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Could Urine Biomarkers Reflect Different Stages of Disease?

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Abstract

Diseases involve different biological processes and exhibit different pathophysiological states at different time points, so there should be different biomarkers at different stages. Urine is an ideal disease biomarker source. As it is not under the control of homeostatic mechanisms, urine can theoretically reflect pathological changes in a sensitive and timely manner. Could urine biomarkers reflect different stages of disease? In the current review, we summarised the results of urine biomarkers at different time points in various animal models of disease. We believe that urine biomarkers at different time points can also reflect different states of human disease. More importantly, urine can reflect systemic changes in the whole body, so studying urine biomarkers at different time points provides clues to explore unknown pathogenesis and to find targets for drug intervention.

Keywords: Biomarker; Urine; Diseases; Different Time Points

Introduction

Biomarkers are measurable changes associated with pathophysiological processes from normal stage to disease stage [1]. Diseases involve different biological processes and exhibit different pathophysiological states at different time points, so there should be different biomarkers at different stages. We should study disease biomarkers at different time points.

Urine is an ideal disease biomarker source. As a filtrate of the blood, urine can accumulate changes of the whole body [2]. As it is not under the control of homeostatic mechanisms, urine can theoretically reflect pathological changes in a sensitive and timely manner [3]. Could urine biomarkers reflect different stages of disease? Recently, our laboratory has established several animal models of disease to search for urine biomarkers at different time points, such as the subcutaneous tumor-bearing model [4], the pulmonary fibrosis model [5], the glioma model [6], the liver fibrosis model [7], the Alzheimer's disease model [8], myocarditis model [9], and the chronic pancreatitis model [10]. In the current review, we summarised the results of urine biomarkers at different time points in various animal models of disease. We believe that urine biomarkers at different time points can also reflect different states of human disease.

Discussion

The Urine Biomarkers at Different Time Points in a Chronic Pancreatitis Rat Model

Linpei Zhang established the chronic pancreatitis (CP) rat model by intraperitoneal injection of diethyldithiocarbamate and analysed urine proteome at three time points to study biomarkers during chronic pancreatitis development [10].

The panel of urinary proteins at each time point was different. At week 2, when no lesion was found in the pancreas, 15 proteins were significantly changed in the urine, and 5 of those proteins were related to pancreatic-related disease. For example, serum amyloid P-component (SAMP) was changed in CP patients [11]. At week 3, when mild inflammation and acinar rupture were found in the pancreas, 29 proteins were significantly changed. At week 4,

when severe inflammation and acinar atrophy were found in the pancreas, 38 proteins were significantly changed. Some of these proteins were associated with CP. For example, Thy-1 membrane glycoprotein (THY1) was elevated on the activated pancreatic fibroblasts in CP [12]. The Venn diagram displays the urinary proteins at three time point (Figure 1).

Functional analysis of urinary proteins was performed by using DAVID [13] (Figure 2), and the biological processes of urine proteins enrichment at each time point were different. At week 2, cell adhesion, antibacterial response and innate immune response were overrepresented. At week 3, acute-phase response, angiogenesis, regulation of peptidase and end peptidase activity were overrepresented. At week 4, cellular responses to glucose stimulus and tissue remodelling were overrepresented.

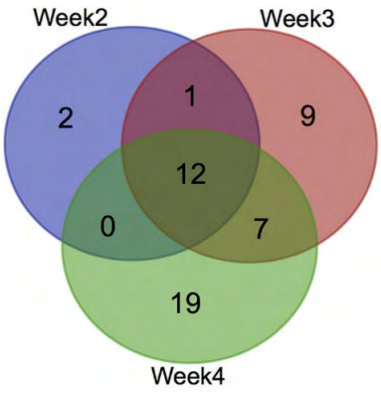

Figure 1: The Venn diagram of the differential proteins identified at weeks 2, 3 and 4 [10].

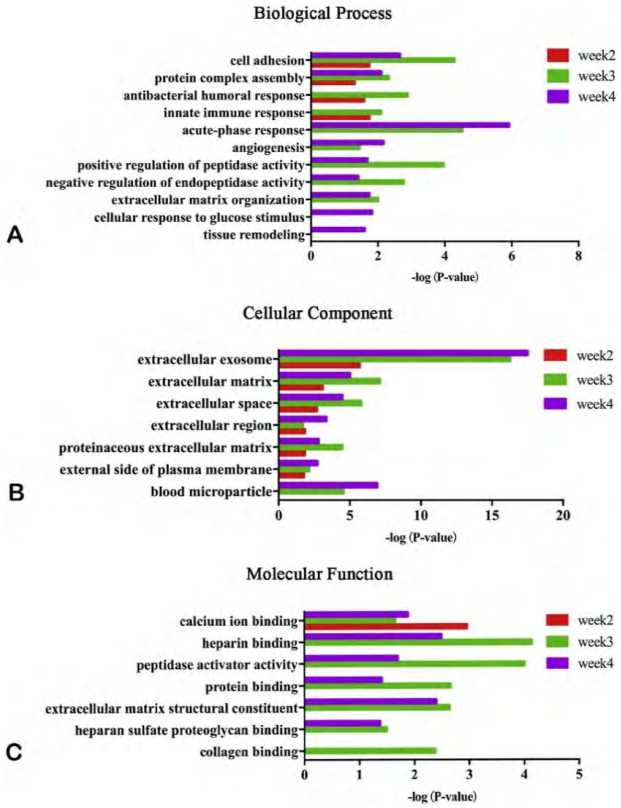

Figure 2: Functional analysis of differential proteins during chronic pancreatitis development [10]. A) Biological process; B) Cellular component; C) Molecular function

The results of the above animal model showed that urine biomarkers at different time points were different and they could reflect different stages of chronic pancreatitis.

The Urine Biomarkers at Different Time Points in an Alzheimer's Disease Mouse Model

Fanshuang Zhang analysed urine proteome at three time points from APP (swe)/PSEN1dE9 transgenic mice to search for biomarkers during Alzheimer's disease (AD) development [8].

The panel of urinary proteins at each time point was different. At month 4, when the amyloid-β-plaque deposition had not yet occurred, 29 proteins were significantly changed, and 15 of those proteins were related to AD. For example,

the Ig kappa chain C (IGKC) region was a potential biomarker of early AD [14]. At month 6, when the amyloid-β-plaque deposits had occurred, 33 proteins were significantly changed, and 8 of those proteins were reported to be related to AD. For example, Kallikrein-1 (KLK1) and Ig kappa chain C (IGKC) are considered as biomarkers of AD [15]. At month 8, when the vast amyloid-β-plaque had been deposited in the hippocampus, 86 proteins were significantly changed, and 31 of those proteins were reported to be associated with AD. For example, Cystatin-C (CYTC) was used for the early AD diagnosis [16]. The Venn diagram displays the urinary proteins at three time point (Figure 3).

Functional analysis of urinary proteins was performed by using DAVID [13](Figure 4), and the biological processes of urine proteins enrichment at each time points were different. At month 4, lipid metabolism and lipid catabolism were overrepresented. At month 6, transport processes, microvillus assembly and the regulation of cell shape were overrepresented. At month 8, proteolysis processes, fibrinolysis, lysosome organization, angiogenesis and other AD-related biological processes were overrepresented.

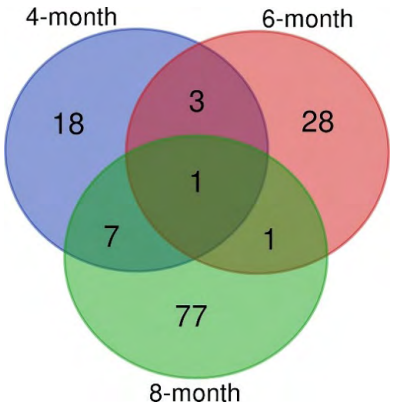

Figure 3: The Venn diagram of the differential proteins identified at month 4, 6 and 8 [8].

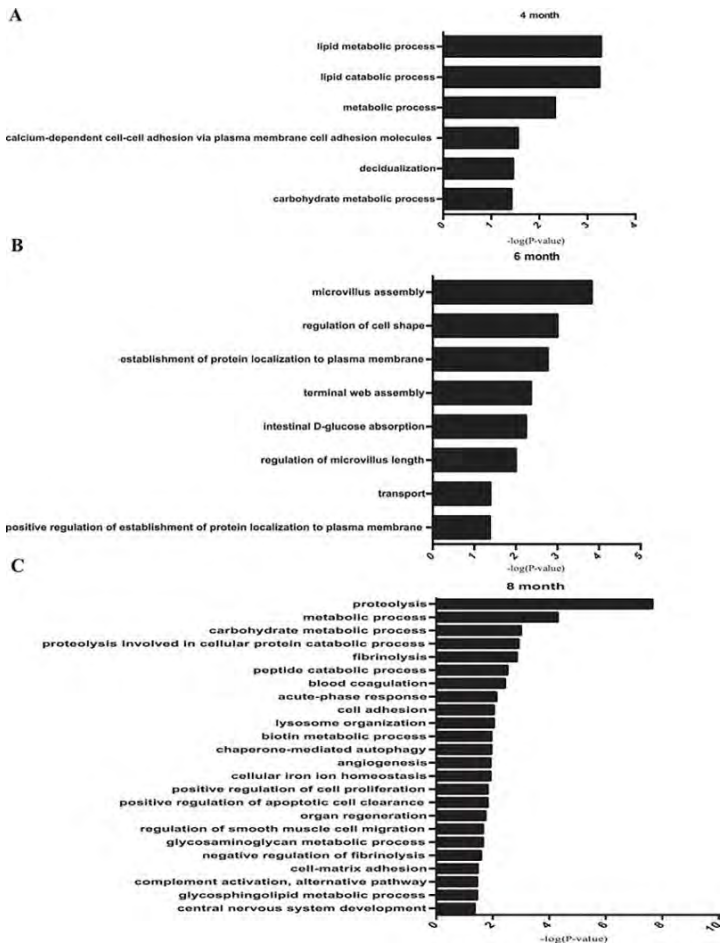

Figure 4: Biological processes of differential proteins in different stages of AD development [8]. A) On 4-month-old B) On 6-month-old C) On 8-month-old

The results of the above animal model showed that urine biomarkers at different time points were different and they could reflect different stages of Alzheimer's disease.

The Urine Biomarkers at Different Time Points in a Subcutaneous Tumor-Bearing Rat Model

Jianqiang Wu established the tumor-bearing rat model by subcutaneous injection of vast Walker-256 cells and analysed urine proteome at four time points to search for biomarkers during cancer development [4].

The panel of urinary proteins at each time point was different. On day 4, when small tumor masses had not yet developed, 12 proteins were significantly changed. On day 6, when a small tumor mass could be detected, 29 proteins were significantly changed. On day 9, when the tumor volume gradually increased, 112 proteins were significantly changed. On day 14, when the subcutaneous tumor gradually deteriorated, 38 proteins were identified. Some of these differential proteins were reported to be significantly changed in the patients with cancer. For example, Cluster of T-kininogen 1(KNT1) was a breast cancer biomarker [17]. The Venn diagram displays the urinary proteins at three time point (Figure 5).

Functional analysis of urinary proteins was performed by using DAVID [13] (Figure 6), and the biological processes of urine proteins enrichment at each time points were different. On day 4, acute-phase response and innate immune response were overrepresented. On day 6, negative regulation of endogenous polypeptide activity, complement activation and inflammation were overrepresented. On day 9, aging and negative regulation of endogenous polypeptide activity were overrepresented. On day 14, negative regulation of tumor necrosis factor production and apoptosis processes were overrepresented.

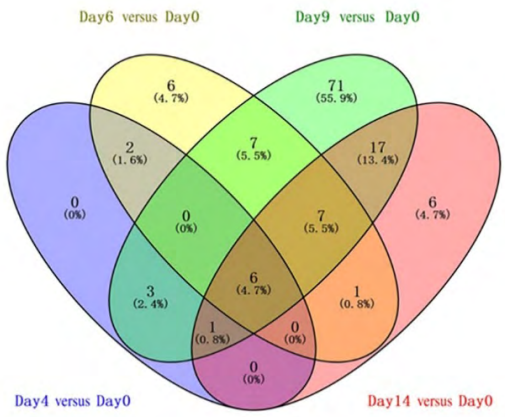

Figure 5: The Venn diagram of the differential proteins identified on day 4, 6, 9 and 14 [4].

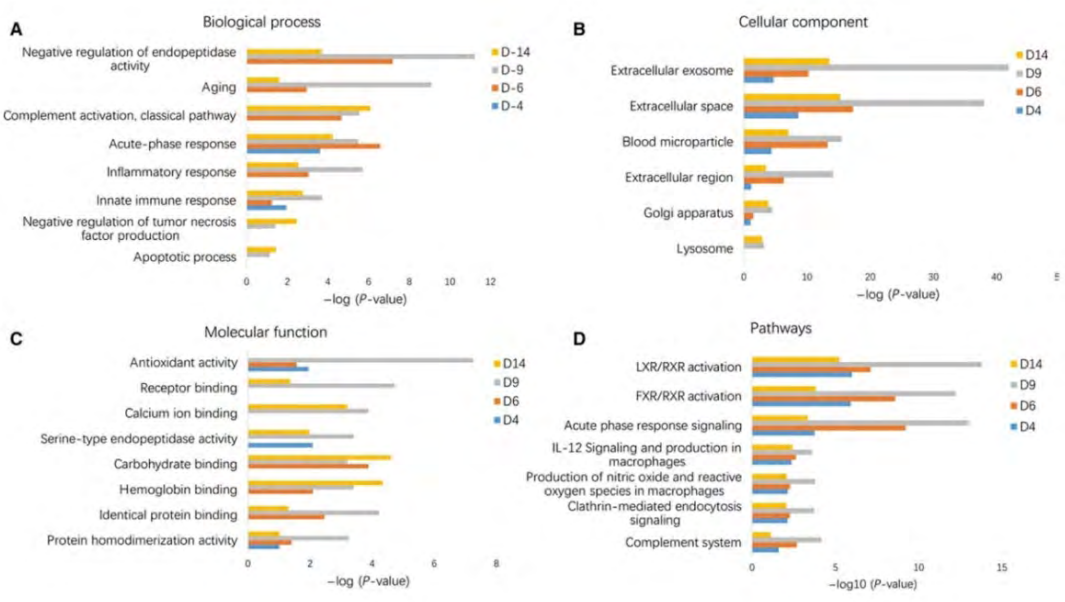

Figure 6: Functional analysis of differential proteins during cancer development [4]. A) Biological process; B) Cellular component; C) Molecular function; D) Pathways

The results of the above animal model showed that urine biomarkers at different time points were different and they could reflect different stages of subcutaneous tumor.

In addition to the above results, we also found that urine biomarkers at different time points could also reflect different stages of diseases in other animal models [18-20].

Future Perspective

The above results suggest that we should pay more attention to different time points of disease when studying biomarkers, which is often ignored. Urine biomarkers at different time points may be more appropriate for complex clinical samples and may promote the application of biomarkers in the future clinical practice. However, urine was still easily affected by various external factors especially in clinical patients, such as gender, age, diet and some certain medications. Therefore, there is an urgent need to draw a better strategy when conducting clinical urine biomarker researches. In our previous animal model researches, we have identified candidate urine biomarkers at different time points through comparing with them before disease onset. In addition, we also compare urine pre-and post-disease to identify candidate urine biomarkers. In future clinical researches, we believe that it should be better to use pre-and post-disease urine samples of the same individual to identify candidate urine biomarkers when conducting clinical urine biomarkers researches.

We advocate that the community should provide additional clinical urine samples at different time points of disease progression to enrich the urine biobank. The urimem is an easy and economical tool to preserve macromolecules in urine [21,22]. The rapid development of big data in the future provides support for the study of biomarkers in clinical samples at different stages of disease. More importantly, urine can reflect systemic changes in the whole body, so studying urine at different time points provides clues to explore unknown pathogenesis and to find targets for drug intervention. In the future, we will dynamically monitor diseases by analysing urine biomarkers in each individual at different time points of disease progression to obtain more effective clinical management decisions and intervention methods to realize personalized medicine.

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Competing Interests

The authors declare that they have no competing interests.

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