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Characterization of the immunostimulatory activity of synthetic analogues of mycobacterial monomycolyl glycerol.

by

Karen Smith Korsholm*, Pernille Nordly*[§], Henrik Franzyk[§], Maja Hauge Nielsen[§], Camilla Foged[§], Hanne Mørck Nielsen[§], Peter Andersen* & Else Marie Agger*

*Department of Infectious Disease Immunology, Statens Serum Institut, Copenhagen, Denmark.

[§] Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark

The mycobacterial glycolipid monomycolyl glycerol (MMG) is a potent stimulator of the immune system¹ and performs well as an adjuvant in tuberculosis challenge experiments (Andersen *et al.*, manuscript submitted). Furthermore, it has been shown that a C₃₂ synthetic analogue retains this adjuvant activity¹. It thus appears to be the glycerol moiety or the linkage between this and the lipid chain which is important for the immunostimulatory activity. However, during synthesis of MMG C₃₂ several versions with different stereochemistry are produced, and these different versions may contribute differently to the immunostimulatory activity of MMG C₃₂². In order to further investigate the effect of the stereochemistry of MMG C₃₂ on adjuvant activity, we have synthesized several analogues of MMG C₃₂; each with a distinct stereochemistry. Immature human monocyte-derived dendritic cells were incubated with these new synthetic analogues and the immunostimulatory activity was determined as upregulation of activation markers and production of cytokines. Furthermore, selected analogues were injected into mice with antigen and a liposomal delivery vehicle to investigate their ability to induce antigen-specific T-cell responses. Our experiments demonstrate that the stereochemistry of MMG C₃₂ has a profound influence on both dendritic cell maturation *in vitro* and antigen-specific T-cell responses *in vivo*.

References

1. Andersen CS, Agger EM, Rosenkrands I, *et al.* A simple mycobacterial monomycolated glycerol lipid has potent immunostimulatory activity. *J Immunol* 2009;182(1):424-32.
2. Bhowruth V, Minnikin DE, Agger EM, Andersen P, Bramwell VW, Perrie Y, Besra GS. Adjuvant properties of a simplified C32 monomycolyl glycerol analogue. *Bioorganic & medicinal chemistry letters* 2009;19(7):2029-32.