**Enhanced humoral immunity is a property of the Piezo1 gain of function variant, which is present in one-third of Africans**

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***Abstract***

B cells, unlike T cells, respond to both soluble and membrane-associated antigens. Scientists have observed that B cells respond differentially to these two distinct antigen forms, but it has been unknown for decades what the underlying mechanisms are. Understanding these disparate responses is crucial for unraveling the mysteries of B cell tolerance and activation regulation. We discovered that optimal B cell responses to membrane-associated antigens require the function of Piezo1, a plasma membrane mechanosensitive cation channel. Simply touching B cells with a glass probe and placing B cells on glass surfaces induced calcium flux via increased plasma membrane tension, blocked by the Piezo1 inhibitor. Critically, B cell responses to membrane-associated antigens, but not to soluble antigens, were inhibited both by the Piezo1 inhibitors, OB-1 and GsMTx4 and by Piezo1 siRNA knock down. We demonstrated that calcium ions entering through Piezo1 modulate enzymes that regulate the B cell cytoskeleton, resulting in distinct behaviors in response to antigen stimulation and inducing a robust metabolic state in B cells. B cells become hypermetabolic in response to simultaneous Piezo1 activation and BCR signaling, which induces both quantitative and qualitative alterations in the mitochondria.
Furthermore, it was validated via in vitro T-B coculture experiments that B cells become more activated and capable of inducing T cell activation and differentiation toward Tfh in conjunction with BCR signaling. Piezo1 is activated. Furthermore, in vivo experiments demonstrated that when Piezo1 is hyperactivated in B cells (B cell specific Piezo1 gain-of-function variant), the GC response increases, as does the antibody response. Additionally, in a B cell-specific Piezo1 gain-of-function (GOF) mouse model, we observed an improved survival curve and reduced parasitemia following malaria infection. Thus, this phenomenon holds significant implications for understanding the maintenance of B cell tolerance to soluble self-antigens through Piezo1 regulation, and that the Piezo1 gain-of-function (GOF) variant confers heightened resistance to infectious diseases by enhancing humoral immunity.