THERAPY OF RENAL FIBROSIS BY INHIBITION OF THE AXL RECEPTOR TYROSINE KINASE PATHWAY

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Background and Aim

Chronic kidney disease (CKD) is on the rise world wide and exemplifies a major health issue since its progression eventually will cause organ failure, which requires renal replacement therapies such as dialysis or transplantation. Renal fibrosis represents the common pathway of chronic kidney disease irrespective of it's origin and it is only reversibly at an early stage. Partial epithelial-to-mesenchymal transition (EMT) is known to play an important role in the development of kidney fibrosis. The Axl receptor tyrosine kinase pathway is involved in multiple cellular processes, including survival, proliferation, migration and EMT. Thus the aim of our study was to investigated the role of the Axl pathway in experimental kidney fibrosis due to unilateral ureteric obstruction (UUO).

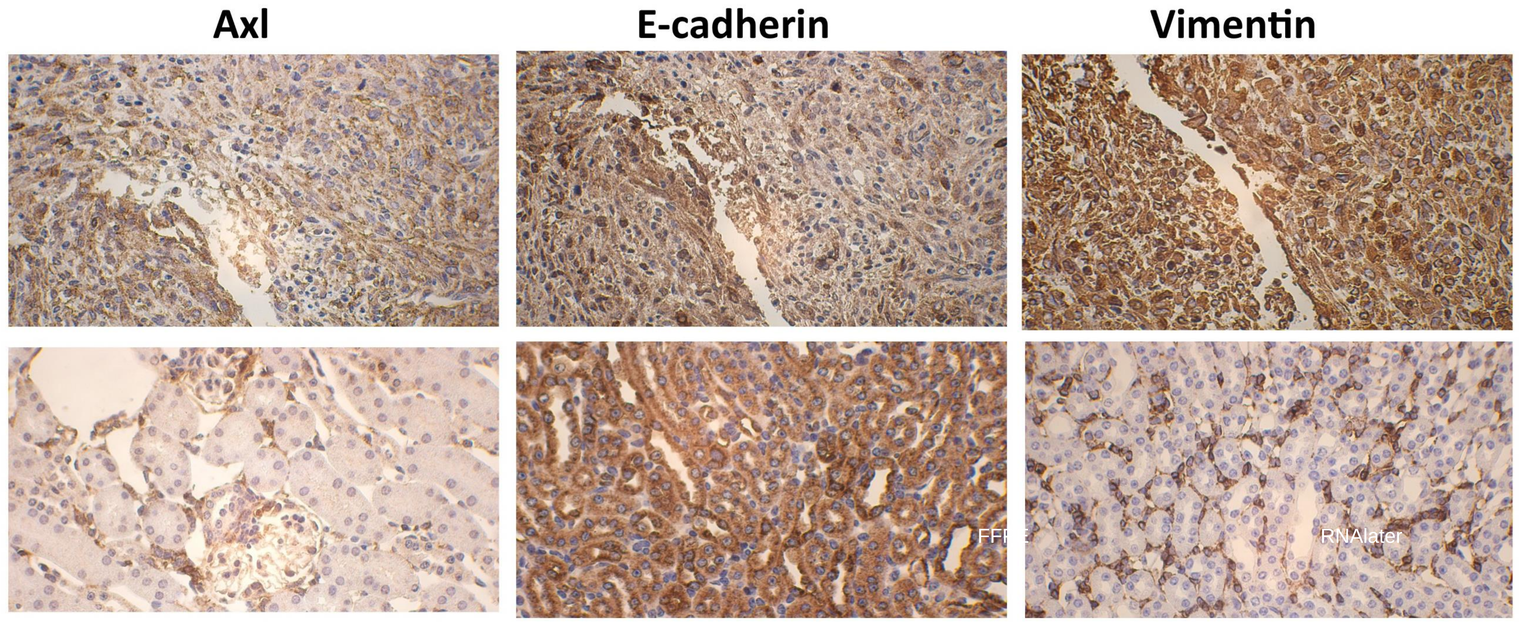
Methods

Eight weeks old male C57BL/6 mice underwent UUO under anesthesia with Isoflurane and were divided into three groups: a) vehicle treatment only (n=12), b) exposure to oral Axl-inhibitor BGB324 (n=12), and c) untreated sham-operated controls (n=3). Treatment was initiated one day before surgery. After 7 and 15 days (d), mice were sacrificed and renal tissues were analyzed by immunohistochemistry (IHC) and by Sirius Red (SR) staining. Fibrosis detected by SR was quantified with automated image analysis (Aperio system) based on a color deconvolution algorithm.

Results

EMT-markers: After 15d of obstruction, ligated kidneys showed increased IHC staining for Axl and Vimentin but decreased intensity for E-cadherin, which is compatible with EMT development. The persistent E-Cadherin staining might indicate partial EMT (Figure 1). Fibrosis assessment: After 7d, there was no difference in the amount of fibrosis measured by SR and computer assisted automated analysis between the BGB324 and the vehicle treated group. After 15d, the BGB324 treated group exhibited the same amount of fibrosis as before. This resulted in an approximately 55% lower fibrosis staining score in SR compared to the vehicle treated group ($p<0.008$; t-test) (Figure 2). There was less αSMA staining in the BGB324 treated group after 15d of obstruction indicating less myofibroblasts and less fibrosis (Figure 3).

Figure 1 (right): EMT markers in UUO. IHC Staining of the EMT markers Axl and Vimentin and the epithelial marker E-Cadherin in ligated (= fibrotic) and unligated (=normal) kidney after 15 days of obstruction.



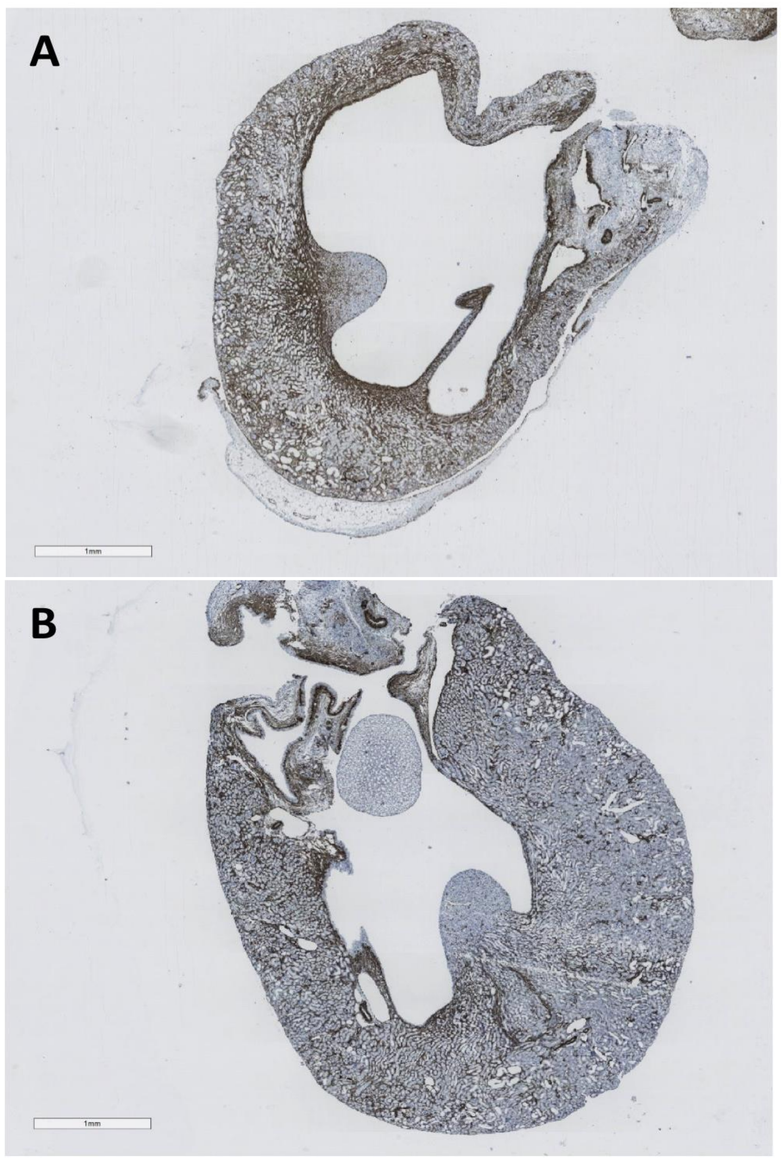


Figure 3 (left): αSMA staining in UUO. IHC of αSMA in ligated kidneys after 15 days of A) vehicle and B) BGB324 treatment.

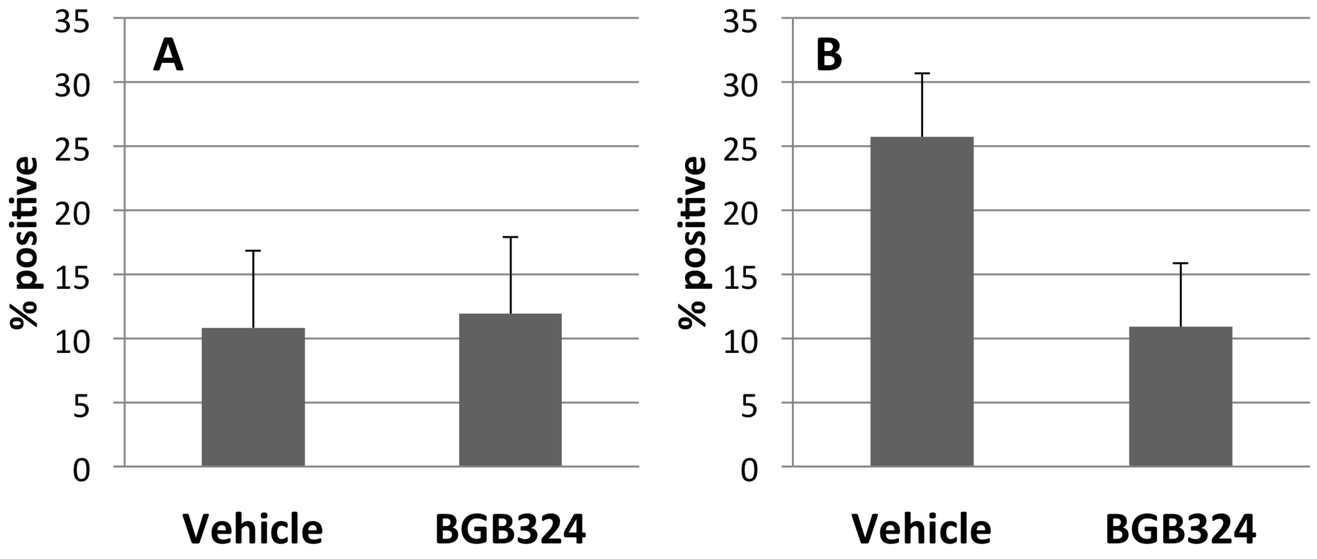


Figure 2 (above): Fibrosis development in UUO after Axl-inhibition measured by SR and computer assisted semi-automated analysis with Aperio: Percentage of positive pixels and thus fibrosis after A) 7 days and after B) 15 days of obstruction.

Summary and conclusion

Pharmacologic inhibition of Axl receptor tyrosine kinase prevents fibrosis development in experimental obstructive nephropathy.

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