Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

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# DOCK2 as a target for control of sight-threatening autoimmune uveitis

**Researchers**
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**Aim**
To discover whether blocking a specific protein (DOCK2) in T lymphocytes (a type of white blood cell) would prevent uveitis (sight-threatening inflammation inside the eye).

**Project Outline/Methodology**
We have developed using genetic techniques an unique mouse which develops spontaneous uveitis and have also genetically knocked out DOCK2 from these mice. We have also looked for DOCK2 in human cells and attempted to block DOCK2 in these cells using a specific inhibitor (siRNA).

**Key Results**
Knocking out DOCK2 was remarkably effective in delaying the onset of uveitis and preventing damage to the retina. We found that both T cells which cause damage to the retina (Teffector cells) as well as T cells which should normally control disease (T regulatory cells) were prevented from accessing the eye. We think that this happenend because both types of T cells although they are activated in the system (lymph nodes) are unable to migrate from the lymph node to the eye in the absence of DOCK2.

We also found that DOCK2 is expressed in human cells and that DOCK2 can be inhibited in these cells using siRNA specific for the DOCK2 gene.

**Conclusions**
DOCK2 is known to regulate aspects of T cell function including migration but knocking out DOCK2 has not previously been shown to be effective in preventing autoimmune diseases such as uveitis. We believe that strategies which can inhibit the function of the T cell specific signalling protein DOCK2 might offer a potential new therapy for treatment of T cell mediated autoimmune diseases such as non-infectious uveitis, multiple sclerosis and rheumatoid arthritis.

**What does this study add to the field?**
We believe this is the first study which investigates the role of DOCK2 in an *in vivo* model of autoimmune disease.

**Implications for Practice or Policy**.
This is a pre-clinical study which will not immediately impact on clinical practice. However, sight-threatening uveitis is a major cause of blindness which can be very difficult to treat. This study offers a new approach for controlling this disease, for instance through the pharmaceutical development of small molecule inhibitors of DOCK2. This also has broader application to treatment of autoimmune diseases generally.

**Where to next?**
The immediate aim is to progress the investigation of DOCK2 expression in patients with uveitis, specifically to determine whether DOCK2 can be inhibited in T cells from patients with uveitis. If this is so, there is potential for autologous T cell therapy using DOCK2 inhibited cells.
We also plan to investigate the role of the gastrointestinal (gut) T cells and innate lymphocytes since recent studies have found that gut T cells may be the source of eye damaging T cells in uveitis and we incidentally observed that DOCK2 deficient mice with uveitis also developed colitis, indicating dysregulation of gut T cells in this model.

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