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•Commentary•

Potential role of the protein interactome in translating TCM theory and clinical practice into modern biomedical knowledge

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With the awarding of the 2015 Nobel Prize in Physiology or Medicine to Chinese pharmacologist Tu Youyou, and the significant contributions of traditional Chinese medicine (TCM) for coronavirus disease 2019 (COVID-19), TCM has garnered increasing attention and interest globally. Although advanced research progress has been made in the efficacy research, mechanism elucidation and target prediction of TCM in recent years^[1], there is still no generic way to understand TCM and apply them to clinical practice from the perspective of modern biomedical science. Recently, Gan *et al.* established a network medicine framework centered on protein interactome (also referred to as protein-protein interaction network) to indicate the probability of co-occurrence of symptoms and the effectiveness of herbs in treating specific symptoms by analyzing network topology relationships^[2]. The authors proposed the network proximity hypothesis that the network proximity of symptom pairs or herb-symptom pairs can predict the co-occurrence of two symptoms or the efficacy of herbs for specific symptoms, which was partially validated through hospitalization data from 1936 cases of cirrhosis. This article contributes greatly to our understanding of TCM principles of diagnosis and treatment in modern scientific terminologies.

Although both TCM and Western medicine (WM) diagnose the patient's condition and subsequently determine the appropriate therapeutic regimen. However, the holistic the-

ory is the core of TCM ideology, which views individuals or patients as systems in different states. TCM places emphasis on syndrome differentiation, that is, summarizing the patient's condition by integrating information such as etiology, symptom, location and nature. While WM focuses on diagnosing diseases (referred to as WM diseases here) based on clinical manifestations and indicators, which are generally diagnosed as a specific disease when one or several clinical manifestations or indicators appear. The relationship between TCM syndrome and WM diseases is very complicated. One TCM syndrome can be observed in different WM diseases, and the same WM disease can be manifested as multiple different TCM syndromes in different patients. Therefore, it is difficult to establish the corresponding relationship between TCM syndrome and WM disease. Symptoms, whether TCM symptoms or WM symptoms, are terms that describe the clinical phenotype of patients, and are also important information clues for TCM syndrome differentiation and WM disease diagnosis. In addition, there are reports that experts, including TCM physicians and researchers, have manually mapped TCM symptoms to WM symptoms. To a certain extent, it is reasonable to associate TCM and WM using symptoms, which is also a feasible solution at present.

Furthermore, In WM, cells serve as the structural and functional units of the organism, initiating responses upon exposure to stimuli to ensure their own survival and that of the organism. Under physiological or pathological conditions, cellular responses are mediated by protein-protein interaction networks, which assemble proteins into complexes, signal transduction pathways and other macromolecular assemblies^[3, 4]. Gan *et al.* mapped symptom-related proteins and TCM herb targets to the protein interactome, and then measured the proximity of two networks to quantify the herb's ef-

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fectiveness in treating this symptom [2]. It provided a novel strategy for translating TCM theory and clinical practice into modern biomedical knowledge at the molecular level from a systematic perspective.

Gan *et al.* first proposed a new network medicine framework that predicted an herb's effectiveness against a symptom through protein-protein interactions (PPIs), with the area under the receiver operating characteristic curve (AUC) values between 0.66 and 0.72 [2]. It suggested that there is still a lot of work to be done to achieve higher accuracy. Constructing a high-quality PPI network is one of the promising directions. There are several aspects that need to be considered in order to construct a high-quality protein interactome. Firstly, in multicellular organisms, all cells contain the same genome, but different cell types express distinct proteins. It supports the concept that PPIs are highly variable across different cell types and tissues, indicating that the specificity of the PPI must be considered in constructing high-quality protein-protein interaction networks [5]. As expected, some achievements have been made in deciphering tissue-specific protein interactome [6,7]. And it has been reported that the protein interactome of each cell is responsible for its unique phenotype [8]. By establishing two protein-protein interaction networks in two human cell lines, the study found that shared PPIs form core complexes associated with essential functions, while cell-specific PPIs bridge these complexes to execute specialized cell processes.

Another important issue to note for high-quality protein-protein interaction networks is the dynamic properties of protein interactomes. Although there have been many attempts to construct dynamic protein-protein interaction networks, including experimental methods [9] such as thermal proximity coaggregation (TPCA) and ion-based proteome-integrated solubility alteration assay (I-PISA), as well as advanced computational pipelines [10]. It is still a considerable challenging to characterize PPI network dynamics accurately and fully from a whole-system perspective, because the interactions between proteins are closely related to protein characteristics such as protein abundance, protein re-localization to specific cellular structures, post-translational modifications, transient nature, and physiological or pathological environments. For example, in some settings, specific post-translational modifications can act as switches to make certain transient PPIs reversible. Generally, the occurrence of a PPI is determined by factors such as cell type, cellular state, and the surrounding

environment. The analysis of dynamic and conditional-specific protein-protein interaction networks, rather than static and context-independent ones, will distill more biologically meaningful information with respect to a variety of biological issues. Excitingly, over the past five years, the number of single-cell or spatial data on transcriptional and protein levels generated under different conditions has grown exponentially, making it possible to capture the spatial or temporal dynamic characteristics of protein interactions in different cells [11,12]. In future, if context-specific and dynamic PPIs can be reflected in protein-protein interaction networks, this could facilitate the more precise translation of TCM theory and clinical practice into modern biomedical knowledge.

References

- [1] Li X, Liu Z, Liao J, *et al.* Network pharmacology approaches for research of Traditional Chinese Medicines [J]. *Chin J Nat Med*, 2023, **21**(5): 323-332.
- [2] Gan X, Shu Z, Wang X, *et al.* Network medicine framework reveals generic herb-symptom effectiveness of traditional Chinese medicine [J]. *Sci Adv*, 2023, **9**(43): eadh0215.
- [3] Michaelis AC, Brunner AD, Zwiebel M, *et al.* The social and structural architecture of the yeast protein interactome [J]. *Nature*, 2023, **624**(7990): 192-200.
- [4] Huttlin EL, Bruckner RJ, Paulo JA, *et al.* Architecture of the human interactome defines protein communities and disease networks [J]. *Nature*, 2017, **545**(7655): 505-509.
- [5] Holguin-Cruz JA, Foster LJ, Gsponer J. Where protein structure and cell diversity meet [J]. *Trends Cell Biol*, 2022, **32**(12): 996-1007.
- [6] Skinnider MA, Scott NE, Prudova A, *et al.* An atlas of protein-protein interactions across mouse tissues [J]. *Cell*, 2021, **184**(15): 4073-4089.e4017.
- [7] Luck K, Kim DK, Lambourne L, *et al.* A reference map of the human binary protein interactome [J]. *Nature*, 2020, **580**(7803): 402-408.
- [8] Huttlin EL, Bruckner RJ, Navarrete-Perea J, *et al.* Dual proteome-scale networks reveal cell-specific remodeling of the human interactome [J]. *Cell*, 2021, **184**(11): 3022-3040.e3028.
- [9] Tan CSH, Go KD, Bisteau X, *et al.* Thermal proximity coaggregation for system-wide profiling of protein complex dynamics in cells [J]. *Science*, 2018, **359**(6380): 1170-1177.
- [10] Deciphering protein interaction network dynamics with a machine learning-based framework [J]. *Nat Methods*, 2024, **21**(3): 387-388.
- [11] Bennett HM, Stephenson W, Rose CM, *et al.* Single-cell proteomics enabled by next-generation sequencing or mass spectrometry [J]. *Nat Methods*, 2023, **20**(3): 363-374.
- [12] Tian L, Chen F and Macosko EZ. The expanding vistas of spatial transcriptomics [J]. *Nat Biotechnol*, 2023, **41**(6): 773-782.

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