Systems diagnosis of chronic diseases, explored by metabolomics and ultra-weak photon emission

He, M.

Citation

He, M. (2017, April 13). *Systems diagnosis of chronic diseases, explored by metabolomics and ultra-weak photon emission*. Retrieved from https://hdl.handle.net/1887/47897

Author: He, M.
Title: Systems diagnosis of chronic diseases, explored by metabolomics and ultra-weak photon emission
Issue Date: 2017-04-13

Chapter 7

Summary, Conclusions, and Perspectives

1. Summary and Conclusions

1. 1 Systems-based evaluation of chronic disease

Chronic diseases such as rheumatoid arthritis (RA) and type 2 diabetes mellitus (T2DM) involve complex processes and pathologies that result in multiple interactions within the body, including inflammatory symptoms, complications, an increased risk of morbidity, loss of mobility, and mortality. Under the chronic disease state, complex responses often lead to unpredictable, subtle perturbations and dynamic changes. A systems biology–based analytical approach that integrates comprehensive data may provide unique insight into the underlying pathophysiological mechanisms. Rather than looking for a single target to characterize chronic disease, the studies in this thesis investigated systematic processes relevant to chronic disease using systems level analyses. Specifically, metabolomics was used to measure a large set of small molecule metabolites in combination with measuring spontaneous ultra-weak photon emission (UPE).

In research, animal models of chronic disease are widely used due to their many similarities with human patients. In **Chapter 2** and **Chapter 3**, metabolomics, which provides a comprehensive measure of small molecule metabolites as a readout of physiological status, was applied to mice with collagen-induced arthritis (CIA)—a commonly used mouse model of RA—to evaluate interactions at the metabolic level under chronic disease conditions. Oxylipins are bioactive lipid mediators synthesized from polyunsaturated fatty acids. Because of their important role in inflammatory processes, we measured plasma oxylipin levels in CIA mice in order to gain insight into inflammation- and ROS-related metabolites (**Chapter 2**). Compared to control mice, we found dysregulated oxylipins in CIA mice, reflecting inflammation and increased ROS levels. In addition, we found that collagen-induced arthritis may be associated with a dysregulation of apoptosis, perhaps due to activated NF-κB as a result of reduced levels of PPAR-γ ligands. Given that free amino acids—and their derivative biogenic amines—play essential roles in both energy production and protein synthesis/degradation, we measured plasma levels of amino acid–based metabolites in CIA mice in order to gain a different perspective regarding the levels of energetic metabolites (**Chapter 3**). Our finding of reduced levels of free amino acids together with their biogenic metabolites suggests a link between arthritis and muscle wasting/energy expenditure.

From these studies, we found that both oxylipins and amine metabolites reflecting arthritis but from different perspectives with respect to interpreting putative pathophysiological mechanisms. Systems biology–based metabolomics can provide new ways of improving the diagnosis of chronic disease and can provide insight into of the underlying pathophysiological mechanisms.

Correlation network–based analyses provide the opportunity to integrate data obtained from different technical platforms, thereby providing a correlation-based understanding of systemic interactions and regulation[1]. Interaction networks based on correlation analyses can be visualized and analyzed using software such as Cytoscape[2]. UPE is a non-invasive method for measuring photons emitted from the surface of body and may be correlated with oxidative metabolic processes[3], [4]. UPE intensity was increased in CIA mice[5]. In **Chapter 4**, we performed a correlation networks–based study to explore the relationship between metabolic processes and UPE by integrating the metabolic data described in **Chapter 2** and **Chapter 3** with UPE data measured in the same group of mice. This combination study yielded valuable information and provided insight into the disease process from a systems perspective. Our results revealed that the increase in UPE with arthritis is associated with a specific metabolites processes (primarily lipid oxidation, inflammatory metabolites and/or ROS-mediated metabolic processes). These results provide a window of knowledge into in our attempt to integrate different datasets and analyze complex interactions in RA, and these results provide further evidence to support the relationship between metabolic processes and UPE.

1.2 Personalized medicine-based phenotyping using TCM-based principles

Epidemiology studies have shown a rapid increase in the prevalence of clinic diseases, as well as a large undiagnosed patient population due primarily to mild clinical symptoms. Indeed, mild physiological perturbations can be present for years before the appearance of severe symptoms. The ability to predict disease early and to dynamically observe chronic disease remain challenging and if solved can—to a certain extent—prevent the development of irreversible lesions. In addition, if left undiagnosed long-term, chronic disease can develop in different directions, producing a wide range of phenotypes. Moreover, treatments based on generic observations (i.e., the “one drug-one target-one disease” or “one-size-fits-all” approach) are extremely limited, particularly in the early phases of a disease in which a personalized, systems-based approach is needed. Developing a personalized approach based on systems biology will reveal the unique clinical characteristics in individual patients and may shed light on the complexity and variability of chronic disease.

Traditional Chinese medicine (TCM) is based on a systems view combined with personalized strategies to provide descriptions of disease syndromes and subtypes as a guide to diagnose early syndromes of chronic diseases, an approach that has been shown to improve knowledge regarding personalized diagnostics. Based on TCM-based diagnostics, metabolomics may provide evidence-based biological mechanisms, thereby leading to personalized medicine and establishing a bridge between TCM and Western medicine. UPE reflects both the physiological and pathological status and is a potential tool for clinical diagnostics at the systems level[6] [7]; moreover, TCM-based diagnostics, metabolomics, and UPE each contributes to personalized medicine for treating chronic diseases. Integrating UPE with metabolomics under the guide of TCM-based diagnostics may create new opportunities for personalized medicine, systems-based diagnostics, and systems-based interventions for treating chronic disease (reviewed in **Chapter 5**). Based on the ideas described in **Chapter 5**, we performed an explorative study by combining metabolomics and UPE with TCM-based diagnostics (**Chapter 6**). We examined the relationship between metabolomics and TCM-guided subtypes of early-stage T2DM ("pre-T2DM"), and we identified key metabolites—primarily plasma lipids—that contribute to phenotypic subtypes. In addition, these key plasma lipids were correlated with the UPE parameters that were used to stratify the same cohort of pre-T2DM diabetic subjects, and these correlations differed among subtypes. These differences between subgroups may be used to establish correlation networks for improved diagnostics.

2. Perspectives

Analyses at the systems biology level offer many opportunities for understanding chronic disease from various perspectives by integrating various sets of information. This systems approach requires collaboration among scientists from various fields, including medicine, analytical biology, chemical biology, and bioinformatics. Metabolomics is a systems-based approach for studying comprehensive pathophysiological mechanisms in chronic disease. However, before conducting a metabolomics study, one must select the most suitable metabolomics platform. Future studies require additional metabolomics platforms in order to supplement biochemical information and to provide a link to other techniques, including UPE.

In this thesis, UPE was measured at specific positions on the body. Measuring a larger number of anatomical positions may provide additional information regarding disease, thus helping improve our understanding of personalized medicine. Here, we visualized the relationship between metabolomics and UPE using the statistic network tool Cytoscape (www.cytoscape.org) and based on our Spearman's rank correlation analysis presents in **Chapter 4** and **Chapter 6**. In the future, correlation-based networks may provide more comprehensive data for exploring interactions under a variety of disease conditions.

Animal models have many advantages for studying chronic disease. Specifically, the researcher can easily control and/or exclude potential confounding factors that may affect the results, including age, gender, genetic background, duration of disease, and drug exposure. However, although animal models are qualitatively similar to chronic disease in patients, metabolic differences clearly exist among patients, due to genetic differences and other factors; therefore, any biological mechanisms identified in animal models must be carefully compared to patients and validated in clinical studies involving patients.

Our study in human subjects (**Chapter 6**) illustrates the feasibility of stratifying patients using metabolomics guided by TCM-based diagnostics and provides a molecular correlate to UPE, thus illustrating that both metabolomics and UPE can be used to identify patient subtypes of pre-T2DM. Importantly, combining metabolomics and UPE measurements provides evidence-based data to support TCM-based diagnostics. Nevertheless, additional study is clearly needed in order to expand our knowledge and to achieve a systems view-based approach to personalized diagnostics.

3. References

[1] S. E. Calvano, W. Xiao, D. R. Richards, R. M. Felciano, H. V Baker, R. J. Cho, R. O. Chen, B. H. Brownstein, J. P. Cobb, S. K. Tschoeke, C. Miller-Graziano, L. L. Moldawer, M. N. Mindrinos, R. W. Davis, R. G. Tompkins, and S. F. Lowry, “A network-based analysis of systemic inflammation in humans.,” *Nature*, vol. 437, no. 7061, pp. 1032–7, Oct. 2005.

[2] M. S. Cline, M. Smoot, E. Cerami, A. Kuchinsky, N. Landys, C. Workman, R. Christmas, I. Avila-Campilo, M. Creech, B. Gross, K. Hanspers, R. Isserlin, R. Kelley, S. Killcoyne, S. Lotia, S. Maere, J. Morris, K. Ono, V. Pavlovic, A. R. Pico, A. Vailaya, P.-L. Wang, A. Adler, B. R. Conklin, L. Hood, M. Kuiper, C. Sander, I. Schmulevich, B. Schwikowski, G. J. Warner, T. Ideker, and G. D. Bader, “Integration of biological networks and gene expression data using Cytoscape.,” *Nat. Protoc.*, vol. 2, no. 10, pp. 2366–82, Jan. 2007.

[3] P. Pospíšil, A. Prasad, and M. Rác, “Role of reactive oxygen species in ultra-weak photon emission in biological systems,” *J. Photochem. Photobiol. B Biol.*, vol. 139, pp. 11–23, Oct. 2014.

[4] A. Rastogi and P. Pospísil, “Spontaneous ultraweak photon emission imaging of oxidative metabolic processes in human skin: effect of molecular oxygen and antioxidant defense system.,” *J. Biomed. Opt.*, vol. 16, no. 9, p. 096005, Sep. 2011.

[5] E. van Wijk, M. Kobayashi, R. van Wijk, and J. van der Greef, “Imaging of ultra-weak photon emission in a rheumatoid arthritis mouse model,” *PloS one*, vol. 8, no. 12. p. e84579, Jan-2013.

[6] J. A. Ives, E. van Wijk, N. Bat, C. Crawford, A. Walter, W. B. Jonas, R. van Wijk, and J. van der Greef, “Ultraweak Photon Emission as a Non-Invasive Health Assessment: A Systematic Review,” *PLoS One*, vol. 9, no. 2, p. e87401, Feb. 2014.

[7] R. Van Wijk, E. Van Wijk, H. van Wietmarschen, and J. Van der Greef, “Towards whole-body ultra-weak photon counting and imaging with a focus on human beings: A review,” *J. Photochem. Photobiol. B Biol.*, vol. 139, pp. 39–46, Oct. 2014.