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Abstract: 90O

A molecular mechanism for the lupus causing mutation in the RNA receptor TLR7

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RNA originating from pathogens is detected in humans by toll-like receptors 7 & 8 (TLR7 & TLR8) to initiate an innate immune response. In TLR7, this is done by binding the single nucleotide degradation product guanosine at an active site, initiating a conformational change and starting a downstream signalling pathway. Recently we demonstrated that a single point mutation in TLR7 can cause the auto-immune disease systemic lupus erythematosus (SLE). This single point mutation Y264H , sits near the guanosine binding site and selectively increased sensing of guanosine and was sufficient to cause lupus when introduced into mice. Surprisingly, the mutation does not increase sensitivity to a guanosine analogue drug (Resiquimod) and does not directly contact guanosine in the binding site.

To understand the basis of increased guanosine sensing we used extensive molecular dynamics simulations (more than 45us in total) to determine the change in binding free energy caused by this mutation. We were able to explain the increased sensitivity to guanosine as a consequence of enhanced binding affinity in the mutant. This is caused by the introduction of a water filled pocket that can solvate the polar ribose ring of guanosine. In contrast, Resiquimod has a hydrophobic group at this location and the extra water molecules do not enhance its binding affinity. Not only does this provide an interesting example of mutations at 'distant' sites influencing substrate binding, it opens the door to designing new drugs to treat the specific causes of auto-immune disease.