

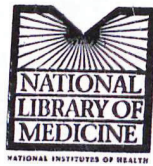
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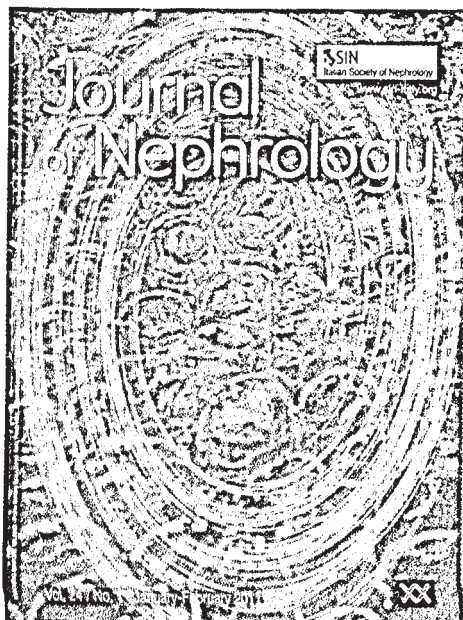
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CONTENTS

THOROUGH CRITICAL APPRAISALS

Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review 1
Giovanni Cerasola, Emilio Nardi, Alessandro Palermo, Giuseppe Mulè, Santina Cottone

Dietary acid load and rapid progression to end-stage renal disease of diabetic nephropathy in Westernized South Asian people 11
Else van den Berg, Frédérique A.P. Hospers, Gerjan Navis, Marielle F. Engberink, Elizabeth J. Brink, Johanna M. Geleijnse, Marleen A. van Baak, Rijk O.B. Gans, Stephan J.L. Bakker

REVIEW

Renal epithelioid angiomyolipoma: a malignant disease *free online* 18
Seema Varma, Shilpi Gupta, Jotica Talwar, Frank Forte, Meekoo Dhar

Inflammation in the pathophysiology of essential hypertension *free online* 23
Fabrizio Montecucco, Aldo Pende, Alessandra Quercioli, François Mach

Achieving effective pain relief in patients with chronic kidney disease: a review of analgesics in renal failure 35
Shobhana Nayak-Rao

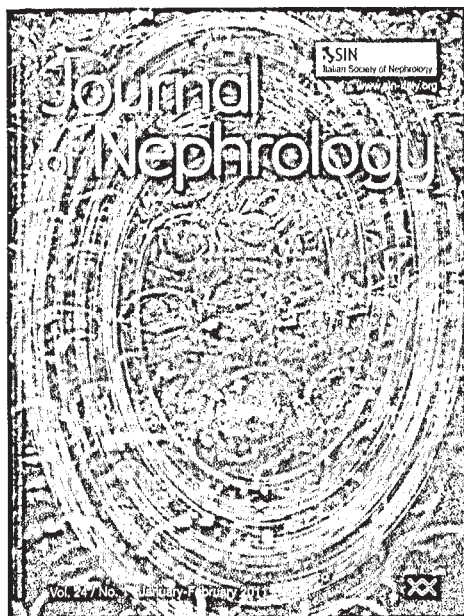
ORIGINAL ARTICLES

The management of left ventricular systolic dysfunction in patients with advanced chronic kidney disease 41
Vera Dounaevskaia, Andrew T. Yan, David Charytan, Laura DiMeglio, Howard Leong-Poi, Abdul Al-Hesayen, Marc B. Goldstein, Ron Wald

The effect of anemia and left ventricular geometric patterns on renal disease progression in type 2 diabetic nephropathy 50
Sung Jin Moon, Ki Sun Bae, Hyeong Cheon Park, Jwa Kyung Kim, Jung Tak Park, Jung Eun Lee, Se Joong Rim, Sung Kyu Ha

Urinary monocyte chemotactic protein 1: marker of renal function decline in diabetic and nondiabetic proteinuric renal disease 60
Roberta Camilla, Soumeya Brachemi, Vincent Pichette, Pierre Cartier, Alexandra Laforest-Renald, Tara MacRae, François Madore, Stéphan Troyanov

Characterization of renal hemodynamic and structural alterations in rat models of renal impairment: role of renal sympathoexcitation 68
Ibrahim M. Salman, Omar Z. Ameer, Munavvar A. Sattar, Nor A. Abdullah, Mun F. Yam, Hafsa S. Najim, Muthanna F. Abdulkarim, Ghassan Z. Abdullah, Gurjeet Kaur, Md. Abdul Hye Khan, Edward J. Johns



ORIGINAL ARTICLES

- Hypercalcemia secondary to persistent hyperparathyroidism in kidney transplant patients: analysis after a year with cinacalcet *free online* 78
Rita Guerra, Ingrid Auyanet, Ernesto J. Fernández, Miguel Ángel Pérez, Elvira Bosch, Ana Ramírez, Santiago Suria, María Dolores Checa
- Effect of a single hemodialysis session on endothelial dysfunction *free online* 83
Prabhakar Reddy Errakonda, Ramakrishna Paladugu, Aparna R. Bitla, Suchitra M. Musturu, Jayaseelan Lakshman, Srinivasa Rao V.L.N. Pemmaraju, Sivakumar Vishnubhotla
- Bone morphogenetic protein-7 expression is down-regulated in human clear cell renal carcinoma 91
Nikolina Basic-Jukic, Tvrtko Hudolin, Margareta Radic-Antolic, Marijana Coric, Renata Zadro, Zeljko Kastelan, Josip Pasini, Daniela Bandic-Pavlovic, Petar Kes
- Vitamin D supplementation and recombinant human erythropoietin utilization in vitamin D-deficient hemodialysis patients *free online* 98
Victoria A. Kumar, Dean A. Kujubu, John J. Sim, Scott A. Rasgon, Philip S. Yang
- Effect of IL-11 on glomerular expression of TGF-beta and extracellular matrix in nephrotoxic nephritis in Wistar Kyoto rats 106
Maria Stangou, Gurjeet Bhargal, Ping-Chin Lai, Jennifer Smith, James C. Keith Jr, Joseph J. Boyle, Charles D. Pusey, Terence Cook, Frederick W.K. Tam
- Gypenosides inhibit renal fibrosis by regulating expression of related genes in rats with unilateral ureteral obstruction 112
Yong Zhang, Jian-E Zhang, Hou-Qin Xiao, Ping-Yong Wu, Shou-Jun Bai
- High-sodium diet promotes a profibrogenic reaction in normal rat kidneys: effects of Tempol administration 119
María Inés Rosón, Silvana Lorena Della Penna, Gabriel Cao, Susana Gorzalczany, Marcela Pandolfo, Carolina Cerrudo, Belisario E. Fernández, Jorge E. Toblli

CASE REPORTS

- Life-threatening hypercalcemia in patients with rhabdomyolysis-induced oliguric acute renal failure 128
Giorgio Graziani, Albania Calvetta, David Cucchiari, Serenella Valaperta, Alessandro Montanelli

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

Maria Stangou¹, Gurjeet Bhargal¹, Ping-Chin Lai^{1,2}, Jennifer Smith¹, James C. Keith Jr³, Joseph J. Boyle⁴, Charles D. Pusey¹, Terence Cook^{1,4}, Frederick W.K. Tam¹

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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- β 1, 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- β 1, 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- β 1 (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 ($9.6\% \pm 2\%$ vs. $92\% \pm 2.5\%$ of glomeruli, $p < 0.01$; and $26\% \pm 4.9\%$ vs. $94\% \pm 1.9\%$ 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- β 1 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- β 1 (TGF- β 1), 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- β 1 and ex-

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