

RECENT ADVANCES IN UNDERSTANDING NEPHROTIC SYNDROME – LIGHT AT THE END OF THE TUNNEL

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An enigmatic disease

Nephrotic syndrome (NS) is a potentially devastating condition, in which the natural filtering ability of the kidney breaks down, with a consequent massive leak of essential proteins from the bloodstream into the urine. This results in the typical body swelling due to leakage of fluid from the bloodstream into the tissue spaces, and complications such as infections and thrombosis because of loss of circulating antibodies and clotting factors.

NS is one of the commonest kidney diseases in childhood, and the current treatment is non-specific and highly toxic, with many potentially life-threatening complications. A proportion of children progress to kidney failure, despite years of frustrating treatment regimes, and one of the most devastating aspects of the disease at this stage is that even after transplantation the original disease can rapidly recur in the new kidney.

We need to understand the biology

One of the most difficult aspects of the condition, namely post-transplant recurrence, is from the scientist's point of view one of the most fascinating. This is because this phenomenon indicates that the primary abnormality in NS occurs in the circulating blood, rather than the kidney itself, and therefore this must be a unique disease entity that is not directly analogous to any previously described disease mechanism.

For many years now, clinicians and scientists have been searching for the elusive circulating 'nephrotic factor' that is causing the disease, but up until now in vain. The reason for this is unclear, but recently our group has made some surprising discoveries.

We have done this by concentrating more on the target of the unknown 'factor(s)' in the kidney, than the factor(s) themselves. This target is postulated to be a highly specialised type of cell in the kidney called the podocyte. Podocytes form a layer of cells that sit between tiny kidney blood vessels and the urinary space, thus acting as a mesh that filters out toxic substances from the bloodstream, while retaining crucial proteins within the bloodstream - one of the key functions of the kidney. In NS, the podocyte is the first and often the only cell disrupted, indicating that it is the primary target for any toxic factor. Damage to the podocyte results in the inappropriate passage of blood proteins into the urine, which are then lost. Our studies have focussed on understanding how the podocyte is damaged in NS.

Lessons from children with rare forms of NS

Some exciting discoveries in podocyte genetics have helped us to make progress in this area. In the last few years the study of children with rare inherited genetic forms of NS has revealed specific mutations that cause NS. These mutations occur in genes that are responsible for maintaining podocyte shape and integrity, and therefore if they go wrong, the podocyte layer is damaged and leaks protein. Two particular molecules, named nephrin and podocin, have been the subjects of much subsequent

investigation. The implication is therefore that these molecules are essential for podocyte health, and will be central to the development of NS in many if not all patients.

With the consent of the parents concerned, we have taken damaged kidneys removed from children with these congenital mutations, when they are removed as part of their clinical management, and been able to grow their podocytes in the laboratory to study the roles of those important molecules. This is the first time this has been achieved, and provides a powerful model system, with which to approach the conundrum of recurrent NS.

Advances in understanding recurrent NS

When children with renal failure due to NS receive their kidney transplant, between 40-60% will get dramatic recurrence of the disease often hours or days after the transplant operation. An intensive but useful way of subduing this process is to use plasma exchange, a method of removing circulating blood plasma from the child, and replacing it with inert protein. This in theory removes a toxic substance that is responsible for damaging the podocyte cells.

We decided to use the removed ('toxic') plasma, to see if it could damage podocytes grown in a dish. We used sophisticated techniques to examine the effects of this plasma on important podocyte molecules such as nephrin and podocin, as well as examining the shape and dynamic behaviour of the cells. An important insight from these studies has been that it appears that there may not be a specific toxic factor in plasma from these children, but rather there is missing an essential element of normal plasma that is responsible for keeping the podocyte healthy¹. The next important challenge therefore is to work towards identifying this substance, so that specific therapies aimed at restoring the balance can be generated. This is something our laboratory is now working on, using powerful new proteomics techniques that allow mass screening of proteins in biological samples.

Families involved in the research

The efforts involved in basic kidney research such as this involve many scientists and clinicians at all levels, and importantly the input of motivated and enthusiastic families, both to keep the professionals focussed in their search for advances in treating this type of distressing disease, and to raise awareness and funds to find a cure.

In recent years, with the particular involvement of two such parents of children with NS, David Yearsley and Wendy Cook, we have set up a research charity specifically for this disease, called NeST (Nephrotic Syndrome Trust. www.nstrust.co.uk). Wendy's son, David, is unfortunately a typical example of how the disease can affect the lives of children with NS. He is now 10 years old but has had the disease for several years and undergone many attempts at therapy, and eventually in 2004 the removal of his kidneys, and placement on dialysis. He had a transplant in 2005, but got recurrence, and is now managed with immunosuppression and weekly plasma exchange treatments – quite a burden on both his and his family's life. Both he and Wendy have strived tremendously to raise awareness about the condition, and in fundraising, and are active supporters of NeST. The ambassador for this trust is Jonah Lomu, the New Zealand rugby star, who has had a kidney transplant for a form of nephrotic syndrome, and is now incredibly back to playing professional rugby.

Already several sterling efforts at raising money have been undertaken, such as long-distance cycle rides, and creative charity events. This is hugely useful both in helping take the research further and also as a resource to help sufferers and carers discuss their problems and feel that they can put something positive back towards finding a cure.

With further persistence, and the backing of all the families and friends who have helped out in this endeavour, there is now genuinely hope that a specific therapy for this disease is on the horizon.



Left to Right: David Yearsley, James Yearsley, Jonah Lomu, Moin Saleem – At the official launch of Nest, Twickenham, June 2005

¹Nephrotic plasma alters slit diaphragm dependent signalling, and translocates nephrin, podocin and CD2AP in the human podocyte
Richard JM Coward, Rebecca R Foster, David Patton, Lan Ni, Dave O Bates, Steve J Harper, Peter W Mathieson, Moin A Saleem.

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