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Early NK cell activation as a result of MPL and QS-21 combination controls the adjuvant effect induced by the human Adjuvant System AS01

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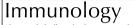
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contains both monophosphoryl-lipid A (MPL) and the saponin QS-21 and is used in the RTS,S malaria candidate vaccine. AS01 induces a transient activation of innate immunity, leading to increased number of activated antigen-presenting dendritic cells, but the impact of combining MPL and QS-21 on innate immune activation has not been investigated. We combined immunological and data analysis tools to identify the mechanism by which AS01 activates innate immunity, leading to improved adjuvant capability. Using a novel statistical framework for mRNA expression analysis, we unravelled the combinatorial effect of AS01 components and identified an emergent early IFNy signature elicited by AS01. The IFNy response was mediated by innate cells, including NK cells that secreted IFNy in the draining lymph nodes (dLN) as early as 2 h after injection of mice with AS01. Depletion strategies showed that NK cells were essential for the development of T cell immunity. Interestingly, a similar activation was observed in the dLN of AS01-injected macaques as well as in the blood of individuals receiving AS01-adjuvanted vaccine.

Our multidisciplinary, cross-species analysis of AS01 mode of action shows that combination of immunostimulants resulted in the induction of novel pathways associated with improved vaccine response. It also highlights a key role for early NK cell activation in AS01 adjuvant effect, providing novel hypotheses on the contribution of this adjuvant in the protection conferred by the AS01-adjuvanted vaccine in humans.

459 Early NK cell activation as a result of MPL and QS-21 combination controls the adjuvant effect induced by the human Adjuvant System AS01

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Combining immunostimulants in adjuvants can improve the quality of the immune response to vaccines. The Adjuvant System AS01