Partial-Body Radiation Diagnostic Biomarkers and Medical Management of Radiation Injury Workshop
May 5-6, 2008, AFRRI, Bethesda, Maryland USA

Biomarkers for Renal Radiation Injury

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Biomarkers are molecular signs of an injury that are not necessarily critical to its mechanism or expression. Thus, serum levels of troponin are very reliable biomarkers of myocardial injury, but do not in themselves cause morbidity or mortality. Biomarkers may precede expression of tissue injury, and thereby provide a time window for use of agents that can mitigate injury. Truly useful biomarkers must be linked to later outcomes such as organ failure, and their modification should be correlated with improved later outcomes.

In clinical and experimental acute kidney injury (AKI, also known as acute renal failure) biomarkers under study include KIM-1 (kidney injury molecule 1), NAG (N-acetyl glucosaminidase), and IL-18, and others. In AKI, their increase in the serum precedes the elevation of serum urea or creatinine (i.e., it precedes the expression of reduced kidney function). KIM-1 and NAG derive from damaged renal tubular epithelium, while IL-18 is a cytokine that is induced after AKI. While promising, biomarker testing is not used clinically in the setting of AKI, in part because of variable sensitivity and specificity of the biomarkers. No single marker is able to discriminate common causes of AKI, such as sepsis with hypotension, gentamicin toxicity, or cis-platinum toxicity. Markers for chronic kidney disease are less well-studied.

Although urinary protein is elevated within weeks of sufficient kidney or total body irradiation, it is a manifestation of injury rather than a true biomarker. It is also non-specific because proteinuria occurs in most kidney injury, acute or chronic.

We have shown that n-acetyl-glucosamine is increased in the urine of rats exposed to renal irradiation; it coincided with proteinuria, and preceded azotemia. In these studies, there were no consistent changes in gamma-glutamyl transpeptidase, an enzyme of the brush border of proximal renal tubular epithelium. More recently, we have shown early glomerular structural and functional changes within hours of 10 Gy single-fraction total body irradiation (TBI). Analysis of the rat urinary proteome at 24 hours after 10 Gy TBI shows over 700 proteins of interest, compared to unirradiated controls. Notable proteins found after TBI include kallikrein-like peptides and cystatin-C. Gene ontology analysis suggests the presence of proteins from all cellular compartments, nucleus to membrane, and of diverse function, e.g. anti-apoptotic, proteolytic, inflammatory, and others. KIM-1 and IL-18 were unchanged, which is different than is the case of AKI.

It is possible, but unlikely, that a single protein or other chemical biomarker will be found for renal radiation injury. Non-renal effects of TBI, with urinary excretion of resulting substances, require consideration; and studies urine of proteome changes after local renal irradiation are in progress. In a combined injury, such as body fluid depletion and hypotension plus irradiation, interpretation of urinary biomarkers would be very difficult.