Australian Synchrotron
USER MEETING 2014
20 – 21 November
National Centre for Synchrotron Science

Contribution ID : **103** Type : **Poster**

Strain specificity in a fully conserved epitope of a malaria vaccine candidate

Thursday, 20 November 2014 17:30 (90)

Merozoite surface protein 2 (MSP2) is an unstructured protein of the Plasmodium falciparum merozoite. The two allelic forms of MSP2, 3D7 and FC27, differ in a central variable region which is flanked by conserved N- and C-terminal regions. Vaccine trials using 3D7-MSP2 have shown evidence of strain specific protection despite the detectable presence of conserved region antibodies. This work focuses on an N-terminal epitope recognised by the mouse monoclonal antibody, 6D8. Despite recognising a fully conserved epitope, 6D8 shows strain specificity. Understanding the determinants of 6D8 specificity will assist the designing of a broad-spectrum MSP2-based malaria vaccine. 6D8 was re-engineered into antibody fragments (scFv and Fv) and validated by SPR and ITC. Additionally, a series of N-terminal peptides were synthesised to locate the minimal binding region (NAYNMSIRR, KD = 6 nM) and investigate the strain specificity of 6D8. High-resolution (1.2 Å) crystal structures of four N-terminal peptides bound to 6D8 Fv revealed identical binding mechanisms irrespective of N- or C-terminal extensions from the minimal epitope. However, binding data indicates that the strain specificity of 6D8 to 3D7 and FC27-MSP2 requires the first 5 C-terminal residues of the variable region, and suggest that entropic effects of unbound variable residues determine the strain specificity of 6D8. This progress will underpin the design of effective strain-transcending MSP2-based malaria vaccines and may have wider implications for our understanding of the immune response towards unstructured proteins.

Keywords or phrases (comma separated)

Immune system, Untructured antigens, Malaria, Vaccine, MSP2, Strain specificity

Summary

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Session Classification : Welcome Function, Poster Session, Exhibition

Track Classification : Structural Biology