Effective immunosuppressive therapy is essential to prevent transplant rejection but renders patients vulnerable to opportunistic infections. The present study investigates the effects of common immunosuppressive drugs on the course of septic peritonitis in an experimental mouse model. We show that treatment with a combination of tacrolimus, mycophenolate mofetil, and methylprednisolone resulted in highly elevated lethality of septic peritonitis. When immunosuppressive drugs were combined with antibiotic therapy, however, mice were almost completely protected. The combination of mycophenolate mofetil and methylprednisolone was shown to be required and sufficient to improve outcome of septic peritonitis in the presence of antibiotic therapy. Combined immunosuppressive and antibiotic therapy, but not antibiotic therapy alone, resulted in enhanced bacterial clearance. These beneficial effects were linked to an elevated expression of activation markers and an increased production of reactive oxygen metabolites by peritoneal neutrophils and correlated with a reduced messenger RNA expression of the inhibitory cytokine IL-22. In contrast, systemic or peritoneal levels of IL-10, IL-12, TNF-alpha, keratinocyte chemoattractant, and monocyte chemoattractant protein 1, and splenic messenger RNA levels of
IFN-gamma were not influenced by the immunosuppressive therapy. These results therefore suggest that combined immunosuppressive and antibiotic therapy may improve bacterial clearance and survival of septic peritonitis by a mechanism that involves enhanced activation and antimicrobial activity of neutrophils and reduced production of IL-22.