Journal of nephrology.
v. 24, no. 1 (Jan-Feb 2011)
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SUBSCRIPTION 2011
Six issues: INDIVIDUAL: Europe € 249; Other countries € 290. INSTITUTION*: Europe € 369; Other countries € 410. RESIDENTS: Europe € 187; Other countries € 228. ONLINE ONLY: Individual € 191; Institution € 290; Residents € 110.
Single copy: € 65.
Back issue: € 70.
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INDEX MEDICUS / MEDLINE
CURRENT CONTENTS® / CLINICAL MEDICINE
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RESEARCH ALERT®
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Published bimonthly by
Wichtig Editore
Via Friuli, 72
20135 Milano - Italy
Tel. 0039 02 55195443 or 02 5455122
Fax 0039 02 55195971
www.wichtig-publisher.com

PUBLISHING MANAGER: Diego Brancaccio
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PRINTED BY
Print Management Group srl
San Giuliano Milanese, Milano - Italy

© Società Italiana di Nefrologia 2010
ISSN 1121-8428
E-ISSN 1724-6059
Reg. Tribunale di Milano n. 488 del 7-8-1992
DIRETTORE RESPONSABILE: Diego Brancaccio

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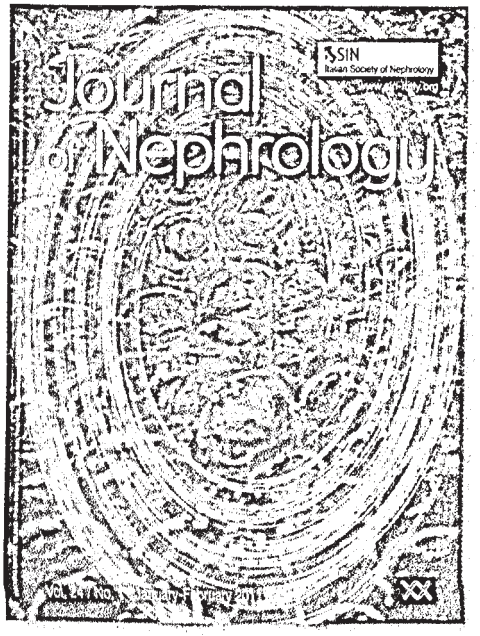

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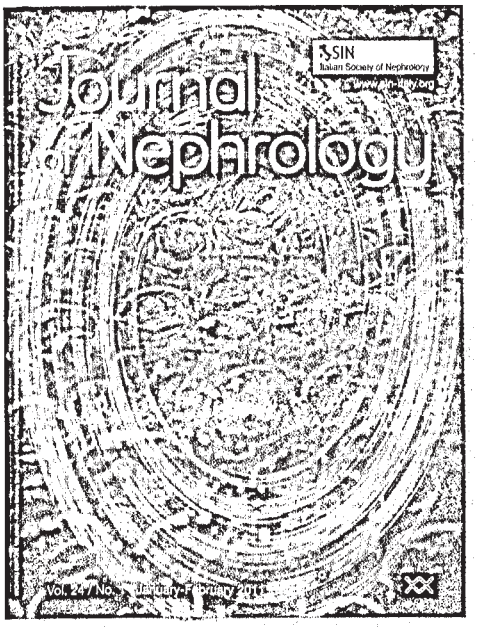

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ORIGINAL ARTICLE

JNEPHROL 2011; 24(01): 106-111

DOI:10.5301/JN.2010.5094

Effect of IL-11 on glomerular expression of TGF-beta and extracellular matrix in nephrotoxic nephritis in Wistar Kyoto rats

Maria Stangou [1], Gurjeet Bhangal [1], Ping-Chin Lai [1,2], Jennifer Smith [1], James C. Keith Jr [3], Joseph J. Boyle [4], Charles D. Pusey [1], Terence Cook [1,4], Frederick W.K. Tam [1]

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ABSTRACT

Background: **The effect of interleukin-11 (IL-11) on transforming growth factor-β (TGF-β) is controversial and has not been examined in renal diseases. In this study, we (i) characterised the up-regulation of TGF-β1, phospho-p38 MAPK (p-p38 MAPK) and extracellular matrix during pathogenesis of glomerulonephritis and (ii) examined the effect of rhIL-11 on these processes in vivo.**

Methods: **Following induction of nephrotoxic nephritis, expression of TGF-β1, α-smooth muscle actin (α-SMA), fibronectin and p-p38 MAPK was detected in the kidney. Rats were treated either with vehicle or rhIL-11 at a high or low dose and culled on day 6.**

Results: **A high dose of rhIL-11 resulted in a significant reduction in the glomerular expression of TGF-β1 (0.4 ± 0.1 vs. 2.04 ± 0.4 semiquantitative score, $p<0.005$), α-SMA (0.6 ± 0.2 vs. 1.5 ± 0.3, $p<0.01$) and fibronectin (0.6 ± 0.1 vs. 1.5 ± 0.1, $p<0.02$). The periglomerular expression of α-SMA and fibronectin was significantly reduced in rats treated with the high dose of rhIL-11 (9.6% ± 2% vs. 92% ± 2.5% of glomeruli, $p<0.01$; and 26% ± 4.9% vs. 94% ± 1.9% of glomeruli, $p<0.005$, respectively). There was a slight but insignificant reduction of p-p38 MAPK in IL-11 treated rats. Treatment with low-dose rhIL-11 did not reduce expression of these molecules.**

Conclusion: **IL-11 suppresses glomerular expression of TGF-β1 and extracellular matrix deposition in experimental glomerulonephritis.**

Key words: *Extracellular matrix, Glomerulonephritis, IL-*

INTRODUCTION

Interleukin-11 (IL-11) is a pleiotropic cytokine which exerts different actions in various cell types (1-3). Recombinant human IL-11 (rhIL-11) is clinically indicated in the treatment of chemotherapy-induced thrombocytopenia (4, 5) and in von Willebrand disease (6). The effect of IL-11 on fibrosis is controversial. It inhibits fibroblast proliferation in vitro (7) and ameliorates fibrosis in the HLA-B27 rat model of inflammatory bowel disease (8), but its overexpression in transgenic mice leads to lung fibrosis and airway obstruction (9). In previous studies, we have demonstrated that treatment with rhIL-11 reduces acute inflammation in nephrotoxic nephritis (NTN) in rats and mice (10, 11). NTN resembles human necrotizing and crescentic glomerulonephritis. Its pathogenesis and natural history have been characterised previously (12).

In this study, we report the effect of IL-11 on the expression of transforming growth factor-β1 (TGF-β1), a key profibrotic growth factor; α-smooth muscle actin (α-SMA), a myofibroblast marker; fibronectin, a component of extracellular matrix; and phospho-p38 MAPK (p-p38MAPK), a signal transduction pathway, in NTN in rats. TGF-β, as a positive regulator of myofibroblast differentiation, has a central role in the development and progression of fibrosis. The MAPK signalling pathway has been shown to exhibit cross-talk with the TGF-β signalling pathway; TGF-β-induced α-SMA expression and myofibroblast differentiation require the activation of MAPKs (13, 14).

To our knowledge, this is the first evidence that IL-11 treatment may retard glomerular expression of TGF-β1 and ex-

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