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Role of microRNAs in the molecular pathogenesis HIV/SIV induced gastrointestinal dysfunction/ disease

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Background: The gastrointestinal (GI) tract is a major site of viral replication, CD4+ T cell depletion, viral dissemination and reservoir formation. Chronic GI inflammation, a hallmark of progressive HIV/SIV infection is associated with disruption of the intestinal epithelial barrier leading to microbial translocation and contributing to localized and systemic immune activation/ inflammation which drives AIDS disease progression. Recent evidence suggests critical roles for small non-coding regulatory RNA molecules called microRNAs (miRNAs)that regulate gene expression through post-transcriptional gene silencing in controlling and managing certain aspects of the inflammatory process.

Methodology: To understand their immunoregulatory role in the GI tract, we collected serial resection segments (6-8 cm) from the jejunum before and again at 21, 90 and 180 days post SIV infection (DPI) of rhesus macaques and separated the different mucosal compartments (epithelium, lamina proprialeukocytes (LPLs), intraepithelial lymphocytes and fibrovascular stroma). Using TLDA microRNA arrays, qRT-PCR, luciferase reporter assays and ISH/Immunofluorescence methods we investigated changes in miRNA expression and characterized specific differentially expressed miRNAs exclusively in the LPLs.

Results: At 21DPI, ~21 and 9 miRNAs were up and downregulated, respectively. However, at 90 DPI (n=66) and 180 DPI (n=44), ≥75% of differentially expressed miRNAs showed decreased expression. Additionally, several T-cell activation associated miRNAs (n=6) showed significantly decreased expression at 90 and 180DPI. Interestingly, the SIV-induced miR-190b showed elevated expression at all three time points and confirms our recently published studies demonstrating its expression to be induced in response to viral replication and not by the accompanying immune/inflammatory responses. At 180DPI, among the small number of upregulated miRNAs was a lipopolysaccharide (LPS)-responsive miRNA that showed increased expression in the LPLs. The elevated expression of this miRNA was confirmed in primary intestinal macrophages following in vitro LPS treatment. Furthermore, using luciferase reporter assays we validated two critical signaling transducing components of the TLR4 pathway as direct targets of, at least, two downregulated miRNAs. Finally, expression of both downregulated miRNAs inversely correlated with protein levels of the two TLR signaling proteins in the intestinal epithelium and LPLs.

Conclusions: To our knowledge, these studies for the first time clearly identify miRNA expression signature/s associated with key pathogenic events such as viral replication, chronic immune activation/inflammation and microbial translocation. As miRNAs have been demonstrated to regulate several aspects of the immune response such as immune cell differentiation, migration, cytokine production and TLR signaling, the global miRNA down regulation observed in the LPL compartment can potentially disrupt the translational control of proinflammatory signaling molecules and cytokines. In the setting of HIV/ SIV infection, such drastic reductions in the LPL miRNAome, although essential to help activated cells mount an immune response, can paradoxically enhance proinflammatory protein translation thereby facilitating proinflammatory signaling, persistent GI inflammation, epithelial barrier disruption, microbial translocation, immune activation and disease progression.

Biography

Mahesh Mohan received his Veterinary Medicine degree from the Madras Veterinary College, India, a Masters from the University of British Columbia and a PhD from Oklahoma State University, Stillwater, Oklahoma. Soon after completing his Post-doctoral training at the Tulane National Primate Research Center he was promoted to Assistant Professor (tenure track). His research is currently funded by R01 grants from the National Institute of Diabetes, Digestive and Kidney Diseases and National Institute on Drug Abuse and is focused on the molecular pathogenesis of HIV/SIV in the gastrointestinal tract.

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