Abstract: P360

TWEAK or Fn14 insufficiency inhibits neointimal hyperplasia through reduction of Cyclin/CDKs expression and impaired vascular smooth muscle cells proliferation

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Background: Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and its receptor FN14 participate in the inflammatory response associated with vascular remodelling. However, the effect of TWEAK on vascular smooth muscle cells (VSMCs) is not completely elucidated.

Methods: We have utilized next generation sequencing-based methods to identify genes and pathways regulated by TWEAK at the transcriptional level in VSMCs. We used the DESeq2 under the R statistical software environment to analyze the RNA-Seq data set for differential expression between groups (control and TWEAK-stimulated VSMCs).

Results: Gene expression analysis identified 14948 RNAs. Of that, TWEAK up-regulated 1613 and down-regulated 1094 genes in cultured VSMCs. Through gene set-like network enrichment analysis (NetworkMiner Tool) we obtained the minimal protein connected network. The functional characterization of the net showed 13 significant Gene Ontology biological processes, all of them related with cell proliferation.

In vitro experiments in wild-type or Fn14 deficient VSMCs demonstrated that TWEAK increased cyclins (cyclinD1), cyclin-dependent kinases (cdk4/cdk6) and decreased cyclin-dependent kinase inhibitors (p15lnk4b) mRNA and protein expression. TWEAK also increased the number of VSMCs in S phase (flow cytometry) and the total number of VSMCs proliferative cells (MTS proliferation assay). In addition, TWEAK stimulation increased VSMCs motility (transwell assay) and migration (wound healing assay).

Finally, TWEAK (n=14) or Fn14 (n=10) deficiency and anti-TWEAK administration (10 mg/kg twice a week; N=12) decreased neointimal formation (% stenosis and intima-media thickness) compared with wild type (N=12) or IgG-treated (10 mg/kg twice a week; N=12) mice in wire-injured femoral arteries.

Conclusions: TWEAK/Fn14 axis increases proliferation and migration of VSMCs in vitro and exacerbates intimal hyperplasia after wire injury in mice. These findings suggest that TWEAK and/or Fn14 may represent potential target molecules for treating vascular remodelling, including restenosis after angioplasty.