Mutant variant of the *Unc93B1* gene confers recognition of CpG-A by Toll-like receptor 9

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Background

- CpG-A and CpG-B are two ligands of Toll-like receptor 9 (TLR9), a receptor expressed on the endolysosomal membrane
- Previous studies show that TLR9 requires cathepsins B, L, and the DNase2a enzyme in order to recognize CpG-A and CpG-B, but that they are not sufficient
- Understanding the mechanisms of TLR9 activation is important because TLR9 dysregulation has been associated with various autoimmune diseases such as SLE and psoriasis

Methods

- The cDNA library of plasmacytoid dendritic cells (pDCs, CpG-A responsive cells) was functionally cloned to isolate a gene that regulates TLR9 function
- The cDNA library was cloned into Murine pro-B cell line Ba/F3 and diluted to single clones
- After cloning, the cDNA of the colony PCR+ CpG-A responsive clones were sequenced

Results

- Two forms of the *Mus musculus unc-93 homolog B1 transcript variant 1* (Unc93B1) gene were separately identified as a requirement for TLR9 activation by CpG-A
- One form had mutation S547L, the other had a valine-serine-arginine (VSR) variant inserted after the 33rd leucine and mutation G521E

Future Direction

1. The individual functions of the mutants and variant in the gene must be separated to dentify the independent effects of the different mutations and splicing variant
2. Adding *Unc93B1* mutant variants in other immune cells and observing TLR9 activity
3. Observe the localization of TLR9 in cells with different *Unc93B1* genes

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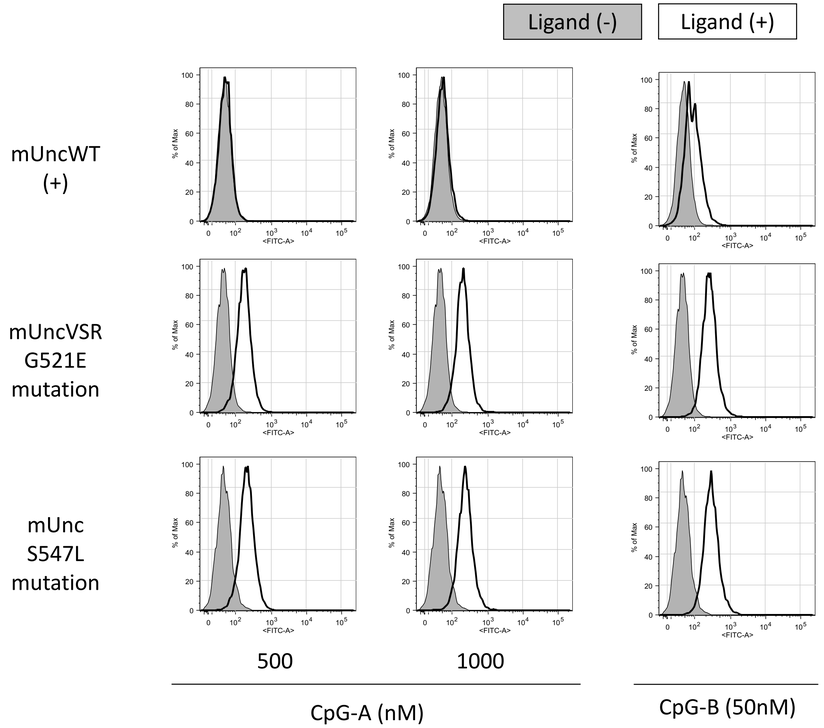

Figure. Ba/F3 cells expressing wt Unc93B1 did not recognize CpG-A nor CpG-B (row 1). Thus, the unique *Unc93B1* variants derived from pDC cells confers CpG-A recognition. Each panel shows FITC-A intensity against % population.

References

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