Leukocyte immunoglobulin-like receptor B1 is a co-receptor for antibody-depedent dengue infection

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The distribution of both dengue virus and its mosquito vectors globally has made acute dengue a major public health burden throughout the tropical and sub-tropical world. Vaccine development has been complicated by the need to protect against each of the four antigenically distinct virus serotypes. Furthermore, secondary infection with a heterologous dengue virus (DENV) serotype is epidemiologically associated with increased risk of severe dengue. During such secondary infection, it is hypothesized that sub- or non-neutralizing antibodies that opsonizes DENV enhance infection of monocytes, macrophages and dendritic cells via the Fc-gamma receptor (FcγR), a process termed antibody-dependent enhancement (ADE) of DENV infection. However, this is curious as cross-linking of activating FcγRs signals an early antiviral response by inducing the type-I interferon-stimulated genes (ISGs). Entry through activating FcγR would thus place DENV in an intracellular environment unfavorable for enhanced replication. Thus, to escape this antiviral response, antibody-opsonized DENV co-ligates leukocyte immunoglobulin-like receptor-B1 (LILRB1) to inhibit FcγR signaling for ISG expression. This immunoreceptor tyrosine-based inhibition motif (ITIM)-bearing receptor recruits Src homology phosphatase-1 (SHP-1) to dephosphorylate spleen tyrosine kinase (Syk). As Syk is a key intermediate of FcγR signaling, LILRB1 co-ligation resulted in reduced ISG expression for enhanced DENV replication. Furthermore, the differential activation of Syk and SHP-1 also led to fundamental differences in phagosomal trafficking of the virus cargo into cellular compartments that favor either enzymatic degradation of DENV or uncoating of its capsid and genome. Our findings suggest that co-ligation of LILRB1 provides DENV with a means to modulate intrinsic cellular responses to infection.

(Abstract should be within this page)