USP18 AND DKK3 PROTEINS IN KIDNEY AND CARDIOVASCULAR SYSTEM DISEASES

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ABSTRACT:

New groups of proteins involved in kidney and heart muscle damage have been recently identified. These include USP18 (ubiquitin-specific peptidase 18) and Dkk3 (Dickkopf-3) proteins. Both represent cardioprotective properties, which result from the inhibition of cardiac muscle remodelling process upon increased afterload. Moreover, Dkk3 is secreted by the renal tubules in response to various damaging factors and may promote renal fibrosis. Dkk3 has been described as a prognostic tool in short-term loss of glomerular filtration rate and long-term progression of chronic kidney disease (CKD) regardless of the underlying cause. The aim of this PhD dissertation was to assess the roles of USP18 and Dkk3 in pathologies involving kidneys and cardiovascular system, especially as potential biomarkers in CKD and heart failure.

The aim of the first research article was to assess the relationship between serum USP18 concentration and the incidence of hypertension in patients which are naïve to treatment, as well as the analysis of the relationship between serum USP18 and cardiovascular risk factors. Significant differences in serum USP18 depending on blood pressure values were found. The mean value in the group with systolic-diastolic hypertension (426.7 pg/ml) was 6.2 times higher than in the group without hypertension (69.3 pg/ml, $p=0.03$) and 4.7 times higher than in the group with isolated diastolic hypertension (90.1 pg/ml, $p=0.19$). Significant correlations adjusted to classical risk factors of hypertension and atherosclerosis were found between serum USP18 and systolic blood pressure ($r=0.31$, $p=0.008$), pulse pressure ($r=0.37$, $p=0.002$), and heart rate ($r=0.24$, $p=0.04$).

In the second study, the relationship between serum and urine Dkk3 concentrations in patients at various stages of CKD and clinical, laboratory and histopathological indicators of kidney disease activity was assessed. The most important observation in this study was to find the highest urinary Dkk3 concentration adjusted to urinary creatinine in patients with stable CKD (7050 pg/mg), which was significantly higher than in other groups (i.e. healthy controls, patients with proteinuric glomerulopathies, kidney transplant recipients). Moreover, the urinary Dkk3 concentration in the kidney transplant group (5710 pg/mg) was twice as high as in the

population without renal disease (2650 pg/mg) and the glomerulopathy group (2470 pg/mg), although in all groups glomerular filtration rate was normal. Another important observation was the correlation between urinary Dkk3 and serum creatinine only in the groups of patients with stable CKD (r=0.41, p=0.009) and after kidney transplantation (r=0.39, p=0.043), i.e. in the groups with the most advanced kidney disease.

The review article describes the structure, mechanisms of action and role of USP18 in response to infectious agents, in carcinogenesis, in the development of autoimmune diseases and in cardiac remodelling.

Based on the observations presented above, the increase in serum USP18 seems to result from the left ventricle overload and may reflect ongoing counterregulatory processes at the cellular level. Another conclusion is that urinary Dkk3 may reflect renal injury and its advancement. The presented original papers appear to confirm the potential roles of USP18 and Dkk3 as a biomarkers of heart and kidney damage.

KEY WORDS: chronic kidney disease, chronic heart failure, renal tubular injury, cardiac muscle remodelling