SP044

MICRO-RNA REGULATED PODOCYTE - GLOMERULAR BASEMENT MEMBRANE INTERACTION IN PROTEINURIC KIDNEY DISEASES

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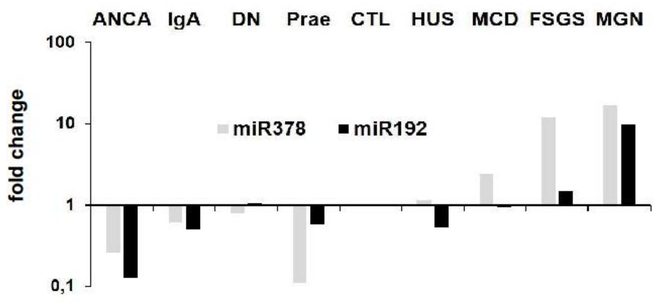
Background

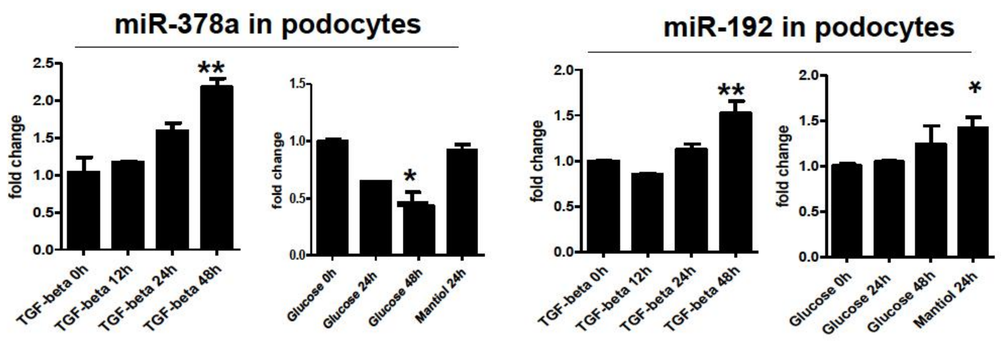
Even though different gene mutations and soluble factors can result in primary glomerular nephropathy, the pathophysiology of many proteinuric kidney diseases is still unknown. Micro-RNAs (miRs) play an important role in gene regulation and therefore seem to be promising candidates involved in glomerular diseases.

Results

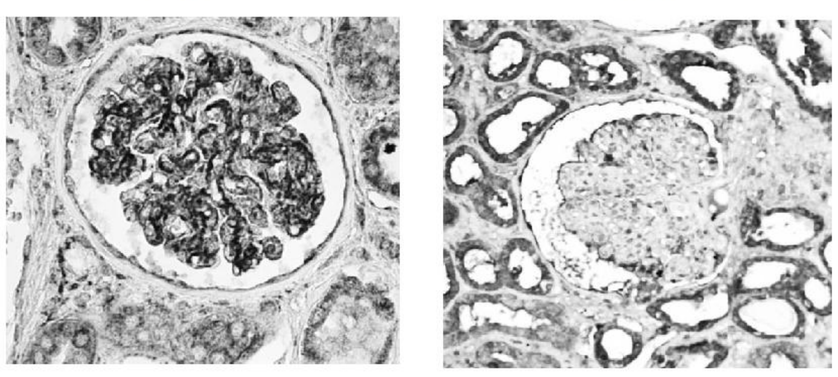
1. MiR-378a and miR-192 are up-regulated in urines from patients with FSGS and MGN.



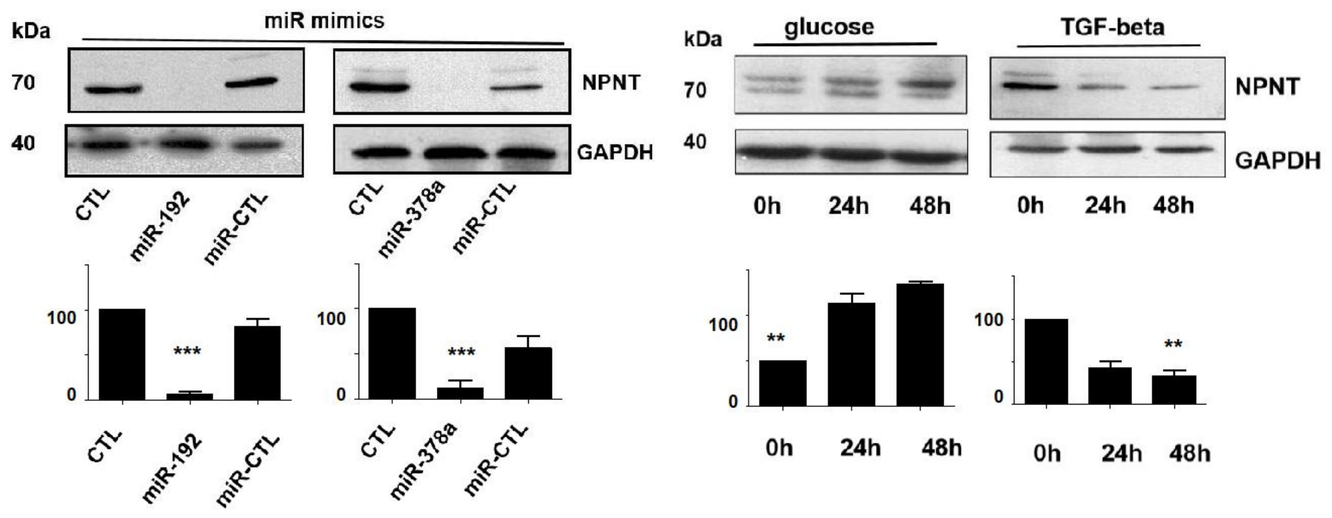
2. TGF-β up-regulates miR-378a and miR-192 whereas glucose up-regulates miR-378a but down-regulates miR-192 in h. podocytes.



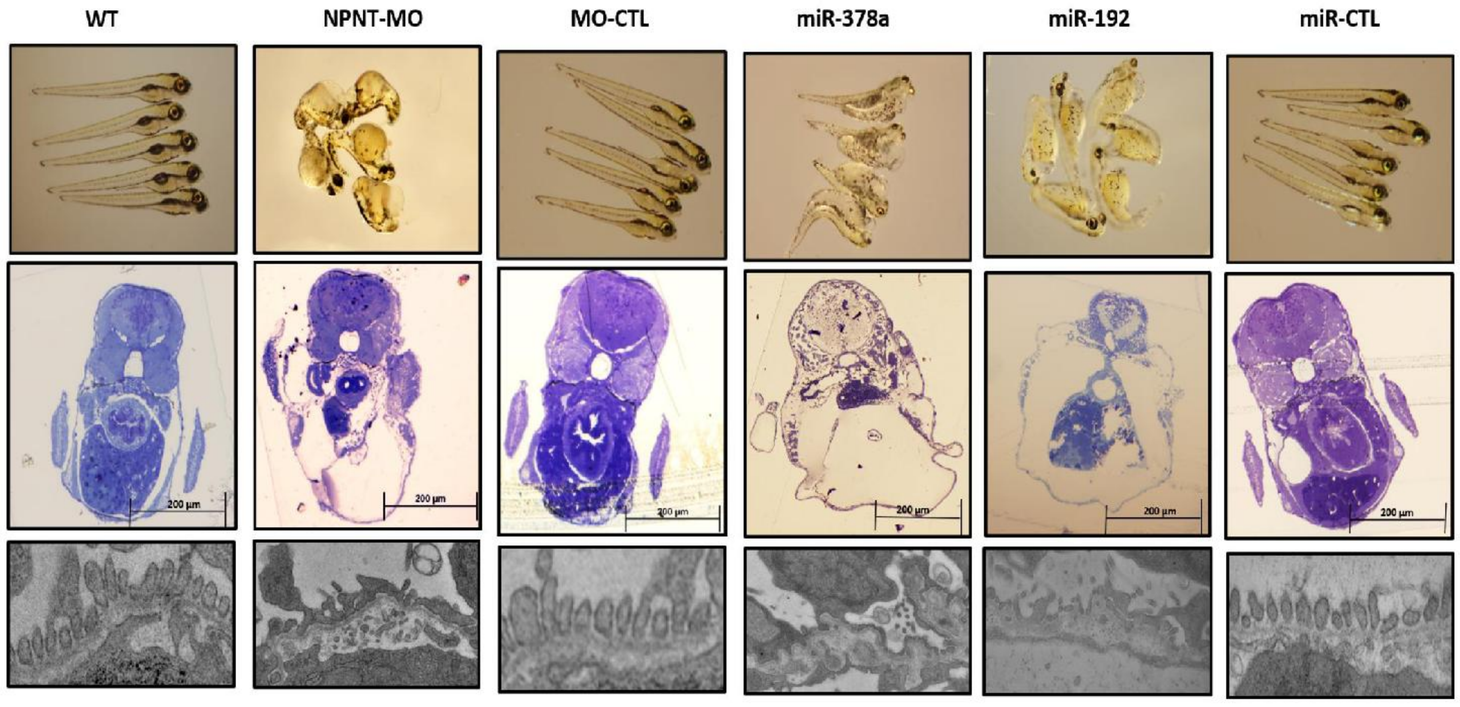
3. Podocyte NPNT expression is reduced in MGN compared to healthy control.



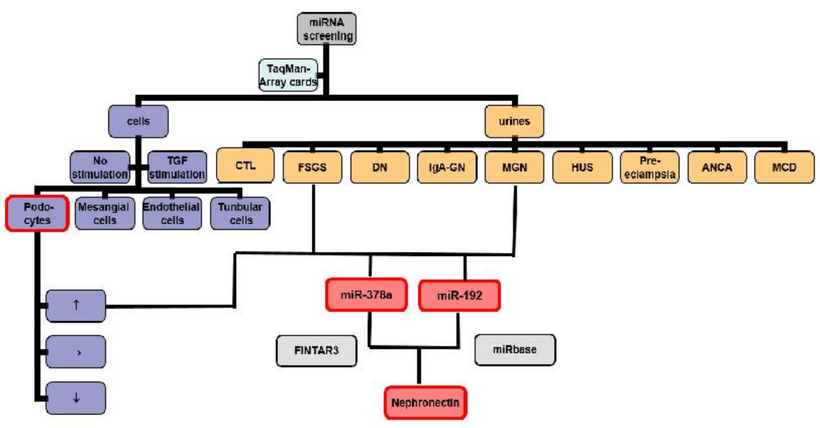
4. MiR-192, miR-378a, glucose and TGF-β regulate NPNT expression in h. podocytes.



5. Injection of NPNT-MO, miR-378a and in zebrafish embryos results in edema, podocyte effacement and thickening of the glomerular basement membrane.

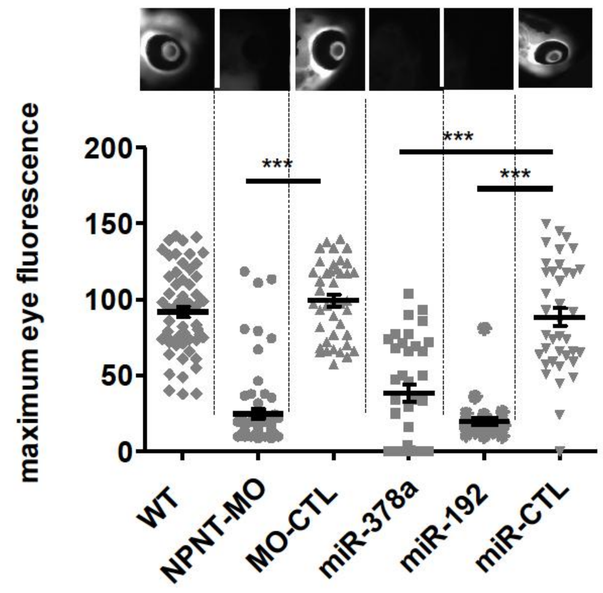


Methods



Baseline and stress-induced miR-profiles of h. glomerular cells as well as miR-profiles of urines from patients with different glomerular disease were screened for overlap of miRs.
Regulation of the common miR-378a and miR-192 target gene nephronectin (NPNT) was investigated in cultured h. podocytes.
A NPNT-morpholino (NPNT-MO), miR-378a- and miR-192-mimics were injected in zebrafish embryos. The resulting phenotype, proteinuria and glomerular ultrastructure were analysed.
A transgenic zebrafish expressing a green fluorescent plasma protein that can be seen in the eye was used to quantify proteinuria.

6. Injection of NPNT-MO, miR-378a and miR-192 in zebrafish embyos leads proteinuria indicated by loss of fluorescent plasma proteins in the fishs` eyes.



Conclusion

NPNT seems to play an important role for the integrity of the glomerular filtration barrier. MiR-controlled NPNT expression might to be a novel regulator of podocyte-glomerular basement membrane interaction.
Urinary miR-378a and miR-192 could be novel non-invasive markers for active glomerular diseases in patients and NPNT a novel target for therapeutic strategies.

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