NON CANONICAL NFKB ACTIVATION PROMOTES EXPRESSION OF CCL21 IN PODOCYTES

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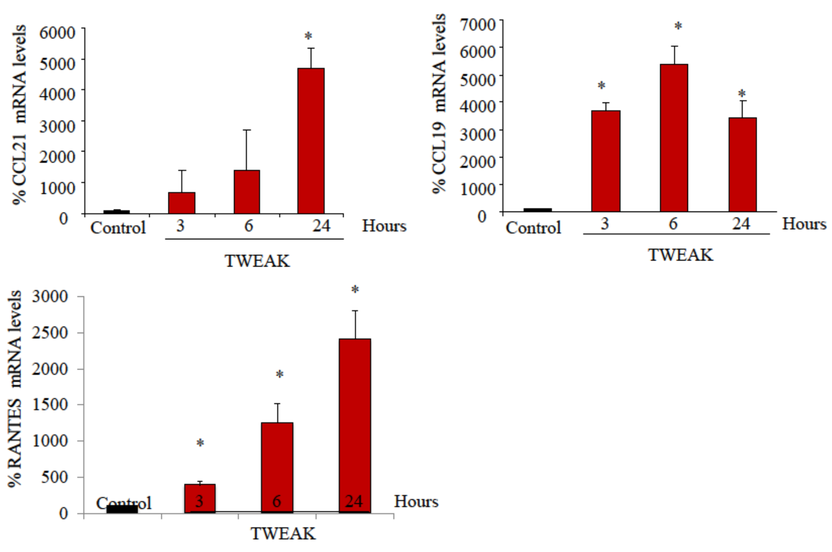
Background and Aims

The TNF-like weak inducer of apoptosis (TWEAK) receptor Fn14 is expressed by podocytes and Fn14 deficiency protects from proteinuric kidney disease in experimental animals. However, the downstream effectors of TWEAK/Fn14 in podocytes are poorly characterized.

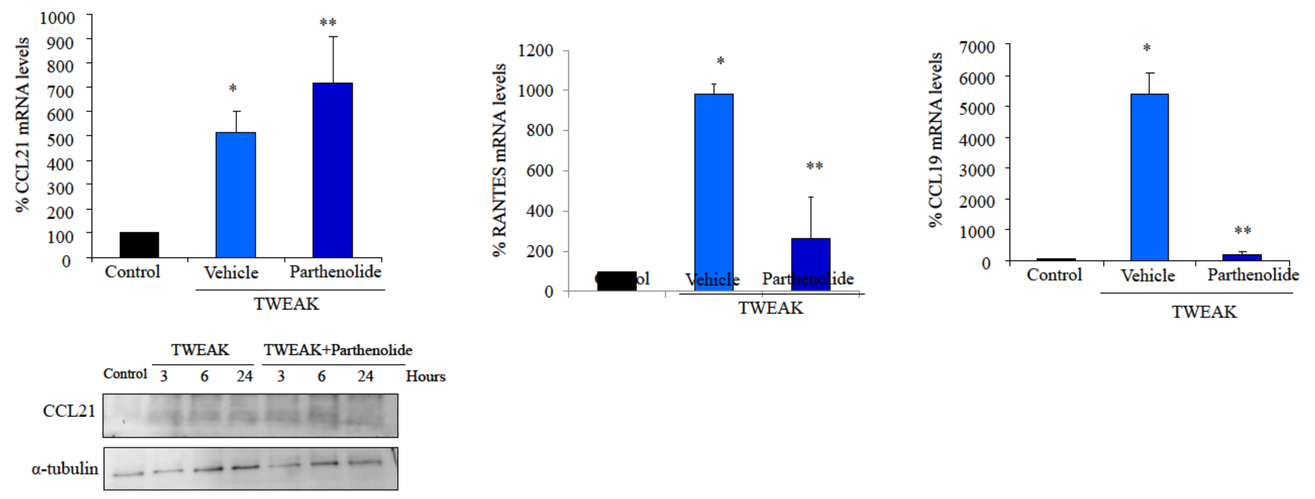
AIM: To explore TWEAK activation of non-canonical NFκB signaling in podocytes. Cultured murine podocytes and experimental rat nephrosis induced by puromycin were studied.

Methods and Results

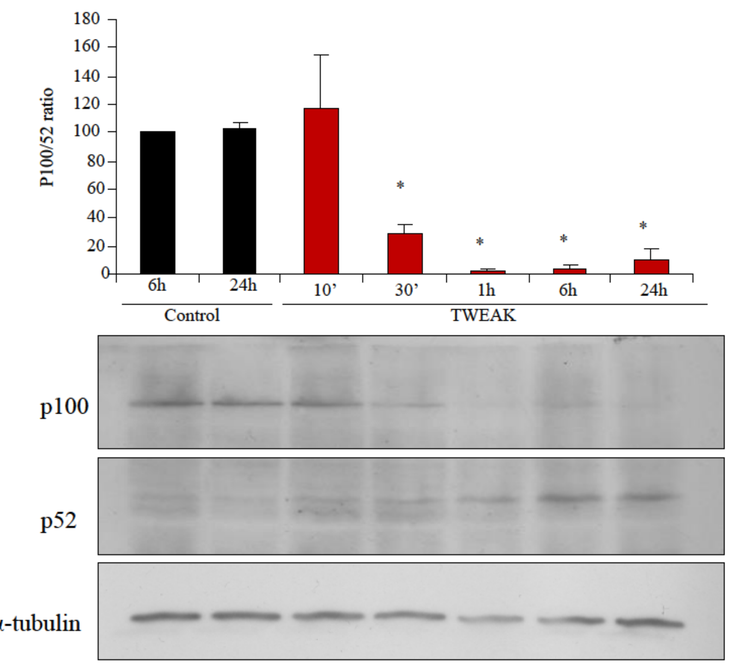
TWEAK induces expression of CCL19, CCL21 and RANTES mRNA in cultured podocytes. CCL21a and RANTES expression progressively increased over 24 h. However, CCL19 expression peaked at 6h and was already decreasing at 24h

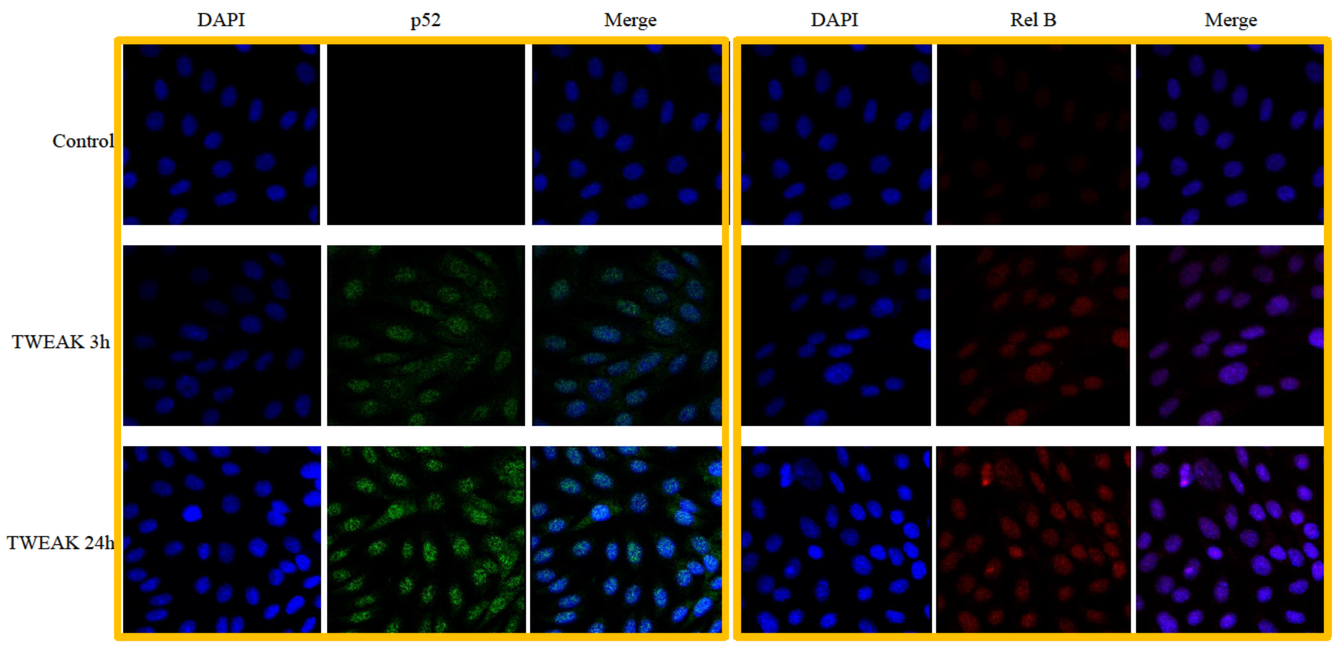


Targeting of classical NFkB with parthenolide modulates RANTES and CCL19 but not CCL21 expression. Parthenolide inhibits the degradation of IκB-α and RelA nuclear translocation and thus, canonical NFκB activation. Parthenolide prevents the increased expression of another canonical RelA target, RANTES, in response to TWEAK. Parthenolide did not prevent CCL21a mRNA or protein up-regulation induced by TWEAK suggesting that RelA does not mediate CCL21a transcription. However, parthenolide did prevent the upregulation of CCL19 mRNA suggesting a differential regulation of both chemokines in podocytes

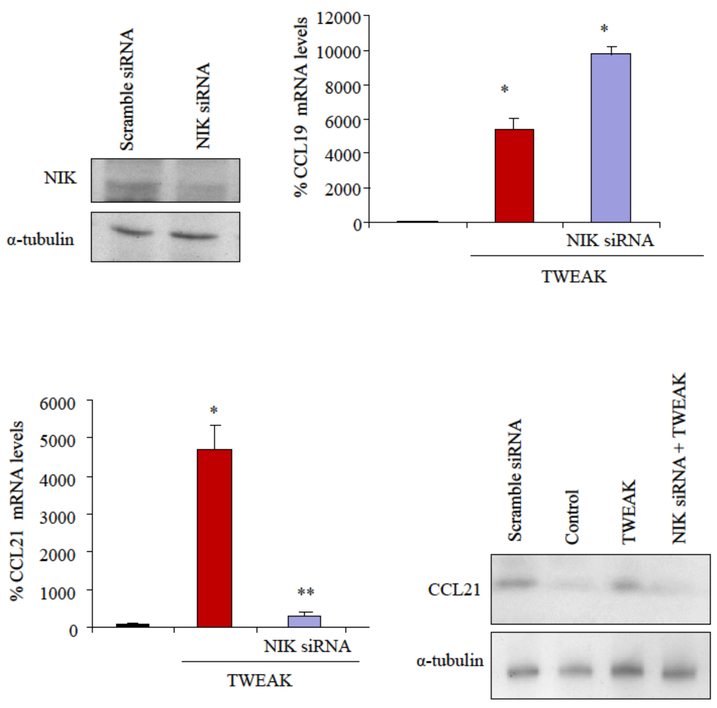


TWEAK induces NFκB p100 processing to NFκB p52 in cultured podocytes in a time-dependent manner and p52/RelB nuclear translocation in cultured podocytes

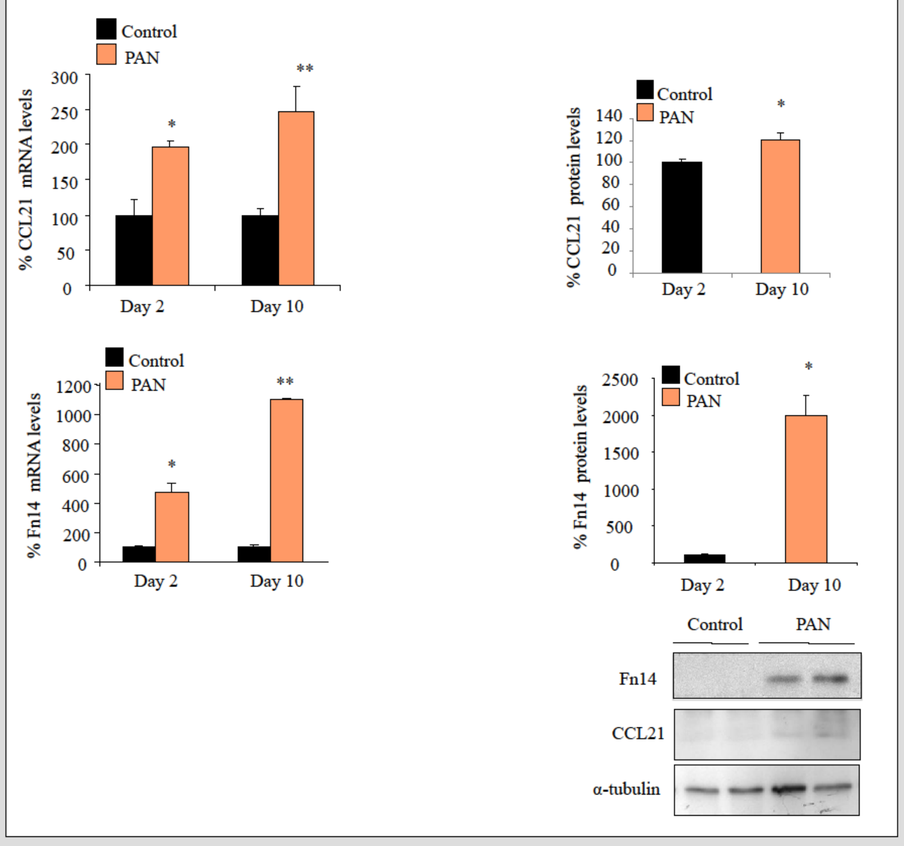




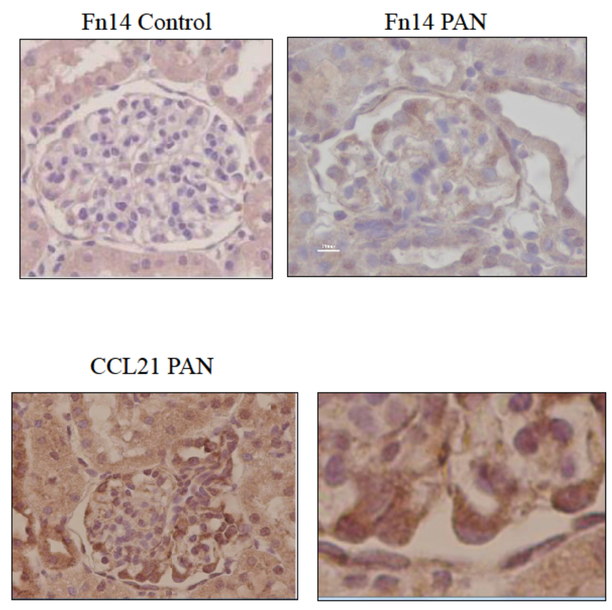
NIK targeting prevents TWEAK-induced CCL21 but not CCL19 expression



Increased podocyte CCL21 in experimental proteinuric kidney disease. Increased whole kidney CCL21 mRNA and protein expression was noted in PAN-injected rats 2 and 10 days post-injection. Moreover, TWEAK receptor (Fn14) mRNA and protein was also increased, following a similar time course



Increased podocyte CCL21 in experimental proteinuric kidney disease. Fn14 and CCL21 protein were localized to podocytes



Conclusions

TWEAK activates the non-canonical NFκB pathway in podocytes, leading to upregulation of CCL21 expression
The non-canonical NFκB pathway should be explored as a potential therapeutic target in proteinuric kidney disease.

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B) Cell signalling. Cell biology. Hormones.
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