Acute renal failure. III. The role of growth factors in the process of renal regeneration and repair

Hammerman, Marc R., Robert Safirstein, Raymond C. Harris, F. Gary Toback, and H. David Humes.
Acute renal failure. III. The role of growth factors in the process of renal regeneration and repair. Am J Physiol Renal Physiol 279: F3–F11, 2000.—This review, which is the final installment in a series devoted to controversial issues in acute renal failure (ARF) (3, 47), will examine available information regarding the role of growth factors in ARF. In general, studies in this area have fallen into two broad categories: 1) those that have examined the renal expression of genes encoding growth factors or transcriptional factors associated with the growth response that is induced after ARF, and 2) those that have examined the efficacy of exogenously administered growth factors in accelerating recovery of renal function in experimental models of ARF. Despite the vast amount of information that has accumulated in these two areas of investigation, our understanding of the mechanisms involved in the process of regeneration and repair after ARF, and the role of growth factors in this response, remains rudimentary. This overview, contributed to by a number of experts in the field, is designed to summarize present knowledge and to highlight potentially fertile areas for future research in this area.

epidermal growth factor; insulin-like growth factor; hepatocyte growth factor; regeneration; early growth response genes

ALTHOUGH ACUTE RENAL FAILURE (ARF) in humans occurs under circumstances far too complex to be recapitulated by any one animal model, acute renal injury induced in the rat has been used to gain a better understanding of the disease in humans and to determine how the kidney is able to repair itself postsinsult (20, 65, 75, 77). The process of recovery from ARF is accompanied by a complex pattern of gene expression that bears a resemblance to that exhibited by growth factor-stimulated cells in culture (14, 65). The kidney is a known site of synthesis for several growth factors, including epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor I (IGF-1) (20, 65). The evidence that these growth factors produced at this site participate in the regenerative

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
response that occurs after ARF includes observations describing changes in renal expressions of these agents after experimentally induced ischemic ARF in rats (13, 20, 64). The rationale for the successful use of exogenous EGF, HGF, or IGF-I as growth-promoting therapeutic agents in experimental ARF is provided by these observations and also by a number of findings confirming that the renal proximal tubule is a “target” for these agents (19, 20). EGF, HGF, and IGF-I all enhance DNA synthesis in regenerating proximal tubule. However, IGF-I has beneficial effects that are not shared by other growth factors tested thus far. These include an increase in the glomerular filtration rate and a generalized anabolic action reflected as amelioration of weight loss after ARF (20).

The successful use of growth factors in rats has led to clinical trials for IGF-I in humans. We showed that IGF-I administered postoperatively to patients undergoing surgery during which blood flow to the kidneys is interrupted is well tolerated and eliminates the fall in glomerular filtration rate that occurs in placebo-treated subjects. The incidence of ARF in our study population was too low to permit any conclusions regarding an action of IGF-I to ameliorate the course of postoperative ARF (15). The low incidence, even in patients at risk, represents one difficulty in establishing the efficacy of any agent to prevent ARF. A second clinical trial conducted to test the efficacy of IGF-I in established ARF was terminated after an interim analysis demonstrated no beneficial effect. It was suggested that the severity of systemic illness, heterogeneity of causes for ARF (surgery, trauma, hypertension, sepsis, or drugs), or a delay in starting IGF-I (for as long as 6 days after the onset of ARF) might have contributed to the negative outcome (21). Whatever the case, it appears as if IGF-I may not be a “magic bullet” for the treatment of ARF in humans.

It is possible that, in addition to acting directly on their receptors in renal tissue, growth factors act indirectly to stimulate the expression of genes coding for other agents in kidney that are important effectors of the regenerative response. Such products, once identified, could serve as “second-generation” therapeutic agents and may prove to be far more efficacious than the growth factors that enhance their synthesis. One approach to identify such products is to identify the genes, the expression of which is induced by acute renal injury and further enhanced by the administration of one of the growth factors described above. The first gene product that, in our hands, showed increased expression after induction of ischemia, and further increased expression in IGF I-treated rats with experimental ARF, was identified as osteopontin. Its expression was enhanced by 12 h postischemia in the medullary thick ascending limb (mTAL), and at 5 days postinjury in the regenerating proximal nephron (59). Could osteopontin be an effector of renal regeneration postischemic injury? If so, how does it act?

Osteopontin contains an arginine-glycine-aspartic acid (RGD) cell-attachment sequence by which it binds to several integrins (51). Administration of the RGD-containing peptide cyclo-RGDfV to rats reduces tubular obstruction postischemia and ameliorates the course of ARF (52). This agent is thought to prevent tubular plugging by inhibiting the cell-cell binding of detached proximal tubule epithelial cells that express integrins on their plasma membranes to damaged cells remaining attached to the basement membrane that express integrins on their apical surface. Osteopontin expression at 12 h postischemia in kidney may serve to provide the organ with an endogenous source of RGD-containing peptide in the distal nephron. Alternatively, or in addition, it could act as a chemoattractant for macrophages and monocytes and/or could act to stimulate matrix formation, to inhibit apoptosis (anoikis) that occurs during the cell migration that is necessary to reepithelialize the damaged S3 segment (38), to regulate renal blood flow and solute transport by inhibiting renal nitric oxide synthase (NOS) (51), or could serve, if secreted into tubular fluid, to inhibit stone formation after acute renal injury. Whatever its mechanism of action and the timing of the expression of osteopontin and its receptor (CD44) postischemia (38), the magnitude of enhanced expression and the localization of osteopontin production are consistent with a role for the peptide in the process of tubular regeneration that occurs after ischemic injury. Also consistent with a key role for osteopontin is the observation that mice with a targeted disruption of the osteopontin gene do not recover normally from acute ischemic renal injury (51).

The expression of a number of genes in addition to osteopontin is enhanced in rat kidney after induction of acute ischemic injury (4, 58, 65, 82). It is possible that the product of one or more differentially expressed genes (perhaps a novel one) will carry our therapeutics for ARF in humans beyond the use of growth factors. 

M. R. Hamerman

The reaction of the renal tubular epithelial cells to stress is heterogeneous. Some cells die, others enter the cell cycle and proliferate, and still others appear indifferent to the injury. Renal growth factors have been demonstrated to accelerate repair and improve survival in a number of experimental models of ARF (9, 29, 33, 46, 55, 84). We propose that growth factors achieve these positive effects on the course of ARF by both upregulating cytoprotective responses and by downregulating responses that are cytoreductive.

Elements of the Renal Stress Response

Cells exposed to a hostile environment mount a molecular response that is similar to that initiated by growth factors (23), including a typical immediate early (IE) gene response (5). However, by contrast to the proliferative effect of growth factor induction, the IE response induced by stress is antiproliferative. c-jun, a prototypical IE gene, is activated by both growth factors or stress, but via distinct members of the mitogen-activated protein kinase (MAPKs) family. Stress induction of c-jun occurs via jun-N-terminal kinases (JNKs), which bind to and phosphorylate...
c-JUN directly, whereas growth factor induction of c-jun is indirect via the activation of other transcription factors by the extracellular regulated kinases (ERKs) (10, 11, 37, 62). Importantly, the principal c-jun activators after renal ischemia are the JNKs (62) and inhibiting them postischemia improves renal function and repair (12). This is consistent with other observations on the cytoprotective effects of JNK activation (7, 43, 83).

Renal stress also induces the cyclin kinase inhibitors (CKIs). The CKIs are nuclear proteins that are the major regulators of the two “checkpoints” of the cell cycle, G1/S and G2/M (6, 70). Oxidative stress and DNA damage (41), two particularly relevant models of stress in the kidney, provoke CKI expression. Both ischemia- and cisplatin-induced renal injury increase the expression of p21, a CKI that causes arrest by inhibition of G1 and G2 cyclin kinases. The increased expression of p21 may depend on ERK activation (41). Importantly, p21 inhibits JNK activity (71). The expression of p21 has been demonstrated to be antiapoptotic during myocyte (81) and neuroblastoma cell differentiation (61) and protects colorectal carcinoma cells from prostaglandin A2-mediated cell death (18). Growth factors inhibit apoptosis induced by DNA damage in some cells, and this function is p21 dependent (7). Thus p21 expression may be a survival factor potentially superinducible by growth factor induction of ERK.

Growth Factors and Stress Signaling

It would appear that cell fate during renal stress is determined in part by a balance between cytoprotective pathways, served by JNK, and cytoprotective pathways, served by ERK, and that growth factors are positive regulators of the cytoprotective pathways. Given this framework, we can consider a model in which survival factors, by modifying the stress-induced transduction pathways, may positively regulate survival. Renal cell stress provokes MAPK activation, which leads to a transcriptional program that ultimately determines cell fate. It is suggested that the survival of a cell will depend on the balance between survival signals, such as ERK activation and p21 transcription, and death signals such as JNK activation and apoptotic gene expression. The balance will depend on a particular cell’s intrinsic stress response machinery, the intensity of the stress, and whether other survival signals exist in the particular environment in which the stress is provoked. The hypothesis proposed here is that growth factors will promote survival by enhancing the survival pathways.

Survival Pathways and Growth Factors

Specific examples of growth factor intervention in this stress signal pathway do exist. EGF and TGF-α commit cells to the cell cycle by activation of ERK and increase DNA synthesis after ischemic and nephrotoxic renal failure (9, 55). Growth factors limit cell loss by inhibiting programmed cell death during stress (44, 50) and in the developing kidney (26). Cell death subsequent to the detachment of stressed cells from the underlying substratum, or anoikis, depends on JNK activation and is inhibited by growth factors (16). Growth factors may inhibit pathways that promote injury. An interesting example of this possibility is the apparent mitigating effect of indicible NOS (iNOS) inhibition on the course of ischemia-induced renal failure (53). EGF, IGF-1, and FGF among others inhibit cytokine-induced iNOS induction in vascular endothelial cells (69), and EGF reduces NO-induced cytotoxicity in neurons (42). Thus growth factors may alter signaling induced by counteracting potentially cytoprotective cytokine pathways. Growth factors may improve repair by increasing cell motility (54), which is responsible in part for the relining of the injured tubule epithelium. The increase depends on the activation of the ERK pathway (36).

More general affects of growth factors that could promote cell survival, such as increased renal blood flow (5), and promotion of anabolism (5) may also depend on such a transduction pathway but have not been clearly linked as yet to the MAPK pathway.

In summary, there is increased evidence that acute renal injury leads to the increased expression of a variety of growth-promoting substances. The timing and localization of a number of these growth factors, including HGF, HB-EGF, and IGF-1, and the acceleration of recovery of renal function with exogenous addition of growth factors further suggests a role for these agents in renal injury. Additional studies are needed to understand the signal pathways and downstream targets by which growth factors prevent or mitigate acute renal injury. Fundamental issues of signal transduction and cell cycle regulation addressed by developmental biologists and cancer/cell growth investigators will likely yield important clues about the parts of the pathway that should be targeted and the agents that will likely have the most therapeutic benefits.

R. Safirstein

STUDIES OF GROWTH FACTORS and their role in ARF to date have been largely descriptive or phenomenological. These studies have examined the range of growth factors or their receptors, the expression of which is altered in ARF and administration of which has been reported to limit injury and/or accelerate recovery in experimental models of ARF (1, 2, 17, 22, 24, 31, 32, 49, 67, 72, 76, 78); coupled with these studies is the demonstration that exogenous administration of a growth factor accelerates recovery from experimental injury (9, 33–35, 45, 46, 57). However, this field of investigation has raised a number of interesting and important new questions regarding the role of growth factor in ARF. These as yet incompletely defined areas, which represent the basis for potentially fruitful areas of additional research, are discussed in detail below.
Which Endogenous Growth Factors Actually Mediate Renal Repair After Acute Injury?

Although expression of certain growth factors and growth factor receptors may change after renal injury, no studies to date have convincingly shown that any endogenous renal growth factor is actually playing a role in recovery. Thus, the question remains whether there is any one endogenously produced growth factor or group of growth factors that is necessary and/or sufficient to mediate the repair process. Have all of the relevant growth factors involved already been identified, or are there additional critical growth factors yet to be described (or even discovered)? A proposed paradigm for acute renal injury is that the postischemic tubule recapitulates certain aspects of renal development (82). Do the same growth factors that regulate developmental processes also mediate repair after acute injury? Related issues include the questions of 1) which cells express the relevant growth factors and whether the growth factors act through autocrine or paracrine pathways; 2) what regulates growth factor expression after injury; and 3) whether the same growth factors mediate recovery from all forms of acute renal injury.

What is the Role of Endogenous Growth Factors in Renal Repair?

In addition to determination of which, if any, growth factors are involved, a related question is the mechanism(s) by which growth factors mediate recovery from acute injury. Many of the proposed growth factors are epithelial cell mitogens in vitro, and there have been reports that exogenous administration of at least some growth factors increases tubular DNA synthesis in vivo after injury (e.g., EGF, HGF). However, it is likely that endogenous growth factors may not act solely, or even primarily, as mitogenic agents. Growth factors might mediate increased spreading and motility, as well as proliferation (8). Similarly, endogenous growth factors might regulate cellular repair after sublethal cellular injury (reestablishment of polarity and cell-cell and cell-extracellular matrix attachment). Finally, growth factors might serve as cytoprotective agents, especially in the mTAL segment, where increased expression of a number of growth factors has been reported after acute injury (65, 66, 82).

Why Does Administration of Exogenous Growth Factors Promote Recovery After Experimental Renal Injury?

It is also important to determine whether exogenously administered and endogenously produced growth factors promote recovery from acute injury by the same mechanisms. The beneficial effects that have been reported for exogenous administration of a range of growth factors suggest at least four possible mechanisms. 1) The production of a growth factor normally expressed in the kidney (e.g., EGF and IGF) may decrease or fail to increase appropriately after acute injury. In other words, acute renal injury could induce an absolute or relative “growth factor deficiency state.” If so, exogenous administration of growth factors would serve as “replacement” therapy. 2) Administration of large concentrations of a growth factor that is increased endogenously after injury could still augment or accelerate the recovery process that is regulated by the same growth factor produced endogenously (e.g., HGF). 3) An exogenously administered growth factor may exert “generic” effects that may aid the repair process, such as alteration of transport, metabolism and DNA synthesis, even though endogenous expression of the same growth factor is not necessary for recovery (56). 4) The exogenous administration of one growth factor may induce the endogenous expression of another growth factor and/or receptor, as has been reported for EGF and IGF-1 (13, 25, 40). 5) Certain exogenously administered growth factors may exert biological effects independent of their mitogenic effect, such as the modulation of renal blood flow or neutrophil infiltration, that limit renal injury and/or accelerate recovery.

Is Exogenous Growth Factor Therapy Safe?

There is a potential concern about systemic side effects that might be encountered by administration of agonists with pleiotrophic effects. In addition, there is a second potential concern that under certain conditions growth factor administration might actually worsen renal injury. It is well known that many of the same growth factors suggested to be potentially important for recovery from acute ischemic or toxic injury are also increased in renal inflammatory injury and have been implicated in the development of chronic tubulointerstitial fibrosis. Thus, if there is a significant potentially inflammatory component to the acute injury, for which there is substantial evidence (39), it is possible that exogenously administered growth factors might actually augment the development of tubulointerstitial injury.

R. C. Harris

SECONDARY DISCUSSANTS

F. Gary Toback
Section of Nephrology
University of Chicago
Chicago, Illinois 60637

H. David Humes
Department of Medicine,
University of Michigan Health System
Ann Arbor, MI 48109-0368

RENOAL TUBULAR REGENERATION is one of the most remarkable phenomena in mammalian biology because it can completely restore kidney function and structure after toxic or ischemic injury. Individuals with ARF who are often catabolic and anorectic and experiencing extracellular acidosis, hyperkalemia, hypocalcemia, and hyperphosphatemia nevertheless repair and replace their injured and necrotic tubular epithelial cells. Although
Cell migration and proliferation help restore epithelial continuity at sites of tubular injury (60, 82), most cells along the nephron appear structurally intact after an acute insult. How sublethally injured and noninjured cells orchestrate recovery of renal structure and function has been uncertain, but autocrine and paracrine growth factors released at or near sites of nephron injury were proposed in 1984 as agents that mediate repair (74). Evidence to support a role for endogenous growth factors includes altered expression of genes encoding their protein products and receptors during renal regeneration (17, 24, 31–33, 40, 65, 75, 79) and the observation that administration of specific exogenous growth factors (EGF, IGF-I, or HGF) improves survival and speeds functional recovery (29, 46, 59).

Identifying mechanisms that mediate regeneration after acute tubular injury may provide fresh insights into other pathophysiological processes, such as how the kidney withstands biochemical and metabolic insults during transplantation and the subsequent immunologic assault on it in a new host. These reparative mechanisms might also be activated and/or ongoing in chronic renal diseases, so that progression to an end-stage kidney may be the net result of injury and insufficiently robust repair processes.

Control of Renal Regeneration by Growth Factors: An Hypothesis

A simple paradigm can be used to clarify the role of autocrine and paracrine growth factors as mediators of renal regeneration. It is proposed that renal tubular cell stress or injury triggers release of growth factors (23, 48, 80) that can bind either to the surface of cells that released them or to other cells nearby. Binding of growth factor ligands to their cognate receptors triggers diverse biological responses such as gene transcription and translation, thereby producing protein products that mediate repair of sublethally injured cells, as well as migration, dedifferentiation, and proliferation of surviving cells at sites of tubular injury (60, 82). Renal tubular and interstitial cells, as well as mononuclear cells, can each express growth factors (32). Once the tubule is reepithelialized, one set of growth factors may be turned off and another set activated to mediate cell maturation and restoration of polarity, allowing the organ to return to its basal physiological role as regulator of the internal milieu.

Studies to test this hypothesis will increase understanding of how these proteins act and define their therapeutic potential in ARF. There are many areas for future research. First, it is unclear how renal cell stress or injury by an ischemic or toxic insult triggers tubular cells to release growth factors. If a specific growth factor is critical for the repair process, is it released from a storage site within the cell, from the cell surface, or the extracellular matrix? Is the mRNA encoding it transcribed and/or translated after injury? The rapid fall in EGF and IGF-I mRNA after renal injury (79) complicates the paradigm. Second, it seems unlikely that regeneration after injury is mediated by a single growth factor, as it is known that cells in the kidney release many different ones after regeneration (17, 24, 31–33, 40, 65, 75, 79). Perhaps the critical growth factor(s) has yet to be discovered. In addition, the repair process may be mediated by the release of factors in a time-dependent sequence that is coordinated with the altered expression of receptors. Interactions between growth factors such as EGF and IGF-I and their receptors (1, 13, 19, 64), and the actions of growth factor-induced gene products such as osteopontin (51, 59), could also be critical determinants of repair. Third, it is not certain that growth factors exert their beneficial effects on the ARF syndrome by functioning only as mitogens. Molecules such as EGF and IGF-I, for example, have an astonishingly wide range of biological effects on diverse types of cells, including kidney. Thus the capacity of autocrine growth factors to enhance survival and speed repair after ARF may be mediated by their ability to stimulate plasma membrane uptake of nutrient molecules; modify ion transport or the energy charge of an injured cell; stimulate migration, DNA synthesis, and cell division; reestablish weakened cell-to-cell and cell-to-extracellular matrix linkages; and/or inhibit apoptosis. Fourth, does a growth factor acting alone or in concert with others exert its effect on sublethally injured tubular cells, noninjured cells, or both? Fifth, how do growth factors facilitate repair of injured cells to prevent their detachment and death? As most cells in the kidneys of humans with ARF appear structurally intact, it may be that the important targets of growth factor action are molecules that maintain cell polarity and ion gradients and mediate replacement of sloughed brush-border membranes and denatured proteins. Sixth, do growth factors protect cells from the repeated insults that characterize human ARF (65)? Seventh, do growth factors mediate maturation of nascent tubular cells after mitosis, perhaps by stimulating proliferation of organelles such as mitochondria and the formation of new cell-cell and cell-matrix attachments? Eighth, what are the signals that turn off growth factor synthesis and release and reduce or suppress receptor number and function when the repair process is complete?

New knowledge derived from these inquiries could identify the growth factor signal set that regulates migration, dedifferentiation, and proliferation during regeneration, and an additional signal set that suppresses these activities under physiological conditions. Increased understanding of growth factor physiology should permit the rational design of novel therapeutic strategies to speed repair of the injured kidney.

F. G. Toback

Nephrototoxic and Ischemic ARF, or acute tubular necrosis (ATN), is a dramatic clinical disorder. It is a common disease with an extremely grave outcome. Nearly 200,000 patients develop this disease process in the United States each year, with a mortality rate exceeding 50%. Accordingly, improved understanding of the cellular and molecular basis of ATN may be translated
into new therapeutic approaches. The primary discussants have all reviewed the most recent data and concepts regarding the role of growth factors in ARF.

The discussion by Safirstein develops the important view that growth factors may be important not only to promote replicative repair after renal tubule cell injury but also to play a critical role as cytoprotective agents to minimize cell death, especially the apoptotic pathway. This proposed mechanistic role requires further evaluation to determine whether growth factors are released early enough in ischemic or toxic stress to be cytoprotective as well as reparative. If they are released early in the disease process, the identification of the key growth factors and the source of their production and release need to be clarified.

The comments of Hammerman focus on the role of IGF-1 in this repair process and potential therapeutic efficacy for this disorder, especially with its effects in enhancing both renal blood flow and anabolic processes. A recent clinical trial to test this efficacy in established ATN was not successful. This failed efficacy trial raises a key issue as to whether the use of growth factors 1 or 2 days after injurious insult can be beneficial. The basic hypothesis for the therapeutic use of growth factors in ATN is that these factors will accelerate the naturally occurring replicative repair process necessary for renal function recovery. This acceleration of the natural healing process has been shown experimentally to occur if the growth factor is given just before or immediately after the insult. Administration of the agent several days after renal injury, once the reparative process is advanced, may not provide therapeutic benefit. Further experimental animal studies are required to evaluate this issue. Hammerman also presents recent data that osteopontin may also be important in this repair process. Similar to a number of other important growth and differentiation factors (82), osteopontin gene expression occurs not only in the proximal tubule, the site of prominent cell damage, but also in the distal nephron. The reason for the enhanced gene expression occurring in the uninjured in addition to the injured nephron segments (38, 59) is still unexplained.

The final review, by Harris, raises the intriguing concern that exogenous growth factor administration, rather than enhancing repair, may worsen renal injury by augmenting tubulointestinal injury and fibrosis during the reparative phase of this disorder, which may be dependent on a renal inflammatory response within the interstitium. Further studies directed to this important issue need to be undertaken.

Although much has been learned in this area over the last several years, key issues remain to be further resolved and elucidated. It is now apparent that the renal replicative repair process is dependent on redundant autocrine, paracrine, and endocrine pathways to deliver growth factors to the site of injury (26). The source of these factors and the role of inflammatory cell recruitment need further delineation. In fact, the modest inflammatory response and resulting tubulointerstitial fibrosis is in distinct contrast to acute injury in other organs, such as the liver, heart, and lung. Areas of investigation have in the past focused on the replicative processes in this repair; more evaluation into the processes of differentiation and morphogenesis is required to provide important insights. It is remarkable that this mitotically active repair process is finely regulated to reestablish the precise architecture of the renal tubule for efficient structure-function relationships. A lack of regulatory control could easily result in cellular overgrowth and potential obliteration of luminal conduits for urine formation. Finally, this repair process requires a resilient renal tubule progenitor cell population in the adult kidney to replace the necrotic cells. Further characterization and identification of these progenitor cells may well lead to new insights into developmental morphogenesis.

Ultimately, the goal of a better understanding of the cellular and molecular processes of this disorder needs to be translated into new therapeutic approaches to this serious clinical disorder. In this regard, the ability to selectively grow renal tubule progenitor cells from adult mammalian kidneys may provide a new therapeutic approach (28, 30).

Present therapy for ATN revolves around dialytic and hemofiltrative renal substitution therapy. This present therapy in ATN only substitutes for the filtration function of the kidney but not its cellular and metabolic functions, which reside in the tubular compartments. Replacing these metabolic functions may optimize present renal replacement therapy. In fact, replacing cellular metabolic function to improve the outcome of this disorder is certainly logical because the primary cause of ATN is cell injury and death of the renal tubular cells. In this regard, a renal tubule assist device (RAD) has been developed for placement in an extracorporeal continuous hemoperfusion circuit in series with a hemofilter (27). The RAD consists of up to \( 5 \times 10^9 \) porcine renal proximal tubule cells grown as confluent monolayers from renal tubule progenitor cells in a multifiber bioreactor with a membrane surface area from 0.4 to 1.6/m\(^2\). The cells along the inner surface of the hollow fibers are immunoprotected from the recipient's blood by the hollow fiber membrane. In vitro experiments have demonstrated remarkable differentiated transport, metabolic, and endocrinologic functions of this device (27). Furthermore, in recent experiments in uremic dogs, this device has been shown to tolerate a uremic environment while providing reabsorptive, metabolic, and endocrinologic activity (27). Pilot human trials of the RAD are anticipated within the next year to evaluate its efficacy in improving present renal replacement therapy in ATN.

The added value of this device in ARF therapy may be in the improvement of host defense. The infectious complications with resulting sepsis, septic shock, multiorgan failure, and mortality may develop in ATN due to the loss of these nonfiltrative metabolic functions of the kidney. The RAD has been demonstrated ex vivo to restore multiple metabolic activities, including glutathione, vitamin D3, and cytokine metabolism, to normal levels in the uremic state. The important role of
these factors in host defense and septic shock has been clearly delineated. Reversal of these metabolic deficiencies may diminish the hemodynamic and metabolic abnormalities in the sepsis syndrome, which lead to multiorgan failure and death (73, 85). The tenor of this series of reviews is that the acquisition of new knowledge in this area may be translated into additional therapeutic options to improve the presently grave outcome of this common clinical disorder.

H. D. Humes

EDITORIAL COMMENTS

Two separate issues are raised by virtually every discussant: 1) the efficacy of growth factors in the treatment of ARF and 2) the mechanism of their reparative action in the setting of renal injury. As has been suggested, it is possible, perhaps even likely, that the Holy Grail is not any single growth factor, or even a known one. One issue, alluded to by some of the discussants and worthy of some further consideration, is the possibility that some of the events that modulate the basic cellular processes involved in epithelial morphogenesis and renal tubular development are also important in the regenerative process that occurs after acute renal injury. There certainly is evidence to support this view. As discussed above, some growth factors, known to be important in kidney development, are upregulated in the injured kidney. Also, cultured ureteric bud cells can undergo part of the complex morphogenetic process in response to growth factors such as HGF, EGF, and IGF-1, known to accelerate recovery in experimental models of ARF (63, 68).

Cultured embryonic metanephric mesenchymal cells secrete factors capable of inducing mature and immature renal epithelial cells in culture to proliferate, migrate, and undergo three-dimensional morphogenetic changes (63, 68). There are marked changes in patterns of gene expression during this process (86). The mechanisms underlying these morphogenetic changes are very complex and involve 1) cytoskeletal reorganization of motile, proliferating cells into cuboidal, and then columnar cells; 2) the interaction of tubular cells with and their modification of the substratum; 3) cell-cell adhesion and the formation of junctional complexes; 4) cell polarization; and finally 5) the incorporation of these cells into complex three-dimensional tubular structures. It appears likely that growth factors not yet identified are produced by metanephric mesenchymal cells that are necessary for morphogenesis of renal tubules (63, 68). If so, some of these mitogens may prove to be useful as therapeutic agents for the treatment of ARF. Thus the use of experimental models designed to study renal development may also be useful tools for identifying and screening soluble factors for their potential usefulness in ARF.

Finally, traditional approaches of administering therapeutic agents to patients with ARF are likely to be superseded by newer, more effective methods. One novel approach being developed is the use of undifferentiated cells to replace cells that are deficient in diseased organs such as the brain. It is possible that undifferentiated renal tubular cells could be used in a similar manner in the kidney to promote renal regeneration and repair. Also, gene therapy could be used in the future to increase the expression of those growth factors and their receptors identified by basic research to be important in the recovery process after ARF.

M. R. Hammerman was supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Grants DK-27600, DR-41581, DR-20579, and DK-53487 and through support from Genentech, Inc. (S. San Francisco CA). R. C. Harris was supported by NIDDK Grant DK-51265. D. Humes was supported by NIDDK Grants DK-39255, DK-48175, and DK-50539, National Science Foundation Grant DFM-9560695, the Veterans Affairs Research Service, and nephroTherapeutics, Inc. F. G. Toback was supported by NIDDK Grants DK-39889, DK-37227, and DK-18413 and by nephRx, Inc. Sanjay Nigam was supported by NIDDK grants DK-4517, DK-5211, and DK-53507.

REFERENCES


13. Fervenza FC, Tsao T, and Rabkin R. Response of the intrarenal insulin-like growth factor axis I to acute ischaemic injury...


