ABSTRACT #40  
Influence of Fcγ-receptor polymorphisms on efficacy of antibody-mediated lymphocyte depletion in rhesus macaques  
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The in vivo application of monoclonal antibodies (mAbs) in nonhuman primates has enhanced our understanding of correlates of immune protection. However, the in vivo efficacy of mAbs in nonhuman primates is variable. Investigations in humans treated with mAbs have shown that functional variability may depend, at least in part, on polymorphisms of Fcγ-receptors. We investigated polymorphisms of FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA by sequencing of cDNA in rhesus monkeys (RM) treated with different lymphocyte-depleting mAbs (anti-CD20, anti-CD8, or anti-CD4). Eighty-nine rhesus monkeys treated with anti-CD20 (Rituximab), anti-CD8 (cM-T807), anti-CD4 (OKT4a), or control antibody were examined. Animals were bred and housed at different primate centers; therefore, they represent a heterogeneous pool of unrelated animals. Depending on the duration of lymphocyte depletion, animals were stratified into two groups: efficiently- and inefficiently-depleted. As in humans, we found FcγRI was highly conserved in RM. Two polymorphisms resulting in amino acid changes were observed in FcγRIIB and 3 in FcγRIIIA. Surprisingly, extensive polymorphisms in FcγRIIA were identified. Protein modeling indicated that several polymorphisms cluster in a region that might directly interact with an antibody. Following comparison of polymorphism frequencies between efficiently- and inefficiently lymphocyte-depleted animals, we set a threshold of >20% difference as an indicator for biological relevance. Our results demonstrated overrepresentation of specific polymorphisms in FcγRIIA in inefficiently lymphocyte-depleted animals following anti-CD20, anti-CD4 and anti-CD8 mAb treatments. In addition, overrepresentation of FcγRIIA 265V and 269V were also associated with inefficient depletion of lymphocytes following anti-CD8 mAb treatment but not anti-CD20 or anti-CD4 treatment. In contrast, FcγRIIB polymorphisms did not play a role in mAb-mediated lymphocyte depletion. However, as the correlations between the efficacy of antibody-mediated lymphocyte depletion and Fcγ-receptor polymorphisms were moderate, it remains unclear whether rhesus monkeys should be preselected to increase the number of animals that would likely be efficiently depleted following mAb treatment.