

Increased levels of APOBEC3 and interferon mRNA in PBMC of Highly Exposed Seronegatives Individuals (HESN)

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Background: Innate immune response plays an important defense against different viruses including HIV. Variation in their expression and function could contribute to risk of HIV infection. Type I interferons are induced by a variety of viruses elements or by their genetic sequences through the TLR or RIG pathway. Interferons activate cellular restriction factors such as APOBEC3 (A3) and TRIM5 proteins. Some reports showed significantly increased APOBEC3G (A3G) mRNA in PBMCs from HESN, and stimulated PBMCs of long-term non-progressors (LNTP). The question remains whether cellular restriction factors expression is the result of exposure to HIV or its gene products. To address this question, we measured gene expression of interferon, TLR and RIG pathways in PBMC, monocytes, LB, CD4 and CD8 T cells of Mexican ES and Controllers (CT).

Methods: The study sample consisted of 20 subjects. 5 healthy controls (HC), 5 HESN, 5 CT and 5 HIV infected patients without treatment with >300 CD4+ (PT). Total RNA was extracted from sorted monocytes, LB, CD4 and CD8 T cells of unstimulated and stimulated PBMC either with interferon alfa or TLR's agonists. cDNA quantification of 96 genes including APOBEC proteins and TRIM5 was performed by real time PCR based on Nanofluid technology (Biomark, Fluidigm), relative quantification was done by duplicate. Statistical differences between groups were assessed with Mann-Whitney U test.

Results: There were significantly increased levels in relative quantification of A3A, A3F and A3G mRNA in unstimulated PBMC from HESN compared with HC ($p < 0.05$), and PT ($p < 0.01$). Similarly, interferon-inducible genes like IFI16, IFI44, INFA1, INFA2, INFA4 e INFB1 mRNA levels in unstimulated and interferon stimulated PBMC from HESN were significantly increased compared to HC ($p < 0.05$), and PT ($p < 0.01$). We found no significant difference in mRNA levels of both APOBEC and interferon molecules between CT compared with HC.

Conclusion: Our data suggest that HESN present increased innate immune response mediated by IFNs. Their expression can be transcriptionally up-regulated by type I IFN through ISRE/IRF-E responsive elements in their promoters. Upregulation of these factors might increase the activity of restriction factors that inhibit or block viruses such as retroviruses, including HIV-1.