3’LTR occupancy by MEF-2C/Menin drives Adult T-cell Leukemia via HBZ

Pooja Jain, M.S., B.Ed., Ph.D.

Department of Microbiology and Immunology; Department of Neurobiology and Anatomy
Drexel University College of Medicine, Philadelphia, PA, USA

Background:
Retroviral anti-sense promoter is an underexplored area, especially the 3’LTR of HIV-1/HTLV-1 has been a conundrum in terms of activity and regulation. This study demonstrates the importance of Myocyte Enhancer factor-2 (mainly MEF-2C) in regulating HTLV-1 3’LTR while highlighting novel transcriptional dynamics underlying ATLL pathogenesis. We have been studying this factor for the last few years and have previously established the role of MEF-2A in HTLV-1 transcription from 5’LTR via Tax oncoprotein. The research presented herein provides convincing evidence for the involvement of MEF isoforms in a unique north American ATLL (N-ATLL) cohort. This cohort of patients have very distinct has a very distinct mutational profile and transcriptional profile with high frequency of epigenetic mutations, which led to poor prognosis of the disease and refractory to radiation therapy.

Methods:
Using several molecular and immunologic techniques including Chromatin immunoprecipitation, polychromatic FACS, and siRNA mediated knockdowns, we demonstrate the role MEF-2C has HTLV-1 infection.

Results:
Of four MEF isoforms (A-D), MEF-2A and MEF-2C were found to be highly overexpressed in acute ATLL patients. Their knockdown resulted in the abrogation of Tax and HBZ expression from HTLV-1-infected cells leading to decreased proliferation and cell cycle arrest. At the molecular level, enrichment of MEF-2C occurred at the 3’LTR along with cofactors Menin, Jun D, and Sp1/Sp3. Direct binding of MEF-2C to repressor protein Menin liberated JunD for transcriptional activity thereby providing a novel mechanism of regulation at the 3’LTR. Chemical inhibition of MEF proteins by MC1568 (a selective Class IIa HDAC inhibitor) resulted in the cytotoxicity of ATLL cells in vitro as well as reduction of proviral load and viral gene expression in vivo.

Conclusion:
This study establishes MEF-2 signaling a potential novel target for therapeutic intervention of ATLL.

Disclosure of Interest Statement:
Nothing to disclose.