Potential gene therapy for patients with rare disease

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Dr Umaimainthan Palendira and Associate Professor Stuart Tangye

Australian scientists have discovered that a biological phenomenon known as 'somatic reversion', when an abnormal gene spontaneously becomes normal again, explains why some patients with a rare genetic disorder live much longer than they should.

The finding provides hope for future gene therapy treatments.

Dr Umaimainthan Palendira and Associate Professor Stuart Tangye, from Sydney's Garvan Institute of Medical Research, realised that a substantial percentage of patients with the rare immunodeficiency known as X-linked lymphoproliferative disease (XLP) were living much longer than expected, and were even approaching the age of 50. Many XLP patients die before they reach 10 years of age, and the majority have a life expectancy of less than 40 years.

The anomaly was explained when Palendira and Tangye found that in

longer-living patients – and within a small population of their immune cells (a subset of 'killer T cells' known as 'effector T cells') – their abnormal gene had reverted to being normal again. This was enough to confer some protection against infection with the Epstein Barr Virus (EBV), which is often deadly for people with XLP. These findings are published in the *Journal of Experimental Medicine*, now online.

"Somatic reversion is a fascinating clinical phenomenon, which has been characterised in a handful of other rare diseases, but never before seen in XLP," said Associate Professor Stuart Tangye.

"Our finding highlights the importance of effector T cells in the case of XLP. This is clinically relevant because it tells us that you only need a small population of cells that are functionally capable of responding to EBV to give you good immune protection."

"If XLP patients were to receive gene therapy in future, it should be possible to confer some protection by getting the gene into a only a small number of effector T cells - a very targeted therapy."

"Gene therapy normally works by modifying bone marrow stem cells – the precursor cells which give rise to all of your blood cells, including T cells, B cells, platelets and macrophages."

"In this case, you would insert the normal gene only into naïve T cells, those T cells which have never seen infection before. When these precursor cells then encounter EBV infection, they would divide and multiply, giving rise to effector T cells, which actually work against EBV."

"While we don't yet know exactly how somatic reversion works in XLP, we can see that it does, and that fact has clinical implications for the future."

Provided by Garvan Institute