Introduction

Hepatitis C virus (HCV) infection remains a major health problem worldwide. Recently, the development of new small molecules that target specific HCV proteins has revolutionised the efficacy of HCV treatment for individuals infected with the common genotype (GT) 1 strain. However, given that these DAAs are unlikely to prevent reinfection, a common occurrence in high-risk HCV exposure populations (Artikin et al., Hepatology 2008), and are financially not viable in resource-poor countries, there is a continuing need for the development of a broadly protective HCV vaccine. Ideally, this vaccine will elicit a combination of antibody and T cell immune responses.

The Delta3 HCV vaccine candidate is derived from HCV glycoprotein envelope 2 (E2) and elicits genotype (GT) cross-reactive neutralising antibody responses, but very little is known about the capacity of E2 to elicit GT-specific CD4 and CD8 T cell responses.

This study characterizes putative CD8+ and CD4+ T cell epitopes within E2 and non-structural HCV genes derived from our population-based genetic approach.

Methods

Reverse genomics

1. We predicted 76 HLA Class I-restricted HCV GT1 T cell epitopes of which 16 were already known. In addition we identified seven putative E2 cell targets. So far 35 novel CD8+ epitopes have been identified with the genetic approach were already known (6 for HLA A- and 10 for HLA B-restricted epitopes).

Figure 1a. Number of CD8+ targets that elicited an IFN-gamma ELISpot response. Some of the epitopes for HLA A and HLA B identified with the genetic approach were already known (6 for HLA A- and 10 for HLA B-restricted epitopes)

Figure 1b. Breakdown of HLA specific T cell targets according to HLA type. The number in brackets indicates the number of subjects tested that carry the particular HLA.

Figure 2. There is limited overlap between GT1 and GT3 HLA Class I (Fig. 2A, Rauch et al. Hepatology 2009) and Class II (Fig. 2B) associated HCV variations

Study subjects: HCV exposed individuals (n=133; 10 spontaneous resolvers, 25 therapy resolvers, 93 chronically infected; 5 with unknown infection status

Results

1. We predicted 76 HLA Class I-restricted HCV GT1 T cell epitopes of which 16 were already known. In addition we identified seven putative E2 cell targets. So far 35 novel CD8+ epitopes have been confirmed. We further identified 26 novel CD4+ T cell targets, of which 10 were known.

2. The Delta3 HCV vaccine candidate is derived from HCV glycoprotein E2 (E2) and elicits genotype (GT) cross-reactive neutralising antibody responses, but very little is known about the capacity of E2 to elicit GT-specific CD4 and CD8 T cell responses.

3. Only a few epitopes are potentially “cross” GT1 and GT3 targets

Hepatitis B vaccine T cell responses

Figure 3: Potential cross genotype targets

A. Epitopes showing evidence of being a cross-GT target. B. IFN-γ response generated against HLA B*08 N53 epitope (GT1 and alternative peptides) by HLA B*08 positive, GT1 infected spontaneous resolver. Amino acids indicated in red are variations found at that position in our population study cohort.

Conclusion

• The prediction of T cell epitopes based on HLA association to HLA-dependent immune T cell pressure allows for the evaluation of wild-type T cell epitopes and their naturally occurring variants
• This approach can detect T cell responses, even in chronic infection, here these responses are commonly directed against variant peptides (data not shown)
• Knowledge about escape patterns and T cell responses to escape variants are critical for optimal T cell based vaccine design
• The development of a universal vaccine against circulating HCV strains will need to include GT1 and 3 specific peptides in addition to cross-GT peptides

Acknowledgements: We thank Australian HCV cohorts, Freemantle Hospital, Western Australia; WA Haemophilia centre, Royal Perth Hospital, Western Australia for providing samples for cellular analysis. We would also like to thank staff at Institute for immunology and infectious diseases, Murdoch University for their technical support. Pooja Deshpande is supported by University of Western Australia scholarship for international research fees (SRIF). Funding for above project received by ACH2, McCusker foundation and Raine Medical Research Foundation.