Structural Conservation Despite Huge Sequence Diversity Allows EPCR Binding by the PfEMP1 Family Implicated in Severe Childhood Malaria

The PfEMP1 family of surface proteins is central for Plasmodium falciparum virulence and must retain the ability to bind to host receptors while also diversifying to aid immune evasion. The interaction between CIDRa1 domains of PfEMP1 and endothelial protein C receptor (EPCR) is associated with severe childhood malaria. We combine crystal structures of CIDRa1:EPCR complexes with analysis of 885 CIDRa1 sequences, showing that the EPCR-binding surfaces of CIDRa1 domains are conserved in shape and bonding potential, despite dramatic sequence diversity. Additionally, these domains mimic features of the natural EPCR ligand and can block this ligand interaction. Using peptides corresponding to the EPCR-binding region, antibodies can be purified from individuals in malaria-endemic regions that block EPCR binding of diverse CIDRa1 variants. This highlights the extent to which such a surface protein family can diversify while maintaining ligand-binding capacity and identifies features that should be mimicked in immunogens to prevent EPCR binding.

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