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OA021-03. Design and development of DNA vaccines for the co-expression of micro-RNA and HIV-1 Env

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Background

Small non-coding micro-RNAs (miRNA) are important post-transcriptional regulators of mammalian gene expression. More recently, miRNAs have been described that regulate key elements of the adaptive immune response, such as T-cell development and activation (miR-181) and antigen presentation and development in B-cells (miR-155. miR-150), and various aspects of innate immunity (miR-146). We examined whether DNA vaccine vectors co-expressing miRNA with Env antigen could influence the magnitude or quality of the immune responses to Env in mice.

Methods

Human miR-155 and flanking regions from the non-protein encoding gene microRNA host gene 2 (*MIRHG2*), were introduced into an artifical intron within an envelope expression vector. Expression of miR-155 and Env was examined by Northern and Western Blot respectively. Using miR-155 sequences as a scaffold, we incorporated novel miRNAs encoded to silence expression of host antiviral proteins, or alternatively, to mimic other endogenous, immunomodulatory miRNAs.

Results

The human miR-155 was efficiently expressed and correctly processed from an upstream intron within an Env-expressing DNA vaccine plasmid in human cell lines. Locating the miRNA expression sequences within the intron did not reduce Env expression. Substitution of the native miR-155 guide sequence enabled the targeting of exogenous marker genes, EGFP and ds-Red. Targeting of cellular genes thought to influence Env expression *in vivo*, such as PKR and SFRS1, significantly down-modulated expression of targeted genes but failed to increase Env expression *in vitro*. In an alternative strategy, vaccine vectors delivering immunomodulatory miRNAs such as miR-155 were used to vaccinate BALB/c mice and the generation of Env-specific T-cells and effective antibody responses was measured.

Conclusion

This study provides evidence that native and engineered miRNAs can be successfully co-expressed with HIV-1 Env antigens. The further characterisation of immunomodulatory miRNAs may enable the development of vaccine vectors better able to shape the immune responses to HIV-1 vaccines towards protective correlates of immunity.