The Role of cGAS-dependent DNA Sensor Pathways in Cancer

Zhang Yaling

Abstract
Recognition of cytosolic DNA during bacteria or virus infection is an important means by which the immune system distinguishes infected cells from healthy cells. Detection of cytosolic DNA by DNA sensors initiates an immune response leading to the elimination of infected cells. Genome-derived cytosolic DNA is present in many cancer cells and mediates type I interferon expression in B-cell lymphomas and prostate cancer cells. Here we show that the cytosolic DNA sensor cGAS (Cyclic GMP-AMP (cGAMP) Synthase) is critical for the recognition of cytosolic DNA and expression of proinflammatory type I interferons in human cancer cells. cGAS co-localized and bound to double-stranded DNA and RNA:DNA hybrids, which are constitutively present in the cytosol of cancer cells. Overexpression of RNASEH1, an endonuclease that specifically degrades the RNA in RNA:DNA hybrids, abrogated RNA:DNA hybrids in the cytosol of cancer cells and reduced type I interferon expression. Attempts to increase the expression type I interferons by transfection of artificial DNA, RNA:DNA hybrids or the cGAS product cGAMP failed to increase the expression of type I IFNs suggesting that the cGAS pathways is suppressed in human cancer cells. Consistent with this possibility, treatment of cells with an inhibitor of STAT3, an well-characterized suppressor of type I interferon expression, significantly enhanced the expression of type I interferons by cancer cells. In summary, cGAS is a major DNA sensor of cytosolic DNA present in cancer cells.

Biography
Zhang Yaling received her Bachelor of Science in 2013 from Nankai University, China. And currently doing PhD in Dr. Stephan Gasser’s lab. Her research interest focuses on understanding the cGAS-dependent cytosolic DNA sensing pathway in cancer cells.

A humanized mouse model for Chikungunya virus infection

Parveen Kaur

Abstract
Chikungunya virus (CHIKV) is a mosquito-borne virus that has re-emerged as a significant public health threat in the last decade. The ongoing epidemic of chikungunya fever in the Western hemisphere demonstrates the ability of CHIKV to establish outbreaks in new geographical areas as a result of global travel. Despite this, there is currently no antiviral treatment for CHIKV infection. The availability of good animal models that recapitulate the in vivo pathogenesis of CHIKV infection is necessary for the development of effective therapeutics. We have recently established a humanized mouse model for CHIKV infection by engrafting human fetal liver cells into NOD-SCID Il2rg−/− (NSG) mice. Infection with CHIKV resulted in transient viremia in the serum, as well as prolonged viremia in the liver, spleen and hind limb muscles. CHIKV-specific human cytokine responses were also detected in the humanized mice, with elevations of IFN-γ and IL-6. Human immune cell infiltrations were observed in the liver and joints as late as two months post-infection, suggesting a possible contributing factor in the chronic arthralgia experienced by some CHIKV patients. By enabling the study of the human immune component during infection, the humanized mouse provides an ideal model for the understanding of clinically relevant CHIKV-associated disease pathologies.

Biography
Parveen graduated with a Bachelor’s degree with honours in Life Sciences from the National University of Singapore (NUS), majoring biomedical sciences. She is currently pursuing her PhD in the Laboratory of Molecular RNA Virology and Antiviral Strategies under the mentorship of Assistant Professor Justin Chu in the National University of Singapore. Her current research interest is focused on the discovery of antivirals against chikungunya virus.