Valery A Petrenko et al., J Vaccines Vaccin 2016, 7:8(Suppl)
http://dx.doi.org/10.4172/2157-7560.C1.051

Discovery of host cell-binding sites in the hemagglutinin of influenza virus using polyvalent (landscape) peptide phage-displayed library as a molecular adaptation system

Valery A Petrenko and **James W Gillespie**
Auburn University, USA

During natural evolution, viruses have evolved into molecular structures with optimized relationships with a host. In particular, viruses acquired surface peptides that allow them to attach to a host cells and invade into the cells through interaction with cellular receptors and co-receptors. Identification of these cell-recognition peptides would offer a strong basis for development of antiviral drugs, vaccines and diagnostics, prediction of viral drifts from one host to another and prediction and control of emergent infections. Bacteriophage Fd possesses no natural tropism to mammalian cells and is suitable as a vector for generating random peptide phage-displayed libraries. It was shown that phages selected from these libraries are able to specifically recognize cellular receptors and penetrate into sub-cellular compartments during their artificial molecular evolution *in vitro*, similarly to evolution observed with naturally evolved viruses. We hypothesized that selection of cell-associated phage variants from their multi-billion clone libraries and bioinformatic analysis of their cell-binding peptides in comparison with proteins of natural viruses would allow the elucidation of functional virus-host binding sites used during viral pathogenesis. To test our hypothesis, we enriched a subpopulation of phages that interact with human small airway epithelial (SAE) cells and identified the recovered sequences by next-generation sequencing. We then analyzed the phage sequence library against consensus sequences of representative viral proteins, such as hemagglutinin (HA) from different influenza strains over the past 6 years and 5 of the last major pandemics. Several families of peptides were identified with high structural homology to some previously recognized functional segments of HA in the mature viral particles. The identified regions were associated primarily with the membrane fusion peptide domain and the HA0 cleavage site. However other regions were identified suggesting identification of residues involved with a potential co-receptor binding site (CoRBS). The identified peptides revealed regions of HA that were not previously identified as a receptor binding site (RBS) or common antigenic region. Our findings justify the hypothesis that similar mechanisms of molecular adaptation are used in viruses to adjust HA proteins to mammalian cell receptors. After testing their immunological activity, the identified phage peptides can be used as lead compounds for construction of molecular and phage-based vaccines to protect the host from the corresponding virus.

Biography

Valery A Petrenko is currently a Professor in Auburn University, USA. He was graduated from Moscow State University (1972), received PhD and DSc degrees from the Institute of Organic Chemistry (1976) and Moscow State University (1988) and has ranks of Senior Scientist (1984) and Professor in Bioorganic Chemistry and Molecular Biology (1992) from the Government of the USSR. He has served as a Senior Scientist (1977-1982), Laboratory Head (1982-1985), Associate Director of Research, Institute Director (1985-1989), Vice President of Research and Professor (1989-1993) in the Association "Vector" (Novosibirsk, Russia). In 1993, he has joined the faculty of University of Missouri, Columbia as a Visiting and Research Professor and in 2000 the faculty of Auburn University as Professor. He is the recipient (PI) of grants from the ARO, NIH-NCI, Calvert Research, LLC and AURIC. He is also a Member of National Academy of Inventors Chapter (2013), Auburn University Research Initiative in Cancer (AURIC), National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer (2009) and Phi Zeta Honor Society of Veterinary Medicine. His research interests include monitoring and detection of biological threats, diagnosis of infectious and cancer diseases and tumor targeting.

petreva@auburn.edu

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