Integration of signalling in smooth muscle caveolae

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2010

Caveolae and lipid rafts are plasma membrane microdomains that are considered to play a role in cellular signalling. Caveolins and cavins as well as cholesterol are required for the structure and function of caveolae. The papers summarized in this thesis examine the role of caveolae in smooth muscle function.

Ca^{2+}-sensitization is a contractile process depending on inhibition of myosin phosphatase activity. Here I test whether protein kinase C and Rho-associated kinase-mediated Ca^{2+} sensitization depends on caveolae using gene disrupted (KO) mice. While the process of Ca^{2+} sensitization was unaffected by lack of caveolae in the intestine, α1-adrenergic and protein kinase C-mediated arterial contraction was increased. Arteries lacking caveolae weighed more per unit length, suggesting growth of the arterial wall. I go on to demonstrate that small resistance arteries from KO mice are remodelled, and that these and other changes counterbalance an excessive NO production to normalize blood pressure in caveolin-1 deficient mice.

NO production is required for initiating and maintaining penile erection. Surprisingly, nerve-induced relaxation and relaxation in response carbachol and sodium nitroprusside was impaired in caveolae-deficient corpus cavernosum.

In the last two papers, I examine the role of caveolae in detrusor function. Disruption of caveolae using desorption of cholesterol was first shown to impair contraction of human bladder strips in response to muscarinic receptor activation. I then demonstrate that the membrane density of caveolae increases after bladder outlet obstruction in the rat. The latter effect was due to crowding of the same relative number of caveolin molecules on a smaller relative membrane area.

In conclusion, a considerable body of evidence has been gathered that demonstrate an important and pleiotropic physiological and pathophysiological role of caveolae in smooth muscle.

LUND UNIVERSITY
Faculty of Medicine

Lund University, Faculty of Medicine Doctoral Dissertation Series 2010:111
ISSN 1652-8220
ISBN 978-91-86671-27-3

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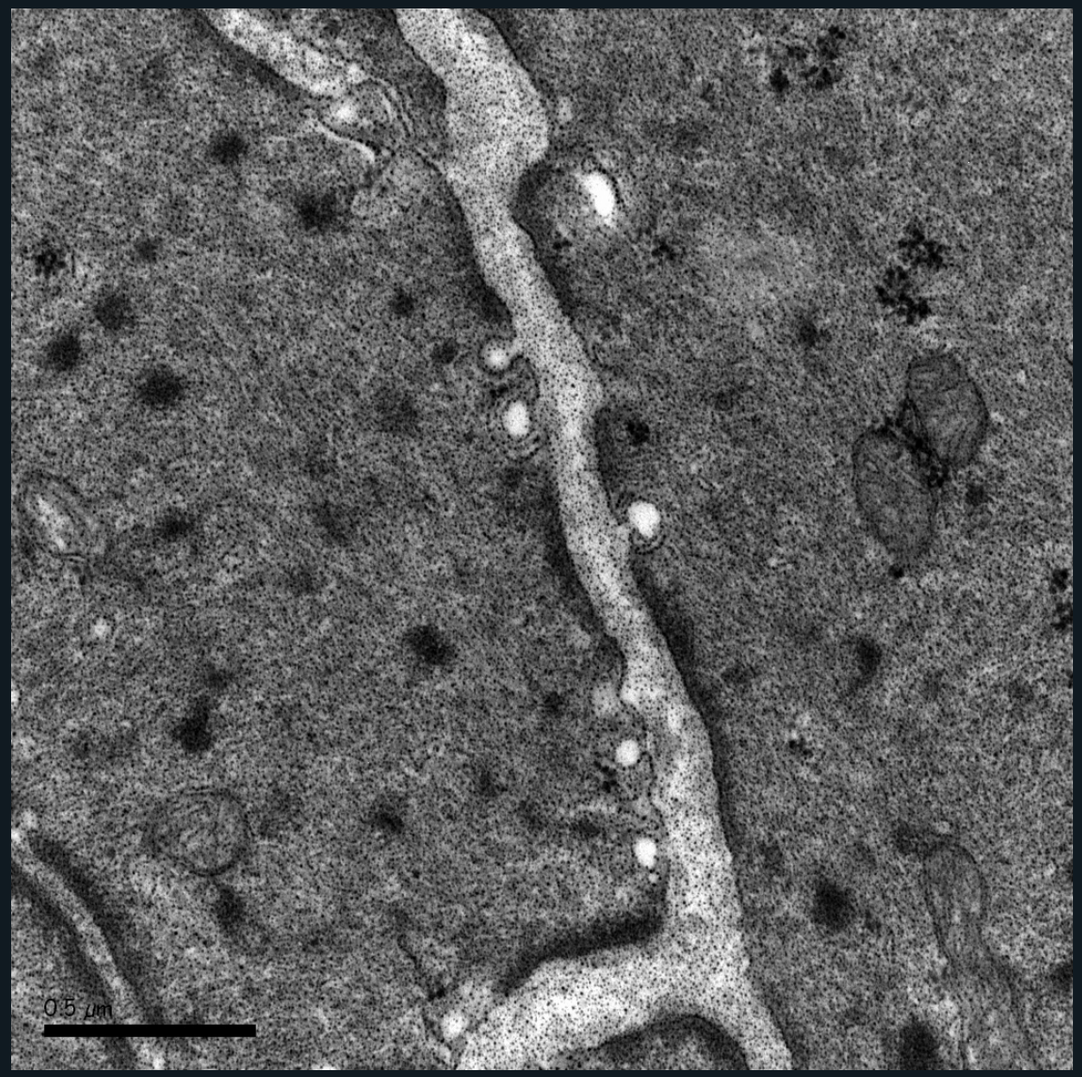

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2010