelling

By combining our findings with a known crystal structure we can get a picture of what the molecule looks like at resolutions as low as 1nm. That’s one-billionth of a metre!

This provides us with a final, computerised model of the molecule.

Preliminary results and conclusions

Thus far, IgA from affected patients with a range of hinge sugars has been analysed via neutrons (SANS) and high speed AUC.

Early results show that there is a small difference in the antibody shape in disease.

The ability to identify whether a patient is likely to require dialysis at an early stage, through antibody shape will be highly beneficial in the treatment of IgAN.

Project Aims

- To identify the structure of IgA from patients and healthy individuals
- Determine whether high or low hinge sugar content affects IgA structure and is a cause for disease


Fig. A – Illustration of an IgA antibody. Antibodies in our body work to fight infection. IgA is very special as it contains a hinge, which in patients with IgA nephropathy is very abnormal. Does this affect shape and cause disease? The sugars (inset) may well play a part in this.

Fig. B – IgA nephropathy can only be diagnosed by renal biopsy. Here on the left we can see that the filtering glomerulus is abnormal, and on the right there are abnormal IgA deposits (green area). The exact cause for this is unknown. Normally IgA helps the body to fight infections, however there are some abnormal features in IgA which are seen in IgAN patients. One of these abnormalities is sugar content. It is only by looking more deeply into the structure and shape of the antibody can we reveal important information on the cause of this disease.

Higher or lower sugar?

Previous research into IgA has shown that the amount of sugar (glycosylation) in the hinge is lower in IgAN patients compared to healthy individuals. The question of whether having a lower sugar content can alter the antibody shape and cause disease is now being defined.

Fig. C

‘Leicester University has the UK’s largest store of IgA nephropathy patient serum’