The urokinase receptor in vascular ageing: regulatory mechanisms and clinical perspectives

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Background

uPA/uPAR system

- uPAR-extracellular serine protease
- uPAR-GPI-anchored receptor
- uPA-extracellular serine protease

Clinical relevance
- Extracellular proteolysis
- Thrombolysis
- Tissue remodeling
- Prognostic marker

Cellular functions
- Proliferation
- Migration
- Adhesion
- Differentiation

Vessel wall structure

Normal vessel
- Contractile VSMC in Media
- Contractile VSMC in Neointima

Ageing
- Neointima formation
- Vessel lumen narrowing
- Increased risk of atherosclerosis

Main findings

1. uPAR expression is upregulated after vascular injury in ex vivo organ culture model

![Figure 1](image)

Porcine coronary artery was dilated by ballooning, incubated for 14 days with (II) or without (III) rosuvastatin, then frozen sections were immunostained for uPAR.

2. uPAR silencing prevents injury-induced vascular remodeling in ex vivo organ culture model

![Figure 2](image)

Dilated porcine coronary artery was infected with control (pLVTHM) or uPARsi lentivirus, incubated for 14 days followed by Papanicolaou stainings and quantification of Intima/Media ratio and the number of proliferating cells.

3. In vitro cell culture model of VSMC aging/phenotypic modulation

![Figure 3](image)

Expression of VSMC contractile markers was studied in cells of contractile and synthetic phenotype. Tubulin was used as loading control.

4. uPAR expression changes during VSMC phenotypic modulation in vitro

![Figure 4](image)

Expression of uPAR in human VSMC of contractile or synthetic state was estimated by immunocytochemical staining (Left), TaqMan analysis (Middle) and western blotting (Right).

5. uPAR silencing regulates VSMC phenotypic modulation in vitro

![Figure 5](image)

Expression of uPAR human VSMC was downregulated using RNAi silencing duplexes and Amaxa nucleofection technology. VSMC contractile markers expression was assessed by western blotting.

6. Regulation of VSMC phenotypic modulation by substrate topographic features in vitro

![Figure 6](image)

SEM image of 2D grating fabricated of ormocer by two-photon laser polymerization technique (Left). Alignment and SM-a-Actin expression in VSMC cultured on ormocer grating.

Conclusions

- uPAR promotes injury/ageing-associated vascular remodeling
- uPAR is a key regulator of VSMC phenotypic modulation in vitro
- VSMC phenotypic modulation may be controlled by substrate structuring

References


Acknowledgements

Dr. Inna Dmuler, Dr. Hermann Haller, Hannover Medical School
Dr. B. Chichkov, Laser Zentrum Hannover, e.V.

Group members