Cyclosporine A and lovastatin: the good and the bad, but who will be the winner?

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FOR THE PAST 30 YEARS, cyclosporine A (CsA) has played a significant role as an immunosuppressive agent in anti-rejection therapy for organ transplantation, including kidney transplants (2). CsA inhibits the protein phosphatase calcineurin, which suppresses the immune response (16). However, even with its many advantages as an anti-rejection drug, CsA exhibits a number of side effects, such as hypertension (7), nephrotoxicity (14, 17), increasing cholesterol levels, resulting in controlled serum lipid levels. Unfortunately, there appears to be a dearth of experimental evidence that targets potential molecular mechanisms by which statins can alter the side effects of CsA at the cellular level. Additionally, is it possible that statins can lessen the side effects of CsA and vice versa? In this issue of American Journal Physiology-Renal Physiology, He-Ping Ma’s group (13) provides very exciting data that suggest that statins might benefit patients that receive CsA after an organ transplant and that CsA may be useful in reducing the side effects of extended statin-induced kidney nephrotoxicity. Ma and colleagues (13) used the mouse cortical collecting duct principal cell line (mpkCCDc14 cells) to investigate the reciprocal effects of CsA and lovastatin on transepithelial resistance and cell topography, expression of the tight junctional protein zonula occludens (ZO)-1 via a cholesterol-dependent manner, levels of cholesterol in or around the tight junctional complex, and the induction of apoptosis and ROS levels of mpkCCDc14 cells. Their significant findings include that, first, CsA, which has been shown to elevate levels of cholesterol (19), increased the transepithelial resistance of the epithelial monolayer of mpkCCDc14 cells, which was antagonized by lovastatin. Second, using scanning ion conductance microscopy nanotechnology, for the first time, the authors demonstrated that CsA induced topographic changes in the tight junctional complex of the cell membrane, which increased membrane protrusions near the tight junctions, and this may be responsible for the altered paracellular permeability; these protrusions were alleviated by lovastatin. Third, furthermore, these authors demonstrated remodeling of the tight junctions as CsA increased the amount of ZO-1 in mpkCCDc14 cells, which was abolished in the presence of lovastatin. Fourth, using the cholesterol-binding compound filipin, it was demonstrated that CsA enhanced the levels of cholesterol both in the tight junctional complex and in the apical membrane of mpkCCDc14 cells and that lovastatin attenuated the effect of CsA on the levels of cholesterol. Fifth, lovastatin reduced the induction of apoptosis of mpkCCDc14 cells by high concentrations of CsA. Sixth, sustained treatment of lovastatin resulted in apoptosis of mpkCCDc14 cells, which was reduced in the presence of CsA. Seven, high concentrations of CsA caused oxidative stress, resulting in elevated levels of intracellular ROS in mpkCCDc14 cells by activation of NADPH oxidase potentially via activation of p47phox expression. Finally, in contrast to CsA, lovastatin had no effect on the levels of ROS. Overall, this report provides very convincing evidence that the potential management of dose levels of CsA and lovastatin can be modulated to provide successful analgesic benefits for a kidney transplant patient.

There are some extremely stimulating “take-home” messages from the Ma et al. study (13). Previously, Ma and...
colleagues (19) suggested that modulation of cholesterol levels in the cell membrane or membranous pools might act as a signaling pathway that promotes the observed side effects of CsA. Here, in the present study, Ma and co-workers (13) demonstrated that using lovastatin to inhibit cholesterol synthesis or with exogenous cholesterol can either attenuate or mimic, respectively, the effect of CsA on ZO-1 expression, and they propose that statins can alleviate the CsA-induced modulation in paracellular transport (e.g., increase transepithelial resistance). Second, their observations that CsA increased, whereas lovastatin decreased, the levels of cholesterol in the tight junctional complex is significant because these observations suggest that there may be local synthesis of cholesterol in renal epithelial cells and that the levels of cholesterol in the tight junctions can be modulated locally (13).

This report is very intriguing as we have two different modulators of cholesterol that, under specific conditions, can regulate basic physiology with potentially positive outcomes for the transplant patient. The implications of this report are very thrilling and certainly warrant further investigation into the interactions of CsA andLovastatin on the effect of other transport function by principal cells of the collecting duct. Coupled with those observations, Ma and co-workers (19) suggested that CsA may lead to hypertension by upregulating the epithelial Na⁺ channel via an increase in cytosolic or membrane cholesterol involvement in the inhibition of the ATP-binding cassette transporter (ABCA1). Furthermore, these authors suggested that changes in cholesterol levels in the cell membrane might play a role downstream of ABCA1 (19). Ellison and co-workers (6) demonstrated that tacrolimus (another calcineurin inhibitor) increased activation of the Na⁺-Cl⁻ cotransporter (NCC), which contributed to hypertension in mice. Furthermore, they reported that thiazides (inhibitors of NCC) reduced renal complications of hypertension in renal transplant patients who were receiving inhibitors of calcineurin (6). These studies suggest it would be very tempting for Ma and colleagues to examine the physiologic dynamics of CsA andLovastatin on other ion transport proteins that play a role in overall Na⁺ and K⁺ transport function by principal cells of the collecting duct. Candidate ion transport proteins to pursue would certainly include the epithelial K⁺ channel and Na⁺-K⁺-ATPase.

Finally, we are assured that the use of CsA as an antirejection transplant drug is here to stay. CsA has major advantages to the long-term health benefits and outcome of a transplant patient. Therefore, in light of the various adverse actions of CsA, ameliorating the side effects of CsA is a major research pursuit that clinical and basic scientists must ingratiate. In the end, the health cost-benefit of the patient is our utmost principle concern.

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