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Biochemical aspects of Human Immunodeficiency Virus entry into the brain

The blood-brain barrier in humans shields the brain from various infectious agents and injurious elements. Several studies in the past show that viruses enter into the brain and protect themselves from immune surveillance as well as antiviral treatments. Worth mentioning here is that most of the antivirals cannot penetrate into the brain and thus viruses hiding in the brain sometimes act like silent reservoirs of infections. The passage of viruses into the brain is an active area of investigation and each virus uses different strategies for getting access to the brain. Our laboratory developed human blood-brain barrier and utilized it to understand the passage of human immunodeficiency virus type 1 (HIV-1) into the brain. In general, HIV-1 entry into the permissive cells involves interactions between gp120 expressed on viral envelope and CD4 on the cells acquiring viral infections. Intriguingly, brain cells lacks CD4 receptor, however, HIV-1 enters into the brain. For over a decade, our laboratory evaluated molecular moieties involved in the passage of HIV-1 entry into the brain. A strong support from the US National Institutes of Health and the Pfizer Pharmaceuticals allowed us to utilize state of the art human blood-brain barrier model in deciphering the passage of HIV-1 virus into the brain.

We observed that HIV-1 infected immune cells transfer viral particles into the brain through secreting membrane damaging metalloproteinase thus providing an opportunity for infected cells entry into the brain. In our in vitro blood, brain barrier model monocytes upon viral infection exhibited a substantial increase in secretion of active metalloproteinase MMP-2 and MMP-9, and these increases were reversed by cholesterol depleting drugs statins. Because none of these MMPs were detectable in T-cell conditioned media, regardless of infection, we performed gene array studies focused on mRNAs relevant to cell interactions. HIV-1 infection of T cells increased the mRNA of MMP-17, which is a membrane-type metalloproteinase, and suppressed the mRNA expression of tissue inhibitor type-1 (TIMP-1). Furthermore, supplementation of infected monocytes and T-cells with exogenous TIMP-1 substantially suppressed transmigration, indicating a functional role for MMP over-expression supporting virus entry into the brain.

Based on these findings from our laboratory Phase IV clinical trial entitled "Modulation of Monocyte Activation by Atorvastatin in HIV Infection" were initiated by one of our collaborating laboratories." Of note, HIV-1 entry into the brain leads to acquired immunodeficiency syndrome (AIDS) dementia. The finding of clinical trials is mainly observing a reduction in AIDS dementia by statin treatment still needs to be deciphered thus proving our scientific discovery journey.

Biography:

Muhammad Mukhtar has over 25 years teaching experience in biochemistry/microbiology/biotechnology both molecular and cellular levels. He stayed involved in teaching and clinical research for over a decade at the Thomas Jefferson University Medical College of Philadelphia, USA. Besides teaching, he has a very strong portfolio of academic administration. He had a unique experience of serving as a member of Institutional Review Board (IRB) for five years and reviewed hundreds of clinical protocols. He was awarded United States Agency for International Development Scholarship to complete his Ph.D. from the Drexel University of Philadelphia, PA, USA. Additionally, the US government bestowed on him the Outstanding Scientist (O-1) visa award during the years 1995- 2006 for conducting research, training students and young scientists pursuing their careers in medicine and biomedical field in the USA. His contributions were acknowledged with UNESCO Award, a recognition by Sigma Xi in the area of Science and Technology and a most recent fellowship honor by the Pakistani Academy of Medical Sciences.

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