**FIGURE 17-22**
Advantages of insulin-like growth factor (IGF-I) in the treatment of acute renal failure. The limited data obtained to date on the use of IGF-I for acute renal failure demonstrate that the peptide is well-tolerated and may be useful in selected patient populations. Additional human trials are ongoing including use in the settings of renal transplantation and chronic renal failure.

**FIGURE 17-23**
Limitations in the use of growth factors to treat acute renal failure (ARF). The disappointing results of several recent clinical trials of ARF therapy reflect the fact that our understanding of its pathophysiology is still limited. Screening compounds using animal models may be irrelevant. Most laboratories use relatively young animals, even though ARF frequently affects older humans, whose organ regenerative capacity may be limited. In addition, our laboratory models are usually based on a single insult, whereas many of our patients suffer repeated or multiple insults. Until we gain a better understanding of the basic pathogenic mechanisms of ARF, studies in human patients are likely to be frustrating.

**Future Directions**

**FIGURE 17-24**
A list of genes whose expression is induced at various time points by ischemic renal injury. The molecular response of the kidney to an ischemic insult is complex and is the subject of investigations by several laboratories. (Continued on next page)
**Acute Renal Failure**

Well-tolerated

<table>
<thead>
<tr>
<th>GROWTH FACTOR LIMITATIONS</th>
<th>ACUTE RENAL FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of basic knowledge of the pathophysiology of ARF</td>
<td></td>
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<tr>
<td>No screening system for compounds to treat ARF</td>
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<tr>
<td>Animal models may not be relevant</td>
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<tr>
<td>Animal studies have not predicted results in human trials</td>
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<tr>
<td>Difficulty of identifying appropriate target populations</td>
<td></td>
</tr>
</tbody>
</table>

Safe in short-term studies
Experience with diseases of overexpression and underexpression
Did not worsen outcomes
IGF-I—insulin-like growth factor.

FIGURE 17-24 (Continued)

Several genes have already been identified to be induced or down-regulated after ischemia and reperfusion. This table lists genes whose expression is altered as a result of ischemic injury. It is not clear at present if the varied expression of these genes plays a role in cell injury, survival, or proliferation.
MOLECULAR RESPONSE TO RENAL ISCHEMIC/REPERFUSION INJURY

Genes
Transcription factors
- c-jun
- c-fos
- Egr-1
- Kid 1

Cytokines
- JE
- KC
- IL-2
- IL-10
- IFN-γ
- GM-CSF
- MIP-2
- IL-6
- IL-11
- LIF
- PTHrP
- Endothelin 1
- Endothelin 3

FIGURE 17-25
Schematic representation of differential display. In a complex organ like the kidney, ischemic renal injury triggers altered expression of various cell factors and vascular components. Depending on the severity of the insult, expression of these genes can vary in individual cells, leading to their death, survival, or proliferation. A better understanding of the various factors and the signal transduction pathways transduced by them that contribute to cell death can lead to development of therapeutic strategies to interfere with the process of cell death. Similarly, identification of factors that are involved in initiating cell migration, dedifferentiation, and proliferation may lead to therapy aimed at accelerating the regeneration program. To identify the various factors involved in cell injury and regeneration, powerful methods for identification and cloning of differentially expressed genes are critical. One such method that has been used extensively by several laboratories is the differential display polymerase chain reaction (DD-PCR).

In this schematic, mRNA is derived from kidneys of sham-operated (controls) and ischemia-injured rats, some pretreated with insulin-like growth factor (IGF-I). The mRNAs are reverse transcribed using an anchored deoxy thymidine-oligonucleotide (oligo-dT) primer (Example: dT[12]-MX, where M represent G, A, or C, and X represents one of the four nucleotides). An anchored primer limits the reverse transcription to a subset of mRNAs. The first strand cDNA is then PCR amplified using an arbitrary 10 nucleotide-oligomer primer and the anchored primer. The PCR reaction is performed in the presence of radioactive or fluorescence-labeled nucleotides, so that the amplified fragments can be displayed on a sequencing gel. Bands of interest can be excised from the gel and used for further characterization. ARF—acute renal failure.

FIGURE 17-26
Schematic representation of a differential display gel in which mRNA from kidneys is reverse-transcribed and polymerase chain reaction (PCR) amplified (see Figure 17-25). The PCR amplification is conducted in the presence of radioactive nucleotides. The cDNA fragments corresponding to the 3’ end of the mRNA species are displayed by running them on a sequencing gel, followed by autoradiography. The arrows show bands corresponding to mRNA transcripts that are expressed differentially 1) in response to insulin-like growth factor (IGF-I) treatment and induction of ischemic injury; 2) in an IGF-I–dependent manner; 3) in response to induction of ischemic injury; and 4) to genes that are down-regulated after induction of ischemic injury. ARF—acute renal failure.
References


