Scientists discover 'switch' to boost anti-viral response to fight infectious diseases

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Singapore scientists from Bioprocessing Technology Institute (BTI) under the Agency of Science, Technology and Research (A*STAR) have for the first time, identified the molecular 'switch' that directly triggers the body's first line of defence against pathogens, more accurately known as the body's "innate immunity". The scientists found that this 'switch' called Bruton's tyrosine kinase (BTK) when turned on, activates the production of interferons - a potent class of virus killers that enables the body to fight harmful pathogens such as dengue and influenza viruses.

While there are anti-viral drugs to treat influenza, the high rates of mutation that are characteristic of the influenza virus have made it difficult to treat with one universal drug or vaccine. As for dengue, there are currently no clinically approved vaccines or cures either. This discovery of BTK's role as a critical 'switch' that boosts the body's anti-viral response, paves the way for developing anti-viral drugs that target the BTK 'switch' to fight infectious diseases.

To investigate the role of BTK in innate immunity, the research team from BTI extracted a class of innate immune cells known as macrophages from both normal mice and from mice deficient in BTK and challenged them with the dengue virus. They found that the BTK-deficient immune cells were unable to produce interferons, and hence had much higher viral counts compared to the healthy immune cells that had high-levels of interferons to fight the virus effectively.

To further demonstrate the critical role of BTK in anti-viral response, the team focussed on BTK's role in Toll-like Receptor 3 (TLR3) signaling. TLR3 is needed for cells to activate the interferon response when cells are infected by viruses. The team examined the effect of having a perpetually-"on" or -"off" BTK 'switch' in TLR3 signaling. They uncovered that a constitutively active or "on" BTK 'switch' enhanced the production of interferon, resulting in a stronger and more lasting anti-viral response with significant reduction in Dengue viral counts. In contrast, a perpetually "off" BTK 'switch' led to a poor anti-viral response with very low levels of inteferons produced, and little protection against Dengue virus infection.

Previously, scientists have always thought that BTK is important primarily in antibody production due to observations made of an inherited genetic disorder in humans called X-linked Agammaglobulinemia (XLA). These patients do not have a functional BTK 'switch', and are unable to produce antibodies because defects in BTK cripple maturation of B cells, a type of white blood cell that produces antibodies.

"We are very excited because this is the first time that the link between BTK and its critical role in the immediate anti-viral responses of the immune system, triggered in response to invading viruses like Dengue, is definitively demonstrated", said Dr. Koon-Guan Lee, the first author of this paper.

Said Professor Kong-Peng Lam, Acting Executive Director of BTI and the Head of the Immunology Group that conducted the research, "This study adds new insights to the understanding of how the body's innate immunity is triggered to create an effective immune response. It is a prime example of how better understanding in basic biological systems brings us a step closer to understanding the mechanism of human diseases, and enables us to find more effective treatment strategies to

combat deadly viral diseases, which we have yet to find cures for.”

More information: The research findings described in this media release can be found in the April 10, 2012 issue of *Proceedings of the National Academy of Sciences* (*PNAS*), under the title, " Bruton's tyrosine kinase phosphorylates Toll-like receptor 3 to initiate antiviral response ” by Koon-Guan Leea, et al. www.pnas.org/content/early/201 … /1119238109.abstract

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