Factor H inhibits liposomal and micellar drug-induced complement activation

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Introduction: Complement activation-related pseudoallergy (CARPA), which includes non-IgE-mediated allergic (infusion) reactions to particulate drugs, can occasionally be severe, or even lethal. This phenomenon represents a major immune barrier to the therapeutic use of many state-of-the-art "nanomedicines", including the antifungal drug, liposomal Amphotericin-B (AmBisome) and paclitaxel (Taxol), the most widely used anticancer drug that is solubilized by Cremophor EL (CrEL) micelles. Both AmBisome and CrEL were shown earlier to activate complement partly via the alternative pathway (AP), and to induce CARPA in model animals, with symptoms mimicking the human anaphylactic reaction to these drugs. Therefore, it was hypothesized that inhibiting complement might interfere with the CARPAgenic activity of these drugs. The main natural inhibitor of the AP is factor H. The aim of the present study was to assess the capacity of factor H to inhibit Ambisome- and CrEL-induced complement activation in vitro.
Methods: Recombinant factor H fragments, the artificial construct "mini-factor H" that combines the complement regulatory and surface-recognition domains of factor H, and the factor H-related protein CFHR1 were produced in Sf9 insect cells. Complement activation was measured in normal human sera by measuring the formation of SC5b-9 with Quidel's TCC ELISA. As positive control we used zymosan A.
Results: Both Ambisome and CrEL caused significant, 4-8-fold increase of SC5b-9 over baseline, although the rise of SC5b-9 was less than that caused by zymosan A. Purified factor H exhibited a dose-dependent inhibiting effect on drug-induced complement activation. Exogenous factor H, added at 200 µg/mL concentration, led to >50% and >80% reduction of liposome- and CrEL-induced complement activation, respectively. Addition of recombinant factor H N-terminal fragment in equimolar amount had similar, but weaker, inhibitory effect on SC5b-9 generation, whereas a factor H C-terminal fragment and the factor H-related protein CFHR1 had no inhibitory effect under the assay conditions. Mini-factor H was a more potent inhibitor of both Ambisome- and CrEL-induced complement activation compared with factor H.
Conclusion: Our data suggest that factor H might play a key role in reducing CARPA and that the use of factor H or factor H-derived inhibitors could be a potentially useful approach to prevent this adverse immune effect of the studied and probably many other nanomedicines as well.

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