Epidermal growth factor receptor ligands and renal epithelial cell proliferation

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A CRITICAL ISSUE IN UNDERSTANDING how the mammalian kidney responds to pathological states and nephrotoxic chemicals involves the identification of modulating agents, growth factors, and signaling pathways that regulate responses. Although some of the modulating agents identified, including chemicals such as thiol reductants (e.g., glutathione, N-acetyl-L-cysteine) or α-tocopherol, can have a significant impact on cellular function, it is likely that they are not directly linked to processes that actually control cell death and cell proliferation. More proximate regulators exist and include a broad range of growth factors, kinases, and phosphatases, among other classes of molecules. Renal cells can synthesize several growth factors, including epidermal growth factor (EGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), fibroblast growth factor 2, and transforming growth factor-α, each with a characteristic ability to promote renal cell growth and proliferation (2, 6, 11, 13). One growth factor that has received some attention is heparin binding-epidermal growth factor (HB-EGF), which is a member of the EGF family and has been found to increase in rats subjected to ischemia-reperfusion injury (3).

Schnellmann and coworkers have studied numerous aspects of renal repair and regeneration in toxicant-treated rabbit proximal tubules. For example, early studies established the occurrence of renal regeneration and proliferation as recovery responses to sublethal injury (1, 4, 9). Although a variety of antioxidants and other protective agents were demonstrated to act through enhancement of recovery (e.g., Refs. 4, 5, 8, 9), these types of mediators, such as ascorbate, glutathione, or α-tocopherol, can be viewed as part of a primary line of defense or response to environmental stress. While they may certainly impact repair and proliferation, they are not, as noted above, the direct mediators of this response. Rather, these types of agents act by modulating signaling pathways. One of the major signaling pathways that is activated by a broad range of stimuli and then modulates cell growth is the EGF receptor and associated kinases, including the ERK1/2 pathway (12, 15).

Over the past several years, Schnellmann and colleagues (7, 10, 14, 16, 18) have demonstrated in several studies that production of EGF and other activators of the EGF receptor play critical roles in renal cell repair and proliferation. The work presented in their current paper (17) builds on these earlier studies and extends them, making some novel findings that have broad implications for understanding the regulation of renal growth, repair, and proliferation. Their in vitro model system, primary cultures of rabbit proximal tubular cells (RPTC), is ideally suited to the study of autocrine and paracrine mechanisms of EGF receptor activation, as these cells have been documented to undergo migration and proliferation following plating and mechanical injury in the absence of serum and exogenous growth factors in an EGF-receptor-dependent manner (16). The present work focused on the role of HB-EGF in autocrine and paracrine pathways of renal cell proliferation following plating or oxidant injury.

Three experimental models of RPTC were used: 1) nearly confluent cells injured by exposure to 1 mM H₂O₂ for 5 h; 2) cells grown to near-confluence, released from the culture surface by trypsin, replated in new culture dishes, and then incubated with various pharmacological inhibitors; and 3) cells grown for 3 days and then incubated for 24 or 48 h in the absence or presence of various pharmacological agents. A multifaceted approach, using HB-EGF small interfering RNA (siRNA) and pharmacological inhibitors of EGF receptor phosphorylation, several metalloproteases, and Src family kinases, were used to probe the signaling molecules that regulate the response of RPTC to mechanical and chemical stresses.

Although previous studies associated EGF receptor activation with various aspects of renal cell repair and proliferation (7, 10, 14, 16, 18), the current study (17) makes the novel observation that following plating (i.e., mechanical injury), RPTC proliferation mediated by EGF receptor activation is controlled by HB-EGF; in contrast, RPTC proliferation following oxidant injury that is mediated by EGF receptor activation is controlled, not by HB-EGF, but by Src. However, when exogenous HB-EGF is added to RPTC following oxidant injury, Src is also involved. Hence, the two distinct pathways for EGF receptor activation, leading to renal cell repair and enhanced proliferation, converge. Studies on shedding of the HB-EGF ectodomain after mechanical stress showed that this critical step is dependent on certain metalloproteases, in particular, ADAM17, whereas there is no shedding of the HB-EGF ectodomain after oxidant injury, likely due to inhibition of metalloproteases.

Thus, by use of a well-characterized and appropriate in vitro model, Schnellmann and colleagues (17) provide additional insight into the critical role of the EGF receptor in the ability of sublethally injured renal proximal tubular cells to undergo repair and proliferation. An important implication of the finding of multiple signaling pathways, depending on the mode of injury, is that different tactics would be necessary to optimize repair and regeneration with distinct forms of injury.

REFERENCES


