

Connective Tissue Growth Factor (CTGF) is a Critical Mediator of Cryoglobulinaemic Vasculitis (CV) and a novel target for therapy

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Introduction

Through a serendipitous discovery we found that ren1-CTGF transgenic mice develop cryoglobulinaemic glomerulonephritis (CGN). CTGF, is a matricellular protein involved in cell proliferation and differentiation with pleiotropic effects. We previously demonstrated elevated serum CTGF levels in patients with HCV induced- and Mixed Essential- CV. To confirm these findings and investigate the therapeutic potential of targeting CTGF we used of the thymic stromal lymphopoeitin (TSLP) Tg mice that develop CV and CGN and targeted CTGF with antisense oligonucleotides (ASO).

Methods

CTGF levels were measured in TSLP mice and WT littermates. TSLP Tg mice were treated with weekly CTGF control ASO therapy or vehicle alone for 10-14 weeks.

Results

TSLP Tg mice show an age dependent increase in serum CTGF levels (median 1128pg/ml and 45360 at 6 and 17 weeks respectively). With CTGF ASO this was suppressed to levels comparable to WT littermates (4112 pg/ml). The incidence of ulcerative ear and neck lesions was 50% lower in the CTGF ASO group ($p=0.0549$). Mice that received CTGF ASO developed significantly lower proteinuria compared with untreated Tg animals ($p<0.001$). There was less severe histological injury in the CTGF ASO cohort (mean mesangial expansion score $1.456 \pm SD 0.310$ vs. $2.078 \pm SD 1.038$, $p=0.0159$). WT mice had preserved glomerular podocyte density that was unaffected by ASO therapy (CTGF ASO treated 288.3 ± 67 vs control ASO treated 285 ± 73 podocytes/ $10^6 \mu\text{m}^3$), while TSLP-Tg control ASO mice had significantly reduced podocyte density which was significantly ameliorated by CTGF ASO treatment (control ASO treated 164.8 ± 57 vs CTGF ASO treated 218 ± 35 podocytes/ $10^6 \mu\text{m}^3$). The podocyte CTGF expression was also significantly lower in CTGF ASO treated mice compared with untreated Tg mice (proportion glomeruli with CTGF expression 0.3333 ± 0.5164 vs 0.8333 ± 0.4082 , $p=0.0462$ respectively).

Conclusion

This study demonstrates that CTGF is an important mediator of CV and CGN, and its antagonism provides a novel therapeutic target. The link between TSLP and CTGF is under investigation, but of interest is the finding that elevated TSLP levels are found in HCV patients with cryoglobulinaemia, suggesting that our animal data may accurately recapitulate findings in patients.

