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The oxidative inhibitor IM156 suppresses B cell activation by regulating mitochondrial membrane potential and contributes to the mitigation of systemic lupus erythematosus

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Objectives: Current treatment strategies for autoimmune diseases, including systemic lupus erythematosus, may not sufficiently control the aberrant metabolism in B cells. To address this concern, we investigated a biguanide derivative, IM156, as a potential regulator for B cell metabolism.

Methods: We investigated the *in vitro* and *in vivo* effects of IM156 on overactive B cells stimulated by the TLR9 agonist CpG oligodeoxynucleotide (ODN). Using RNA sequencing (RNA-seq), we analyzed the B-cell transcriptome expression, identifying the major molecular pathways affected by IM156 *in vivo*. We also evaluated the anti-inflammatory effects of IM156 in NZB/W F1 mice.

Results: We demonstrated that $CD19^+$ B cells exhibited higher mitochondrial mass and mitochondrial membrane potential than T cells and were more susceptible to IM156-mediated oxidative phosphorylation (OXPHOS) inhibition ($P < 0.01$ or $P < 0.001$; N = 3–6). *In vivo*, IM156 inhibited OXPHOS, cell cycle progression, plasmablast differentiation, and activation marker levels in ODN-stimulated mouse spleen B cells. Interestingly, IM156 treatment significantly increased overall survival ($P < 0.05$; N = 3–9) and reduced proteinuria ($P < 0.05$ or $P < 0.01$; N = 3–9) in lupus-prone NZB/W F1 mice. Our data indicate that IM156 suppressed the mitochondrial membrane potentials of activated B cells in mice, which contributed to mitigation of lupus activity.

Conclusions: IM156 may represent a therapeutic alternative for autoimmune diseases mediated by B cell hyperactivity.