Survival gene may be key to controlling HIV and hepatitis

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Dr Marc Pellegrini (left) and Dr Greg Ebert were part of a research team that discovered a gene which is essential to the immune response to infection.

(Medical Xpress)—A newly discovered gene that is essential for embryo survival could also hold the key to treating and potentially controlling chronic infections such as HIV, hepatitis and tuberculosis.

The gene, called Arih2, is fundamental to the function of the immune system – making critical decisions about whether to switch on the immune response to an infection.

Its discovery has implications for the treatment of chronic overwhelming infections, such as HIV, that 'exhaust' and switch off the immune system, as well as for chronic inflammatory (also known as autoimmune) conditions such as rheumatoid arthritis and sepsis.

Dr Marc Pellegrini, Dr Greg Ebert and colleagues from the institute's Infection and Immunity division, with collaborators from the University of Toronto, Canada, led the research. Their findings were published today in the journal Nature Immunology.

Infectious disease specialist and researcher Dr Pellegrini said that Arih2 is found in dendritic cells, the sentinels of the immune system that play an essential role in raising the alarm about the presence of foreign invaders in the body. "Arih2 is responsible for the most fundamental and important decision that the immune system has to make – whether the immune response should be initiated and progressed or whether it should be switched off to avoid the development of chronic inflammation or autoimmunity," Dr Pellegrini said. "If the wrong decision is made, the organism will either succumb to the infection, or succumb to autoimmunity."

Dr Pellegrini said although our immune system works well against many infections, some organisms have developed mechanisms to evade or counteract the immune system, allowing them to persist in the body. "During evolution, some organisms have evolved ways of exhausting our immune system to the point where the immune system just switches off, and this is what happens in HIV, hepatitis B and tuberculosis," he said. "These organisms counter the immune response – exhausting T cells which are stimulated over and over again by the infection and becoming exhausted or paralysed. With this current discovery, what we should be able to do is circumvent these mechanisms and reinvigorate the immune response temporarily to boost the immune system and help clear these infections."

Dr Ebert said the research team was now looking at the effect on the immune response of switching off Arih2 for short periods of time during chronic infections. "We are investigating how manipulating Arih2 and associated pathways promotes immunity in chronic overwhelming

infections, where we know the immune response is inadequate," Dr Ebert said.

He said Arih2 had significant promise as a drug target. "Arih2 has a unique structure, which we believe make it an excellent target for a therapeutic drug, one that is unlikely to affect other proteins and cause unwanted side-effects," Dr Ebert said. "Because Arih2 is critical for survival, we now need to look at the effect of switching off the gene for short periods of time, to see if there is a window of opportunity for promoting the immune response to clear the infection without unwanted or collateral damage or autoimmunity."

Dr Pellegrini said it would take many years to translate the discovery to a drug that could be used in humans. "We are very excited about this discovery," Dr Pellegrini said. "Arih2 is the one of the most important genes involved in the most fundamental and vital decisions that the immune system has to make: whether or not to switch on the immune response to an infection. This discovery has significant implications for manipulating the immune response to infections and suppressing chronic inflammation or autoimmunity because we can target this gene to try to push immune responses in one or other direction – either promoting it or suppressing it," Dr Pellegrini said. "It is probably one of the few genes and pathways that is very targetable and could lead to a drug very quickly."

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More information: www.nature.com/ni/journal/vaop … ent/abs/ni.2478.html