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New theranostic strategies for drug-induced acute kidney cancer

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Introduction

Drug-induced predisposition to acute renal failure (ARF) is a facet of nephrotoxicity hitherto mostly uncharacterized, quite underestimated, and impossible to diagnose, which potentially has a high human and socioeconomic impact. Our study has identified urinary GM2AP as the first of a new class of biomarkers of the enhanced risk of suffering an acute renal failure after a subnephrotoxic treatment with gentamicin. Gentamicin-predisposed animals with no sign of renal cancer develop ARF when exposed to a second potentially nephrotoxic drug, also given at subnephrotoxic doses that are harmless to non-predisposed individuals. Subnephrotoxic gentamicin did not alter renal GM2AP gene expression or protein levels, determined by RT-PCR and Western blot and immunostaining, respectively, nor was its serum level modified. Further experiments indicate that, likely, the origin of the increased level of GM2AP in the urine might be a defective tubular handling of this protein as a consequence of gentamicin action.

Background of the Research

Markers of risk may revolutionize the prevention of ARF by enhancing our monitoring capacity of acquired predisposition to ARF, in a pre-emptive manner. With regard to the aetiological diagnosis of drug nephrotoxicity, we have identified regenerating islet derived protein III beta (reg IIIb) and gelsolin as potentially differential urinary markers of gentamicin's nephrotoxicity. Indeed, both reg IIIb and gelsolin urinary levels differentiate the nephrotoxicity caused by gentamicin from that caused by cisplatin. Reg IIIb is over-expressed in the kidneys of gentamicin-treated rats and poured into the urine, whereas gelsolin proceeds from the glomerular ultrafiltrate. Our results pose a proof-ofconcept for the aetiological diagnosis of AKI through the biochemical analysis of the urine, with potential application for an enhanced drug theranostic and a more personalized medicine of polimedicated and critically ill patients at multifactorial risk of AKI. Furthermore, our studies have identified new urinary markers that differentiate ischemic from toxic acute kidney cancer. Kidney cancer, also known as renal cancer, is a group of cancers that starts in the kidney. Symptoms may include blood in the urine, lump in the abdomen, or back pain. Fever, weight loss, and tiredness may also occur. Complications can include spread to the lungs or brain. The main types of kidney cancer are renal cell cancer (RCC), transitional cell cancer (TCC), and Wilms tumor. RCC makes up approximately 80% of kidney cancers, and TCC accounts for most of the rest. Risk factors for RCC and TCC include smoking, certain pain medications, previous bladder cancer, being overweight, high blood pressure, certain chemicals, and a family history. Risk factors for Wilms tumor include a family history and certain genetic disorders such as WAGR syndrome. Diagnosis maybe suspected based on symptoms, urine testing, and medical imaging. It is confirmed by tissue biopsy. Treatment may include surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy. Kidney cancer newly affected about 403,300 people and resulted in 175,000 deaths globally in 2018. Onset is usually after the age of 45. Males are affected more often than females. The overall five-year survival rate is 75% in the United States, 71% in Canada, 70% in China, and 60% in Europe. For cancers that are confined to the kidney, the five-year survival rate is 93%, if it has spread to the surrounding lymph nodes it is 70%, and if it has spread widely, it is 12%. Kidney masses can be classified by the nature of the cells in the growth, or by its appearance on radiography. The term cancer refers to a malignant tumor, which is an uncontrolled growth of abnormal cells. However, kidney masses can be due to growth of normal tissue (benign), inflammatory (a reaction of the immune system), or vascular (cells of the blood vessels). The most common type of kidney malignancy is renal cell carcinoma, which is thought to originate from cells in the proximal convoluted tubule of the nephron. Another type of kidney cancer although less common, is transitional cell cancer (TCC) or urothelial carcinoma of the renal pelvis. The renal pelvis is the part of the kidney that collects urine and drains it into a tube called the ureter. The cells that line the renal pelvis are called transitional cells, and are also sometimes called urothelial cells. The transitional/urothelial cells in the renal pelvis are the same type of cells that line the ureter and bladder. For this reason TCC of the renal pelvis is distinct from RCC and is thought to behave more like bladder cancer. Other rare types of kidney cancers that can arise from the urothelial cells of the renal pelvis are squamous cell carcinoma and adenocarcinoma.

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