Opinion

Conductance of homeostasis

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Homeostasis should be maintained throughout the whole body to keep us in a healthy state. In different compartments of the body, the priority of homeostasis is different. Homeostasis is dynamic. Nutrients and oxygen move to the higher priority parts and wastes go to the lower priority parts in a constant process. The priority of homeostasis decreases from the intracellular space to the extracellular space to blood and eventually to non-homeostatic urine. In a homeostatic state, unwanted changes (wastes) in the body are constantly moving down the homeostatic stairs. Any physiological and pathophysiological process should produce a combination of waste materials. When homeostatic mechanisms are working, this combination of wastes will not stop in any homeostatic space and accumulate, which would provide us an opportunity to detect stable biomarkers. This is especially true for the very early stage of diseases, when the homeostatic power is still fully reserved. Early and reproducible homeostasis theoretically cannot be achieved at the same time in a homeostatic space. This is probably why we fail to find satisfactorily reproducible and early biomarkers in a homeostatic space, such as blood. If we want a reproducible biomarker in a homeostatic space, we have to wait until the homeostatic power in this space is depleted. Then, we can see steady reproducible changes compared to the healthy state. Unfortunately, when homeostatic power is depleted, the disease is no longer in an early stage. If we want an early biomarker, then we have to understand that in the early stage, the changes we observed at this time in a homeostatic space are constantly removed by the strong homeostatic power. We have to deal with the uncertain reproducibility at this early stage. This is a problem only when we look for biomarkers in a homeostatic space. Theoretically, early and reproducible biomarkers can be found only in a non-homeostatic space. In a non-homeostatic space such as urine, which is not controlled by homeostatic mechanisms at all, changes are continuously accumulating. There is no mechanism to remove any changes associated with the disease from the urine. In the sense of homeostasis, urine as a component is no longer part of our living body, even when it is still in the bladder; it is destined to leave the body.1

Based on the above reasoning, the urine biomarker theory is proposed. Biomarkers are defined as measurable changes associated with disease; these changes are removed from the blood because of the homeostatic mechanisms of the body; and many types of changes collect in the urine, which is, therefore, a better biomarker source for the early detection of disease.2

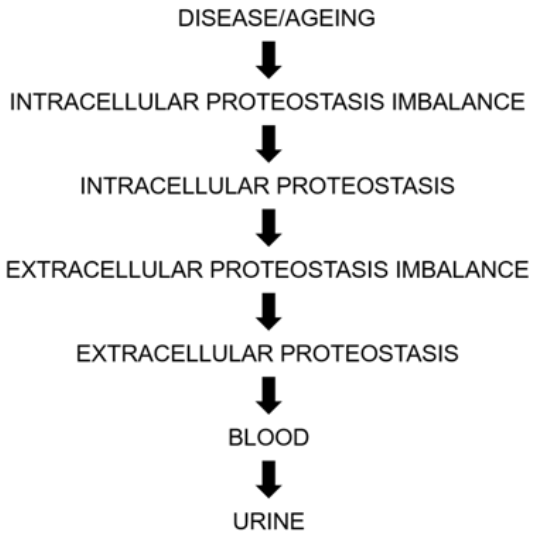
Because of the nature of waste accumulation in a non-homeostatic space, these changes are not just early, they are also very sensitive. The disadvantage is that the changes in a non-homeostatic space are complicated. A non-homeostatic space accumulates not only changes associated with the disease but also changes associated with many other different confounding factors. In studies with human urine, those confounding factors cannot be ignored and cannot be fully controlled without defying ethical principles. A big data strategy may eventually solve this complicated problem. However, big data strategies are costly. Nobody will pay for the cost unless we have absolute confidence that once we have this astronomical amount of data, people will have better lives with less suffering. I believe the easiest and least costly way to build confidence is by using animal models. With animal models, we can minimize confounding factors, and we can study early biomarkers even before the current earliest clinical symptoms appear and laboratory tests are performed in hospitals. In many animal model studies, the experimental results were summarized in a few different review articles that showed that urinary proteins were changed as early as the initiation of disease development.3

It is hard for researchers in the biomarker field to agree with the idea that early biomarkers are located in the non-homeostatic space, because people in the field have been working on blood for decades. The fact that blood is more directly connected to all organs than urine makes people never doubt the current discovery model in blood. In that model, all that needs to be improved are the sensitivity and reproducibility of the machines. To believe and shift to the new paradigm, some people may need to see all the detailed mechanisms of how the information-bearing materials are transported from the diseased organ to urine. Many pieces already exist, but solving the whole puzzle is not easy. The following pieces are definitely not enough to solve the puzzle, but putting them together will help.

For the study of homeostasis, attention has long been given to the following aspects of the internal environment: temperature; pH; osmolality; and the concentrations of sodium, potassium, glucose, carbon dioxide, and oxygen. Are proteins controlled by the homeostatic mechanisms of the body? I believe they are, even though we do not know exactly how yet.

Let me try to delineate how this may happen. We can start with the term proteostasis. “Proteostasis refers to the maintenance of all proteins in the proteome in a conformation, concentration, and location that is required for their correct function”.4 Proteostasis is maintained by the production and disposal of proteins so that cells can be kept in a healthy state. “Proteostasis is critical to maintaining organismal viability and logically must operate in all body spaces”.5 “Deficiencies in proteostasis lead to many metabolic, oncological, neurodegenerative, and cardiovascular disorders. Small-molecule or biological proteostasis regulators that manipulate the concentration, conformation, quaternary structure, and/or the location of protein(s) have the potential to ameliorate some of the most challenging diseases

of our era".4 Ageing and diseases are associated with an imbalance of proteostasis. Inside the cell, protein production and its regulation have been studied and reviewed extensively. Regarding protein removal, attention has mainly been focused on autophagy and the ubiquitin-proteasome system. Actually, not all waste proteins can be degraded inside the cells. Some are disposed outside of the cells, where some of them were degraded. At this point, not all the waste proteins generated during ageing or diseases vanish. Some proteins that escape from the intracellular and extracellular degradation machines are transported to the blood. Other waste proteins are degraded in the blood or in organs that the blood serves. However, there are always a few bad ones that escape all those checkpoints and even pass the kidney and end up in the urine.



How do some of the plasma proteins end up in the urine but most of them are kept in the blood? An interesting clue was found when we comprehensively compared the post-translational modifications of plasma proteins and urinary proteins. For urinary proteins, a significantly higher percentage of cysteine (Cys) was changed to dehydroalanine (Dha). This may cause the loss of disulfide bonds, which, in turn, makes the protein fold incorrectly and lose its normal function. I assume some of those malfunctioning proteins are very toxic to the body, and it makes sense to remove them as soon as possible to the urine rather than to recycle and reuse them.6,7

Anything that is not controlled by homeostatic mechanisms is located in the non-homeostatic space. Based on homeostasis, the breath, sweat, tears and saliva are all great sources of early biomarkers.

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Conflicts of interest

Author declares that there are no conflicts of interest.

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