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Interrelationship between caveolin-1 and e-NOS: a new perspective

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The original intent of the word caveolae is to describe membrane invaginations at the cell surface. Caveolae are reach in glycosphingolipids, cholesterol and structural proteins essential for their formation (Caveolin-1, -2, -3; Anderson 1998; Govers et al. 2001).

It has been shown that endothelial nitric oxide synthase (eNOS) is located in plasmalemmal caveolae and that it directly interacts with the structural proteins of caveolae (in particular with caveolin-1; Feron et al. 2006). This binding determines a negative regulation of eNOS activity and so a decrease of nitric oxide production (Zulli et al. 2006).

Cyclosporine A (CsA), an immunosuppressive drug, decreases cholesterol content in caveolae (disrupting a cholesterol-caveolin complex) and displaces eNOS from caveolae (Lungu et al. 2004).

The aim of this study was to determine if eNOS regulation can plays a role in CsA-induced nephrotoxicity, using also a nitric oxide synthase (NOS) inhibitor, L-NAME.

For this work we used caveolin-1 knock-out mice (cav-1 -/-) and wildtype (cav-1 +/+).

Both cav-1 -/- and cav-1 +/+ mice have been divided in eight groups. The animals were injected with CsA subcutaneously and with L-NAME intravenously. The first four groups treated with CsA (15mg/kg/day) for different times, 10 (group 1), 14 (group 2), 18 (group 3), and 22 (group 4) days. The last four groups treated with CsA (15mg/kg/day) and L-NAME (30 mg/kg/day) at the same times of the previous four groups (10, 14, 18 and 22 days).

We evaluated kidney morphology by standard staining, e-NOS expression by immunohistochemical method and p-eNOS (ser1177) expression by immunoblotting. Our results showed that in the cav-1 -/- mice CsA doesn't alter the renal morphology instead in the cav-1 +/+ and in CsA+L-NAME knock-out and wildtype mice we found alterations like to those found in CsA treated mice. Regarding eNOS expression it is upregulated by CsA treatment in cav-1 -/- mice compared to all the other groups. Immunoblotting analysis showed that p-eNOS is more expressed in cav-1 -/- mice treated only with CsA.

Our results show that the nephrotoxic effect of CsA is caveolae-mediated and that eNOS up-regulation is responsible of protection against CsA-induced nephrotoxicity in caveolin-1 knock-out mice.

Anderson R (1998) The caveolae membrane system. Annu Rev Biochem 67:199-225.

Govers R, Rabelink TJ (2001) Cellular regulation of endothelial nitric oxide synthase. Am J Physiol Renal Physiol 280:F193-F206.

Feron O, Balligand J (2006) Caveolins and the regulation of endothelial nitric oxide synthase in the heart. Cardiovasc Res 69:788-797.

Zulli A, Buxton BF, Black MJ, Ming Z, Cameron A, Hare DL (2006) The immunoquantification of caveolin-1 and eNOS in human and rabbit diseased blood vessel. J Histochem Cytochem 54:151-159.

Lungu AO, Jin ZG, Yamawaki H, Tanimoto T, Wong C, Berk BC (2004) Cyclosporin A inhibits flow-mediated activation of endothelial nitric-oxide synthase by altering cholesterol content in caveolae. J Biol Chem 279: 48794-48800.

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