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Molecular basis identified for tissue specific immune regulation in the eye and kidney

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Scientists at The University of Manchester have made important advances in understanding why our immune system can attack our own tissues resulting in eye and kidney diseases. It is hoped the research will pave the way for the development of new treatments for the eye condition age-related macular degeneration (AMD) and the kidney condition atypical Haemolytic Uremic Syndrome (aHUS).

Both AMD, which affects around 50 million people worldwide, and aHUS, a rare kidney disease that affects children, are associated with incorrectly controlled immune systems. A protein called complement factor H (CFH) is responsible for regulating part of our immune system called the complement cascade. Genetic alterations in CFH have been shown to increase a person's risk of developing either AMD or aHUS, but rarely both. Why this is the case has never been explained until now.

Researchers from the Wellcome Trust Centre for Cell Matrix Research and the Ophthalmology and Vision Research Group in The University of Manchester's Institute of Human Development have been expanding on their previous work that demonstrated a single common genetic alteration in CFH prevents it from fully protecting the back of the human eye. The research teams of Professor Tony Day and Professor Paul Bishop found that a common genetically altered form of CFH associated with AMD couldn't bind properly to a layer under the retina called Bruch's membrane. Having a reduced amount of CFH in this part of the eye leads to low-level inflammation and tissue damage, eventually resulting in AMD.

However, this mutation that changes CFH function in the eye has no affect on the protein's ability to regulate the immune system in the kidney. A cluster of genetic mutations in a completely different part of CFH are associated with the kidney disease aHUS, but these have no affect on the eyes.

In their most recent study, which was funded by the Medical Research Council and published in the Journal of Immunology, the Manchester researchers have identified why these mutations in CFH result in diseases in very specific tissues. Professor Day explains: "For the first time we've been able to identify why these protein mutations are so tissue specific. We're hoping our discovery will open the door to the development of tissue specific treatments to help the millions of people diagnosed with AMD every year."

The research team looked at the two parts of CFH affected by the mutations. Both regions are capable of recognising host tissues, through interacting with sugars called glycosaminoglycans (GAGs). Successfully recognising these GAGs lets CFH build up a protective layer on the surface of our tissues that prevents our own immune system from attacking them.

It had always been believed that the region with mutations associated with aHUS was the most important for host recognition and for years people have been researching how to readdress immune dysregulation based on this belief. However, the recent discovery of a single common genetic alteration in the other part of CFH that is associated with eye disease raised the possibility that this previous opinion was not fully accurate.

The Manchester researchers compared the way the different regions of the protein interacted with eye tissue and kidney tissue. They discovered that the region of CFH that helps protect the kidney had no effect in the

eye. Instead the other part of CFH, which is subject to the AMD-associated genetic alteration, was fundamentally important in protecting the eye, but this region did not contribute to the binding of CFH to kidney tissue.

Their findings show, for the first time, that the level of importance of the two regions of CFH changes depending on which tissue the protein finds itself. This specificity appears to be mediated by the presence of different populations of GAGs.

Dr Simon Clark says: "Our findings suggest that the particular structure within the eye and kidney tissue determines precisely how and where CFH will bind. It's as if the tissues have their own molecular postcodes."

He continues: "We're very pleased to be able to show why mutations in CFH are so tissue specific. This is important because if we're going to improve treatments for devastating diseases, such as AMD, we need to be able to develop tissue-specific therapies."

Professor Paul Bishop, theme lead at the Manchester Biomedical Research Centre and Consultant at the Manchester Royal Eye Hospital says: "The contribution of donor samples from Manchester Eye Bank was vital for this study. Without the tissue samples that had so generously been given for research by eye donors this research would have been impossible to do."

The paper: "Tissue-specific host recognition by complement factor H is mediated by differential activities of its glycosaminoglycan-binding regions" has been published in the February edition of the *Journal of Immunology*.

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Provided by University of Manchester