Researchers examine evolution of genes that trigger the body's immune response to viral infection

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Virginia Commonwealth University Institute of Molecular Medicine researchers have traced the evolutionary origin of two genes that serve as primary cellular sensors of infection with RNA viruses, such as influenza, poliovirus, West Nile virus, and HIV, which may ultimately provide researchers with insight into a possible new pathway for the development of innate immunity.

Recent studies by other investigators have provided information on exactly how humans respond to virus infection and the role of innate immunity in protection from viral pathogenesis. Induction of innate immunity is closely associated with the production of type I interferons. Interferons are a class of proteins that are secreted by the body in response to a viral infection such as rhinovirus, the cause of the common cold.

In the study, published online in the Early Edition of the *Proceedings of the National Academy of Sciences* the week of October 20-24, the VCU team reported that melanoma differentiation associated gene-5 (MDA-5) and retinoic acid inducible gene-I (RIG-I) originated specifically in mammals. These genes induce the production of type I interferons.

"Understanding how these unique genes developed and evolved provides a unique opportunity to understand the origins of innate immunity and to develop ways of exploiting this process to develop new types of

therapies for pathogenic viruses," said lead investigator Paul B. Fisher, M.Ph., Ph.D., professor and chair of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine in the VCU School of Medicine.

According to Fisher, MDA-5, but not RIG-I, orthologs are found in fish, indicating that MDA-5 might have evolved before RIG-I. The unique domain arrangement of MDA-5 and RIG-I evolved independently by domain grafting and not by a simple gene-duplication event of the entire four-domain arrangement. This process may have been initiated by differential sensitivity of these proteins to viral infection.

"Our studies provide insights into the shuffling of gene regions, which culminated in a unique mechanism for protection against viral infection. Additionally, our phylogenetic analyses of these domains provides one of the first direct insights into the temporal pathways of development of innate immunity," said Fisher.

According to Fisher, expression of both MDA-5 and RIG-I can limit viral replication post-entry in cells. In this context, identifying drugs that can effectively turn on either or both of these genes offers promise for decreasing virus-induced pathogenesis.

In related work, the team has identified the promoter region, which controls expression of MDA-5 and RIG-I. Studies are now under way at the VCU Institute of Molecular Medicine and the Burnham Institute for Medical Research in La Jolla, Calif., to use these promoters as part of a screening paradigm to identify small molecules that can be developed into drugs to treat infectious diseases.

Source: Virginia Commonwealth University