PROFILING IMMUNOSUPPRESSANTS IDENTIFIED MYCOPHENOLIC ACID AS A POTENT INHIBITOR AGAINST NOROVIRUS REPLICATION

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INTRODUCTION: Norovirus is the predominant cause of acute gastroenteritis in all age groups worldwide. It results in high morbidity in children, the elderly and mmunocompromised patients. In organ transplantation patients, norovirus infection has emerged as an important cause of complications. Although immunosuppressive medication is generally associated with increased susceptibility to infections, little is known how immunosuppressants directly affect norovirus infection. This study aims to profile the effects and mechanism-of-actions of immunosuppressants on norovirus infection in cell culture models.

MATERIALS & METHODS: A murine infectious norovirus model and a human norovirus replicon model were used. The effects of immunosuppressants, including antimetaboliter (mycophenolic acid; MPA), glucocorticoids (prednisolone and dexamethasone) and calcineurin inhibitors (cyclosporine A; CsA and tacrolimus) on norovirus were studied.

RESULTS: Glucocorticoids have no effect on norovirus replication. Calcineurin inhibitor CsA, but not tacrolimus inhibited human norovirus replication by 82} 3.3% (mean} SEM; n=6, $p<0.01$) at 5 µg/ml. Because cellular factors, including cyclophilin A and B, are targets of CsA, we have evaluated their potential role in norovirus replication by RNAi-mediated loss-of-function assay. Gene silencing of cyclophilin A, but not cyclophilin B, inhibited human norovirus replication by 72} 4.6% (n=4, $p<0.05$), suggesting that the anti-norovirus effect of CsA was through inhibiting cyclophilin A. As an inosine 5'-monophosphate ehydrogenase (IMPDH) inhibitor, MPA inhibits T cell proliferation by depleting cellular guanine nucleotides. We found that MPA at 0.1 µg/ml concentration had already potently inhibited murine norovirus replication by 83} 8% (n=4, $p<0.01$). Furthermore, 1 µg/ml of MPA had inhibited human norovirus replication by 90} 3% (n = 4, $p<0.01$); whereas serum concentrations of MPA in transplant patients ranged from 1 to 10 µg/ml. Exogenous supplementation of guanosine restored norovirus replication, suggesting that MPA inhibited norovirus replication via nucleotide depletion. Furthermore, no evidence of resistance development was observed even after a long-term exposure (20 passages) to MPA treatment in the murine norovirus model.

DISCUSSION & CONCLUSION: These results demonstrated that different immunosuppressants had differential effects on norovirus replication. MPA was identified as a potent inhibitor against norovirus replication with a high barrier towards resistance development. Thus, these findings provide as an important reference for transplant clinicians to choose the optimal immunosuppressants for norovirus infected organ transplant recipients.

Keywords: norovirus, immunosuppressants, mycophenolic acid, guanosine, cyclosporin A
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