



BEN H. BROUHARD, MD, EDITOR

Potential molecular therapy for acute renal failure

H. DAVID HUMES, MD

■ Ischemic and toxic acute renal failure is reversible, due to the ability of renal tubule cells to regenerate and differentiate into a fully functional lining epithelium. Recent data support the thesis that recruitment or activation of macrophages to the area of injury results in local release of growth factors to promote regenerative repair. Because of intrinsic delay in the recruitment of inflammatory cells, the exogenous administration of growth promoters early in the repair phase of acute renal failure enhances renal tubule cell regeneration and accelerates renal functional recovery in animal models of acute renal failure. Molecular therapy for the acceleration of tissue repair in this disease process may be developed in the near future.

□ INDEX TERMS: KIDNEY FAILURE, ACUTE; EPIDERMAL GROWTH FACTOR; GROWTH SUBSTANCES □ CLEVE CLIN J MED 1993; 60:166-168

ISCHEMIC AND TOXIC acute renal failure is commonly seen in acutely ill hospitalized patients. It is reversible, having both an injury and recovery phase. The injury phase is due to structural damage to renal epithelial cells—predominantly, proximal tubule cells.¹ The recovery phase depends upon the repair and replacement of injured and necrotic tubular epithelial cells.² Growth factors are undoubtedly important in this replicative repair process.³

A better understanding of the cellular and molecular mechanisms responsible for renal epithelial cell regeneration and differentiation would permit a rational approach to enhance the repair process and

speed the time of recovery from structural acute renal failure. In elucidating the cellular and molecular basis of regenerative repair following toxic and ischemic acute renal failure, data now support a paracrine, rather than an autocrine, process promoting growth-factor production in areas of injury within the kidney following ischemic and toxic stress.

Data support the following thesis to explain the replicative regeneration repair phase following acute tubular necrosis (ATN): In the area of injury, cell damage occurs after ischemic and toxic stress. This enhances production of various cytokines and growth factors by the injured cells, including platelet-derived growth factor and transforming growth factor beta (TGF-beta).⁴ Since these two factors are extremely potent chemoattractants,^{5,6} the synthesis and release of these factors lead to inflammatory cell recruitment and activation, predominantly of macrophages. The attraction of activated macrophages to the area of injury leads to subsequent production and release of growth

From the Departments of Internal Medicine, VA Medical Center and University of Michigan, Ann Arbor.

Address reprint requests to H.D.H., the Department of Internal Medicine, VA Medical Center, Medical Service (111), 2215 Fuller Road, Ann Arbor, MI 48105.

factors,^{7,8} most likely TGF- α , which then activates the responsive proximal tubular cell to regenerate via the activation of the epidermal growth factor (EGF) receptor.

Because of the delay in the natural process of replicative repair, exogenous administration of growth factors may accelerate renal recovery after toxic or ischemic stress. Exogenous administration of EGF enhances the regenerative repair process, accelerating recovery of renal function in a rat model of reversible ischemic ATN.⁹ EGF promoted accelerated DNA replication, which was associated with lesser degrees of renal failure and an accelerated return to normal renal function compared with animals not treated with EGF. This report is the first demonstration that EGF accelerates the repair processes of a solid organ after an injurious insult.

Exogenous EGF also enhances the recovery phase of mercuric chloride-induced acute renal failure.¹⁰ EGF resulted in greater levels of DNA synthesis in renal proximal tubular cells when compared with nontreated animals. This enhanced cell-replication was associated with the return of blood-urea-nitrogen and serum creatinine levels to near normal approximately 4 days sooner than that observed in animals not treated with EGF. These findings demonstrate that exogenous EGF accelerates the repair process of the kidney after a severe toxic insult similar to the previous results in a model of ischemic renal injury.

Additional data further extend the role of the EGF receptor in the replicative repair process following ATN. These findings suggest that a potential molecular mechanism of thyroid hormone-related enhancement of renal function recovery following various forms of toxic ATN is consistent with an effect of thyroid hormone to increase EGF-receptor gene expression. This effect leads to increases in the number of cell-surface EGF receptors on renal proximal tubular cells and a potentiated mitogenic response to EGF.¹¹

Once the regeneration phase is accomplished, the final repair process must be initiated: the regenerative,

immature tubular cell must differentiate into a mature functional phenotype. Final differentiation of renal proximal tubular cells requires the development of correct spatial arrangement and pattern formation so that the epithelia develop cell polarity within tubular structures to perform their physiological process of vectorial transport. Final differentiation of tissue is critically dependent on both soluble factors (growth promoters and growth inhibitors) and insoluble factors (extracellular matrix molecules, such as collagen, laminin, fibronectin, and proteoglycans).¹²

Support for a role for growth factors along with the extracellular matrix in kidney tubulogenesis is a recent demonstration that EGF or TGF- α , in the presence of Matrigel (a reconstituted basement membrane gel containing laminin), promotes branching tubulogenesis of collecting duct-like cells in tissue culture.¹³ Further evidence for this coordinated interplay among growth factors and extracellular matrix molecules to induce pattern formation in tubulogenesis is found in recent work, which demonstrates that TGF- β -1 and EGF with the retinoid all-*trans*-retinoic acid are necessary and sufficient to induce tubulogenesis in adult renal proximal tubular cells in tissue culture, in a manner highly reminiscent of inductive embryonic kidney organogenesis.¹⁴ Furthermore, these studies also demonstrated that the critical role of retinoic acid (a defined morphogen) in kidney tubulogenesis is determined by its ability to promote laminin production by renal tubular cells. These findings demonstrate the critical importance of matrix molecules in pattern formation and further identify the target protein (ie, laminin) induced by retinoic acid to promote morphogenesis.

These insights identify potential molecular therapy to enhance the recovery rate of this form of renal injury. Preclinical trials are underway to test the efficacy of recombinant EGF in ATN, with the hope that this form of molecular therapy will accelerate the repair process and reduce morbidity and mortality associated with this disorder.

REFERENCES

1. Humes HD, Weinberg JM. Alterations in renal tubular cell metabolism during acute renal failure. *Miner Electrolyte Metab* 1983; 9:290-305.
2. Cuppage FE, Chiga M, Tate A. Cell cycle studies in the regenerating rat nephron following injury with mercuric chloride. *Lab Invest* 1972; 26:122-126.
3. Sporn MB, Roberts AB. Peptide growth factors and inflammation, tissue repair, and cancer. *J Clin Invest* 1986; 78:329.
4. Humes HD, Daniel TO. Proto-oncogene and growth factor messenger RNA levels in the repair phase of ischemic acute renal failure. *Kidney Int* 1990; 37:484.
5. Martinet Y, Bitterman PB, Mornex J, Grotendorst GR, Martin GR, Crystal RG. Activated human monocytes express the c-sis proto-oncogene and release a mediator showing PDGF-like activity. *Nature* 1986; 319:158-160.
6. Wahl SW, Hunt D, Wakefield LM, et al. Transforming growth factor type beta induces monocyte chemotaxis and growth factor production. *Proc Natl Acad Sci USA* 1987; 84:5788-5792.

7. Sekkarie M, Cieslinski DA, Wiggins R, Humes HD. Characterization of the inflammatory response in the kidney during the recovery phase of postischemic acute renal failure. *J Am Soc Neph* 1990; **1**:603.
8. Rappolee DA, Mark D, Banda M, Werb Z. Wound macrophages express TGF- α and other growth factors in vivo: analysis by mRNA phenotyping. *Science* 1988; **241**:708–712.
9. Humes HD, Cieslinski DA, Coimbra T, Messana JM, Galvao C. Epidermal growth factor enhances renal tubule cell regeneration and repair and accelerates the recovery of renal function in postischemic acute renal failure. *J Clin Invest* 1989; **84**:1757–1761.
10. Coimbra T, Cieslinski DA, Humes HD. Exogenous epidermal growth factor enhances renal repair in mercuric chloride-induced acute renal failure. *Am J Physiol* 1990; **259**:F483–F443.
11. Humes HD, Cieslinski DA, Johnson L, Sanchez IO. Triiodothyronine enhances epidermal growth factor induced mitogenesis in renal proximal tubule cells by stimulating EGF receptor gene expression. *Am J Physiol* 1992; **262**:F540–F545.
12. Madri JA, Pratt BM, Tucker AM. Phenotypic modulation of endothelial cells by transforming growth factor- β depends upon the composition and organization of the extracellular matrix. *J Cell Biol* 1988; **106**:1375–1384.
13. Taub M, Yang Y, Szczesny TM, Kleinman HK. Epidermal growth factor or transforming growth factor- α is required for kidney tubulogenesis in matrigel cultures in serum-free medium. *Proc Natl Acad Sci USA* 1990; **87**:4002–4006.
14. Humes HD, Cieslinski DA. Interaction between growth factors and retinoic acid in the induction of kidney tubulogenesis. *Exp Cell Res* 1992; **201**:8–15.

