

4th Glycobiology World Congress

September 17-19, 2018 | Rome, Italy

Rational design of adjuvants, ligands of the C-type lectin Mincle

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Most of the adjuvants available today induce Th2 immune responses poorly adapted to intracellular pathogens such as *M. tuberculosis* and adjuvants inducing cellular immune responses are urgently needed. The mycobacterial cord factor trehalose-6, 6-dimycolate (TDM) and its synthetic analogue trehalose-6, 6-dibehenate (TDB) are potent adjuvants for Th1/Th17 vaccination and are also ligands of the C-type lectin Mincle. We have further investigated the molecular mechanism of the recognition of Mincle ligands and their potential adjuvant activity. Using human or murine Mincle reporter cell lines and a soluble form of the receptor, we identified, in addition to TDM and GroMM, several other glycolipid ligands of the receptor, including GlcMM. From these results, we characterized the minimal motifs required for Mincle recognition of the ligands through a multidisciplinary approach combining molecular modeling and bio guided chemical synthesis. We show that the fine structure of the fatty acids plays an unexpected key role in the interaction between glycolipids and Mincle. We synthesized molecules including mannose and glucose esterified with α ramified fatty acids showing agonist activity similar to TDM. These new ligands induced pro-inflammatory cytokine production by human or murine primary cells. The adjuvant potential of the most active compounds was evaluated in a murine model using the mycobacterial antigen Ag85A and formulated as liposomes with dimethyldioctadecylammonium (DDA). Interestingly, they induced an increased Th1 and Th17 response as compared to TDB. These new synthetic ligands of Mincle could be used as adjuvant inducing Th1 and Th17 response, including in the search for a new subunit vaccine against tuberculosis.

Biography

Alexiane Decout has completed her PhD in 2015 in collaboration with the Institute of Pharmacology and Structural Biology in the team of Jérôme Nigou and InvivoGen in Toulouse, France where she aimed at deciphering the molecular bases and functional consequences of the interactions between the mycobacteria and C-type lectins, including Mincle. She then worked as Research and Development Manager in GLYcoDiag, a small French company specializing in Glycobiology and Glycoanalysis until 2017. She is currently a Post-doctoral Researcher in the team of Andrea Ablasser at EPFL, Switzerland.

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