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New strategies to present an anti-candidiasis synthetic glycopeptide vaccine acceptable for human use

Hong Xin, Jonathan Cartmell, David R. Bundle and Jim E. Cutler
LSUHSC & Children's Hospital Research Institute, USA

Background: Our research on pathogenesis of experimental disseminated candidiasis led to the discovery that antibodies specific for Candida albicans cell surface β-1, 2-mannotriose [b-(Man)3] protect mice against the disease. Use of a 14 mer peptide Fba, which derived from the N-terminal portion of the C. albicans cell surface protein fructose-bisphosphate aldolase, as the carrier for the glycan has resulted in a novel synthetic glycopeptide vaccine b-(Man)3-Fba. This conjugate uniquely induces protective responses against both the glycan and peptide carrier parts of the vaccine in a mouse model of human disseminated candidiasis.

Current work: We have isolated monoclonal antibodies (MAbs) specific for the Fba peptide. Use of these MAbs in flow cytometric and confocal microscopic analyses provide evidence that the peptide is expressed on the fungal cell surface during growth as yeast and hyphal forms. Furthermore, one of the MAbs given passively to naïve mice protects the animals against candidiasis. We conclude that the b-(Man)3-Fba vaccine protects mice by inducing protective antibodies against both the glycan and peptide parts of the vaccine conjugate. We have now modified the b-(Man)3-Fba conjugate by coupling it to tetanus toxoid (TT) in order to improve immunogenicity and allow for use of an adjuvant suitable for human use. b-(Man)3-Fba-TT was administered alone, or as either a mixture made with alum or monophosphoryl lipid A (MPL) adjuvants by subcutaneous (s.c.) injection in mice on days 1, 21 and 62. Mice that received the conjugate vaccine prepared in either adjuvant responded as expected by making robust antibody responses. Surprisingly, mice that received the b-(Man)3-Fba-TT without adjuvant also responded well. All three groups of mice also showed protection against a lethal challenge with C. albicans as evidenced by increased median survival times and reduced kidney fungal burden as compared to control groups that received only adjuvants or DPBS buffer prior to challenge. To confirm that induced antibodies were protective, sera from mice immunized against the b-(Man)3-Fba-TT conjugate were found to transfer protection against disseminated candidiasis to naïve mice, whereas C. albicans-adsorbed immune sera did not.

Conclusion: We conclude that tetanus toxiod is a suitable secondary carrier for the glycopeptide conjugate as it induces robust antibody responses and protective immunity administered with or without adjuvants that may be suitable for human use.

hxin@chnola-research.org