Minuscule molecules pack a powerful punch

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A role for a microRNA in the immune system has been shown by study of one of the world's first microRNA knockout mouse, reported Friday 27 April in *Science*. The microRNA acts as a lynchpin to balance the response of immune defences and the researchers suggest the corresponding human gene will have a similar vital role.

Cells of the immune system in the knockout mice do not work as well as normal cells and the mice develop symptoms similar to those of human autoimmune disease. They are also less able to resist infection by bacteria, such as Salmonella. The team suggest that the equivalent human microRNA will play a major role in the human immune system.

MicroRNAs are copied from DNA but do not contain code for protein. Rather, they are themselves active in controlling the activity of other genes, often by inducing destruction of protein-coding messenger RNAs or by preventing their activity in the cell.

The research team, led by the Wellcome Trust Sanger Institute, targeted a gene called Bic/microRNA-155 (or miR-155) in embryonic stem cells which they used to transfer the mutation into mice. Previous research showed that miR-155 was active in cells of the immune system and overactivity was found in lymphoma development.

"Very little is known about the function of the hundreds of microRNA genes," said Dr Antony Rodriguez, lead author on the paper from the Wellcome Trust Sanger Institute. "Although plentiful, this class of gene had never before been knocked out in mice, the best model for human

disease.

"But we simply did not know whether microRNA knockouts would have an effect in mice: previous knockout studies in nematode worms suggested that most microRNAs were not essential. Our findings were dramatically different."

The effects of the miR-155 knockout swept across the immune system. The team showed that, although knockout of miR-155 did not appear to affect normal growth and development of cells in the immune system, each major cell type - T-cells, B-cells and dendritic cells - performed less well.

"These findings demonstrate the importance of this level of control in the immune system and will lead immunologists to rethink how the immune system works," said Dr Martin Turner, Head of the Laboratory of Lymphocyte Signalling and Development at the Babraham Institute.

The deficits in response were significant: the knockout mice were less able to resist infection by bacteria than mice with normal miR-155, producing lower levels of antibody and a reduced response by T-cells. They also develop changes to lung tissue, with scarring that is similar to some human systemic autoimmune disorders.

To uncover how miR-155 might cause such widespread disruption of the immune system, the team used genomic studies to identify protein genes whose activity was controlled by miR-155 in T-cells. Activity of more than 150 genes, with a large range of biological functions, was reduced by miR-155, demonstrating its role in the immune system. The team showed that a particularly important gene, c-Maf, which is critical for function of populations of T-cells, is a target for the action of miR-155.

The consequences of removal of active miR-155 are altered activation of

other genes, failure to mount an effective immune response, susceptibility to autoimmunity and susceptibility to infection.

"This dramatic finding reflects a large amount of work by collaborating groups," said Professor Allan Bradley, Director of the Wellcome Trust Sanger Institute. "Showing that knocking out a microRNA has such dramatic effects opens new doors to understanding this novel class of gene regulation, with consequences for human health and disease.

"Our work builds upon the sequences of the human and mouse genomes, the power of computer analysis and microarray work and exemplifies why whole-organism research can bring understanding that cannot be developed in any other way."

The study emphasizes the value of the ES cell based knockout technology, currently being pursued on a large scale through the KOMP and EUCOMM programmes at the Wellcome Trust Sanger Institute. This success illustrates the power of the mouse to reveal function and indicates a wider role for microRNAs in animals with large genomes.

Source: Wellcome Trust Sanger Institute