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Molecular mimicry between Chikungunya virus and host components: a possible mechanism for arthritic manifestations

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Background: Arthralgia is the hallmark feature of Chikungunya virus (CHIKV) infection. Molecular mimicry as the cause of prolonged joint manifestations seen in 10-20% of infected patients has not been investigated despite reports suggesting that this phenomenon may be operational in the pathogenesis of the disease.

Objective: We investigated molecular mimicry between CHIKV and host tissue components by: (i) identification of homologous regions between CHIKV proteins and host tissue using bioinformatics tools, (ii) establishing cross reactivity between CHIKV positive serum samples and peptides exhibiting molecular mimicry (iii) validating the ability of the cross reactive peptides in inducing joint and muscle pathology in a mouse model.

Methods: CLUSTALW revealed two possible "arthritogenic" motifs (SKD & KCA) within CHIKV E1 glycoprotein. These motifs are present only in arthritogenic alphaviruses (CHIKV, RRV, ONNV) but not in 'encephalitogenic' alphaviruses (SFV, VEEV). Four immunodominant epitopes (Peptides A, B, C, D) in the E1 glycoprotein were deduced from IEDB and EMBOSS. The SKD and KCA motifs were also present in Peptides A and B respectively. Homology comparisons between E1 glycoprotein and human proteins were studied. BLAST results revealed a sequence homology of four consecutive amino acids TQLV/TELV between E1 glycoprotein and HLA-B27, while BioXGEM revealed structural homology between Von Willibrand Factor domain of C3 and E1 glycoprotein. These amino acid sequences were also present in the E1 glycoprotein of Peptides A and B. On combining the above data and a logical algorithm, Peptides A and B were selected as possible candidates of molecular mimicry. An ELISA was designed to assess the immunoreactivity of serum samples from patients with confirmed CHIKV infection (n=36) and healthy controls (n=31). We further investigated if Peptides A & B were capable of inducing pathology in C57BL/6J mouse model.

Results: Antibodies to Peptide A and B were detected in 24/36 (66.66%) and 27/36 (75%) serum samples from CHIKV infected patients respectively indicating that these two peptides are recognized by the host immune system. Histopathology results revealed that both the peptides on their own were able to induce significant inflammation in the muscle of C57BL/6J mice and this was comparable to that observed in animals injected with CHIKV alone. Additionally, mice that were primed initially with CHIKV followed by an injection of the two peptides, exhibited enhanced inflammation as compared to animals that were injected with peptides or virus alone.

Conclusion: Molecular mimicry does exist between CHIKV E1 glycoprotein and host proteins and may contribute to enhanced pathology in CHIKV infection.